Comparative Information on New Medicines

availability, quality and usage

Johan van Luijn

The work presented in this thesis was performed at the Division of Pharmacoepidemiology & Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, The Netherlands in collaboration with the Health Care Insurance Board/College voor zorgverzekeringen, Diemen, The Netherlands

Picture on the cover by Gerard van Luijn

Publication of this thesis was supported by Health Care Insurance Board

CIP-gegevens Koninklijke Bibliotheek, Den Haag

Van Luijn, J.C.F.
Comparative information on new medicines – availability, quality and usage
Thesis Utrecht University – with ref. – with summary in Dutch

ISBN: 978-90-393-5252-6

Comparative Information on New Medicines

availability, quality and usage

Vergelijkende informatie over nieuwe geneesmiddelen

beschikbaarheid, kwaliteit en gebruik
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. J.C. Stoof, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op woensdag 13 januari 2010 des ochtends te 10.30 uur

door

Johannes Cornelis Franciscus van Luijn

geboren op 28 april 1951 te Bakel en Milheeze

Promotoren:

Prof.dr. F.W.J. Gribnau
Prof.dr. H.G.M. Leufkens

About the picture on the cover

The picture on the cover illustrates the author's years of experience in assessing the therapeutic value of new medicines.
It has often been simply a matter of *"ploughing with the oxen that one has"*.
Assessments were often complicated by a lack of the desired studies, in which new medicines are compared with existing medicines intended for the same therapeutic indication. Nevertheless, an attempt was always made to form well-deliberated opinions on the basis of the other available studies.
The fact that these assessments could – and should – be improved was the driving force behind this thesis.

Contents

Chapter 1

General introduction

Introduction

An important option in the treatment of patients is the prescription of a medicine. In order to choose the right medicine for the right patient, insight is needed in differences and similarities between medicines intended for the same therapeutic indication. Results from clinical research that help in making a choice between alternative treatments are regarded as comparative information. An optimal pharmacotherapy would be served by a good balance between the demand for and supply of this information.

Development of knowledge

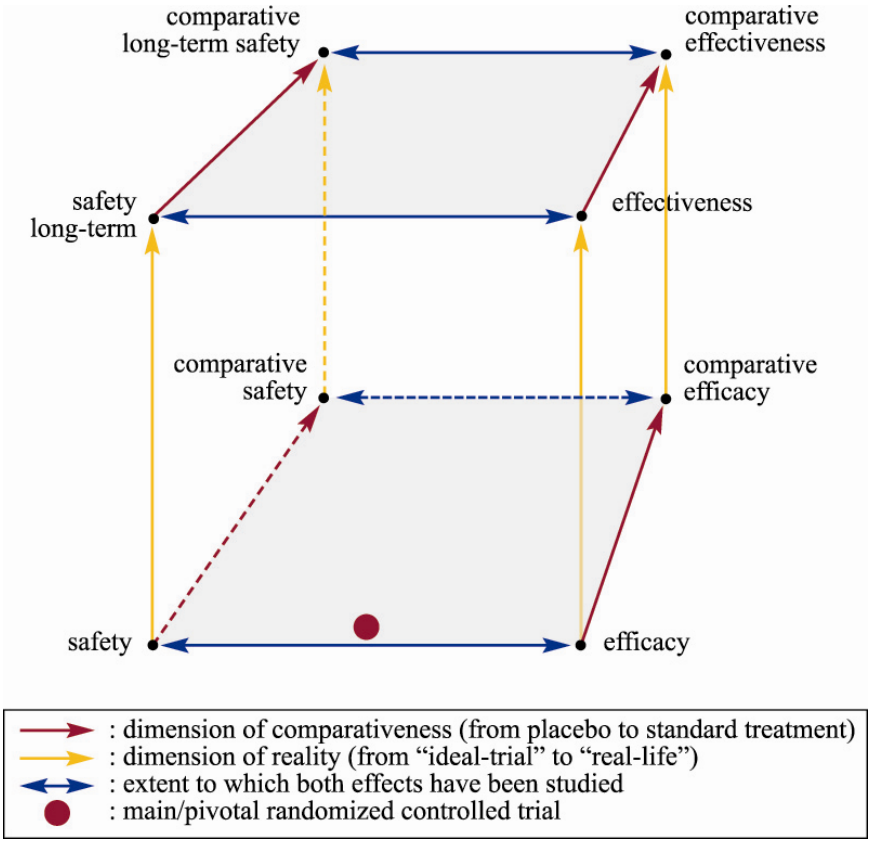
We all are aware that our knowledge on the clinical effects of a new medicine is limited at market entry. As no premarketing study can answer all of the questions and insights into therapy and health care changes, the postmarketing development of knowledge is a continuous learning cycle [1,2].

In the premarketing phase in the life cycle of medicines, the focus of the clinical research is on demonstrating efficacy and safety. New medicines are approved to enter the market if the benefit/risk profile has been shown to be favourable, i.e., their therapeutic efficacy has been sufficiently substantiated and the risks in terms of adverse effects are acceptable [3]. Randomized controlled trials form the pivotal cornerstone in accumulating evidence for assessing this balance. Placebo controlled trials are widely considered as the most robust evidence, as they measure the total pharmacological effect of the drug, the absolute efficacy and safety [4,5].

By all means, it is necessary to gain more in-depth knowledge due to the limitations of premarketing research [6,7]. Such research takes place under more or less ideal circumstances (homogeneous groups of patients, proper guidance, etc.), focused on the reliability or accuracy of the results of the study (internal validity). Therefore there is a preference for a placebo as control group to demonstrate efficacy and safety. Furthermore, research is often limited with respect to duration and size. For this reason, in order to demonstrate efficacy, use is often made of surrogate outcome measures and not of clinical endpoints such as a decrease in mortality and morbidity. Furthermore, it is not possible to adequately distinguish rare adverse effects or ones that only occur after long-term use. This ideal-trial situation differs from the real-life situation. In clinical practice medicines are

undeniably be used in more heterogeneous groups of patients, often with comorbidity and frequently for longer periods. It is therefore important that further clinical research takes these limitations into account. Research could therefore develop along two lines to gain more in-depth knowledge on the clinical effects of medicines: the dimension of reality and the dimension of comparativeness [8].
The first will eventually provide us with more insight into efficacy in daily practice as well as into the intended goal of the treatment (effectiveness) and safety in the long term. The second dimension will eventually provide us with more insight into the differences and similarities with other medicines, preferably the standard treatment (comparative effectiveness and safety). The both dimensions are applicable to benefits as well as the risks of the medicine in the same or in separate studies.

Figure 1 – Box with Studies on Benefits and Risks



When both dimensions are applied to efficacy and/or safety, the development of our ideal knowledge on the clinical effects of medicines can be represented schematically as a box, the Box with Studies on Benefits and Risks (figure 1).
During the life cycle of a medicine, the Box gets filled with data from different types of clinical trials and registries. The initial studies at the bottom of the Box will be the pivotal/main premarketing studies; comparative research can be part of it.

Comparative research

Different kinds of research can provide comparative information. An obvious and widely accepted way to obtain a clear picture of any differences is a comparison in which both medicines are used under identical circumstances.
A study design could be a randomized controlled trial of a new product with an existing medicine as control group, preferably the standard treatment, a so-called randomized active control trial (RaCT). These studies are used in particular for information on (comparative) efficacy, as they are widely accepted as the scientific standard in the evaluation of intended effects: the effects of a treatment that are hoped for at the start of a study. Although differences in safety may also become evident, drawing firm conclusions on comparative safety remains difficult because the size and duration of an efficacy study make it uncertain whether the new product really is distinguishing itself from the existing product, which often has a known safety profile based on broader experience. Adverse effects are an expected though unintended effect, both with regard to their nature and their extent. The possibility that certain adverse effects will become manifest in greater groups of patients or after long-term use cannot be excluded. This means that observational studies, spontaneous reports and safety databases also play a role in assessing comparative safety profiles [9].
In order to develop postmarketing comparative effectiveness research, initiatives are being taken to improve the validity of nonrandomised studies by studying drug use data, often from large health care utilization databases [10,11].

In recent years various studies have shown that, in the absence of active controlled trials, an adjusted indirect comparison is a welcome additional tool for the assessment of differences between medicines [12-14]. In this approach, the comparison of both medicines of interest is adjusted by the results of their direct comparison with a common control group. In this way the strength of the original RCTs is still partially used, unlike with a direct comparison of the relevant single arms of the trials (naïve indirect comparison).

Efficacy and safety are regarded as the most important properties of medicine, as they determine market authorization, both absolute and in relation to one another, i.e., the benefit/risk ratio. When a range of treatment possibilities are available, all properties relevant to treatment can be compared with one another for an opinion on the position of the new product in therapy. Other properties that could play an role in this assessment are applicability, convenience of administration and experience [15].

Supply of comparative information

Ideally, comparative information should be available at the moment of market introduction of a new drug, which means that an RaCT should have been conducted in the premarketing phase of drug development. However, research in this phase focuses primarily on clinical trials, the objective of which is to obtain marketing authorization.
An RaCT is not compulsory for regulatory approval, but sometimes the authorities expect the new medicine to be compared with the standard treatment [3,16,17].
An RaCT is necessary in cases where a placebo controlled trial would not be ethical. This is the case in conditions in which delaying or denying available treatments would increase mortality or irreversible morbidity in the patients to be studied. However, regulatory authorities also want to be sure that, for new medicines for which good alternatives are available, the possibility has been excluded that patients are treated with a product that is less efficacious or less safe.
Files submitted to the regulatory authorities can include studies that demonstrate efficacy by confirming the absence of a difference (equivalence trial), or by showing that the new medicine is no worse than an existing medicine (noninferiority trial). Besides this, efficacy can also be demonstrated by showing an improved efficacy compared with a medicine already used in practice for the same claimed indication (superiority trial) [5,18].

After market approval the lack of comparative information could be made up with new clinical trials. These studies could be initiated by pharmaceutical companies but also by other stakeholders, such as clinicians and regulators. However, other issues can also be the subject of non-comparative research, such as effectiveness (mortality/morbidity outcomes, patient-related outcomes), long-term safety, refining dose recommendations, etc., as these are all relevant to gain more in-depth knowledge about a new medicine.

Altogether this means that the supply of comparative information of new medicines is very variable and highly dependent on the type of drug and the research policy of the stakeholders.

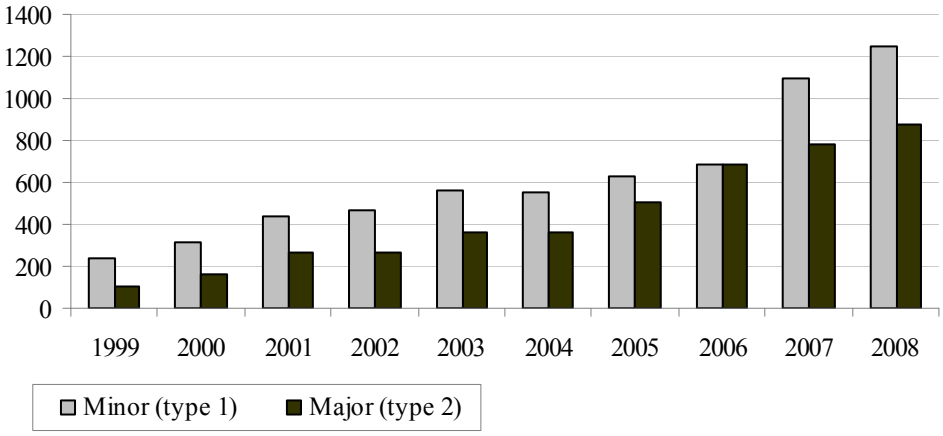
Demand for comparative information

In the scientific and public debate on the use of medicines, there is a need of adequate comparative information [5,10,18-23]. The key issue is that in order to improve quality of treatment and to control health care costs, choices have to be made, and rational choices need to be based on good information. Since the 1990s, a number of developments have drawn increasing attention to this decision-making process.

Firstly, the number of medicines is still increasing, despite the worldwide yearly decline in new medicines with a new active substance. New medicines with an new mechanism of action are being developed for an increasing number of diseases, such as orphan diseases, but also for the treatment of, for example, cancer and rheumatoid arthritis. However, the majority of new products, including generic products, form a supplement to the existing treatment options and belong to an existing therapeutic class. In addition, there is the phased extension of therapeutic indications of even more drugs following their initial market authorization. This has resulted in the regulatory model gradually evolving from one-off marketing authorization to a life cycle approach [24].

Figure 2 shows the increasing number of postauthorization activities of European regulatory authorities on minor and major variations, in terms of market authorization; in ten years the number of major variations such as extensions of indications, safety updates, quality changes, etc., increased from 102 in 1999 to 877 in 2008 [25].
The increased number of new applications for the treatment of patients also means that new therapeutic choices have to be made. The importance of this evaluation becomes even greater if use of the new drug is associated with much higher costs. This is because, apart from improving the quality of treatment by new options, costs are an even more important consideration in decisions on reimbursement and prescribing, as resources for health care are limited. The question we need to ask is, do the added costs weigh up against the added therapeutic value.

Figure 2 - Postauthorization variations in terms of marketing authorization



Source: Annual Reports of European Medicines Agency (EMEA)

A new type of research has been developed in order to answer these questions adequately: pharmacoeconomic research [26,27]. This is currently regarded as a sound methodology for conducting cost-effectiveness studies. In many countries worldwide guidelines are used for designing and conducting this type of research [28]. As a pharmacoeconomic evaluation is always based on comparison with another treatment, all guidelines give recommendations on the choice of medicine with which a new one has to be compared. As for the reliability of these studies, it is important that adequate comparative information is available for underpinning the clinical data in these economical studies [29].

Another important international development during recent decades is the use of methodologies in decision-making, such as health technology assessment (HTA), evidenced-based medicine (EBM) and grading the quality of evidence and strength of recommendations (GRADE) [30-34]. There is strong clinical and political support for the use of these procedures for rational decision-making. HTA is a form of policy research that systematically examines the short- and long-term consequences (societal, economic, ethical, legal) of health technologies, including medicines. The use of EBM is regarded as a way of improving and evaluating patient care; it involves systematically combining the best research evidence with a patient's values in order to make decisions. In many countries, practice guidelines have been developed for the evaluation and treatment of patients with

the same disease, using methods such as EBM and GRADE. The current attention being paid to improving comparative effectiveness research (CER) is an indication of the interest in comparative information based on the best methodological quality [35].

Problem

The urgent and essential need of comparative information on new medicines is insufficiently supplied because of the problem, generally regarded as important, of the paucity or even absence of comparative trials. There is a critical imbalance between the demand for and supply of comparative information.
Until now, the literature has lacked quantitative data and specific analyses on the nature and extent of the problem. A review of submissions for reimbursement in Australia shows that 73% of all submissions between 1994 and 1997 were comprised of trials involving direct comparisons of the new drug with a comparator [36]. In this review, it is unclear what the number is in relation to new medicines with a new active substance: the most important type of new product.
In spite of the absence of comparative information based on the results of clinical research, in clinical practice the position of a new medicine in therapy has to be assessed in the case of a submission for reimbursement or where there is a wish – or where pressure is being exerted – to prescribe a new medicine. The next best available evidence then has to be used.

Objective of the thesis

The main objective of the thesis is to shed light upon the issue of comparative information on new medicines at a crucial moment in their life cycle: the moment they are allowed to enter the market. For this purpose we evaluated the availability, quality and usage of comparative information based on premarketing randomized active control trials.

Outline of the thesis

For the studies in the thesis we used the data from the main/pivotal trials of medicinal products with a new active substance that were authorized through a Centralised Procedure by the European Commission between 1st January 1999 and 31st December 2005.

Information was extracted from the European Public Assessment Reports (EPARs), as these provide an overview of clinical trials submitted by the industry for market approval, and the scientific discussion in the Committee for Medicinal Products for Human Use (CHMP) [37]. New active substances are drugs that have not previously been authorized as medicinal products in the European Union. We excluded diagnostics and vaccines.

Chapter 2 represents three studies on the availability of comparative information. The aim of the first study was to investigate new medicines that had been studied in comparison with existing medicines during the premarketing phase. A second study describes new medicines with improved efficacy. A third study focused on the postmarketing period, analysing whether a lack of premarketing active control trials could be compensated by new studies after marketing approval. A case study was conducted on etanercept.
Chapter 3 describes the quality of the comparative information, a study focusing on the choice of the comparator and an open letter to the regulatory authorities about the quality of their information on noninferiority and equivalence trials.
Chapter 4 describes the usage of comparative information. The time-lag was determined between market authorization and publication of the results of the pivotal active control trials. Another study evaluates the strength of the comparative evidence used in an evaluation of the comparative efficacy.
Finally, the general discussion presented in chapter 5 discusses the main findings in the light of their significance and the consequences for the assessment of new medicines.

References

1. Sheiner LB. Learning versus confirming in clinical drug development. Clin Pharmacol Ther 1997;61:275-91.
2. Stolk P. From new molecules to leads for innovation. Studies on the post-innovation learning cycle for pharmaceuticals. 2008;
3. Koopmans PP, de Graeff PA, Zwieten-Boot BJ, Lekkerkerker JF, Broekmans AW. Clinical evaluation of efficacy and adverse effects in the (European) registration of drugs: what does it mean for the doctor and the patient? (in dutch). Ned Tijdschr Geneeskd 2000;144:756-61.
4. Lewis JA, Jonsson B, Kreutz G, Sampaio C, van Zwieten-Boot B. Placebo-controlled trials and the Declaration of Helsinki. Lancet 2002;359:1337-40.
5. The European Agency for the Evaluation of Medicinal Products. Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96). London: EMEA, 2000.
6. Rawlins M. De testimonio: on the evidence for decisions about the use of therapeutic interventions. Lancet 2008;372:2152-61.
7. Vandenbroucke JP. Observational research, randomised trials, and two views of medical science. PLoS Med 2008;5:e67.
8. The Pharmaceutical Forum. High Level Pharmaceutical Forum 2005 – 2008. Final Report. 2008; Accessed in September 2009 via http://ec.europa.eu/pharmaforum/docs/ev_20081002_frep_en.pdf.
9. Vandenbroucke JP. What is the best evidence for determining harms of medical treatment? CMAJ 2006;174:645-6.
10. Kaplan W. Comparative effectiveness of medicines and use of head-to-head comparative trials. In: Priority medicines for Europe and the world. Den Haag: Ministry of Health, Welfare and Sport, 2004:
11. Schneeweiss S. Developments in post-marketing comparative effectiveness research. Clin Pharmacol Ther 2007;82:143-56.
12. Gartlehner G, Moore CG. Direct versus indirect comparisons: a summary of the evidence. Int J Technol Assess Health Care 2008;24:170-7.
13. Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, et al. Indirect comparisons of competing interventions. Health Technol Assess 2005;9:1-iv.
14. Song F, Loke YK, Walsh T, Glenny AM, Eastwood AJ, Altman DG. Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published systematic reviews. BMJ 2009;338:b1147.
15. College voor Zorgverzekeringen. Farmacotherapeutisch Kompas. 2008. Diemen: Health Care Insurance Board, 2008.
16. Ellenberg SS, Temple R. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 2: practical issues and specific cases. Ann Intern Med 2000;133:464-70.
17. Temple R, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: ethical and scientific issues. Ann Intern Med 2000;133:455-63.
18. U.S.Food and Drug Administration. E 10 choice of control group and related issues on clinical trials. Guidance to industry. Rockville: Food and Drug Administration, 2001.
19. International Society of Drug Bulletins. ISDB declaration on therapeutic advance in the use of medicines. Paris: International Society of Drug Bulletins, 2001.
20. Avorn J. Powerful medicines. The benefits, risks, and costs of prescription drugs. Revised and updated. New York: Vintage Books, 2005.
21. Dent TH, Hawke S. Too soon to market. BMJ 1997;315:1248-9.

22. Garattini S, Bertele' V. How can we regulate medicines better? BMJ 2007;335:803-5.
23. Henry D, Hill S. Comparing treatments. BMJ 1995;310:1279.
24. Eichler HG, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. Nat Rev Drug Discov 2008;7:818-26.
25. The European Agency for the Evaluation of Medicinal Products. Annual reports 1999-2008. 2008; Accessed in September 2009 via http://www.emea.europa.eu/htms/general/direct/ar.htm.
26. Drummond M, Jonsson B, Rutten F. The role of economic evaluation in the pricing and reimbursement of medicines. Health Policy 1997;40:199-215.
27. van Oostenbruggen MF, Jansen RB, Mur K, Kooijman H. Penny and pound wise: pharmacoeconomics from a governmental perspective. Pharmacoeconomics 2005;23:219-26.
28. Hjelmgren J, Berggren F, Andersson F. Health economic guidelines--similarities, differences and some implications. Value Health 2001;4:225-50.
29. Rennie D, Luft HS. Pharmacoeconomic analyses: making them transparent, making them credible. JAMA 2000;283:2158-60.
30. Atkins D, Eccles M, Flottorp S, Guyatt GH, Henry D, Hill S, et al. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. BMC Health Serv Res 2004;4:38.
31. Banta D. What is technology assessment? Int J Technol Assess Health Care 2009;25 Suppl 1:7-9.
32. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. BMJ 2001;323:334-6.
33. National Institute of Clinical Excellence. Guide to the methods of technology appraisal. London: NICE, 2004.
34. Sackett DL, Oxman AD. HARLOT plc: an amalgamation of the world's two oldest professions. BMJ 2003;327:1442-5.
35. Avorn J. Debate about funding comparative-effectiveness research. N Engl J Med 2009;360:1927-9.
36. Hill SR, Mitchell AS, Henry DA. Problems with the interpretation of pharmacoeconomic analyses: a review of submissions to the Australian Pharmaceutical Benefits Scheme. JAMA 2000;283:2116-21.
37. The European Agency for the Evaluation of Medicinal Products. European Public Assessment Reports. 2009; Accessed in October 2009 via http://www.emea.europa.eu/htms/human/epar/eparintro.htm.

Chapter 2

Availability of comparative information on new medicines

Chapter 2.1

Availability of comparative trials for the assessment of new medicines in the European Union at the moment of market authorization

Johan C.F. van Luijn,
Frank W.J. Gribnau,
Hubert G.M. Leufkens

Published: Br J Clin Pharmacol 2007; 63:159-62

Abstract

Aims

To investigate the availability of information about premarketing randomized active control trials (RaCTs) involving medicines with a new active substance at the moment of market authorization in the European Union.

Methods

Information was obtained from the EMEA European Public Assessment Reports and the MEDLINE and EMBASE databases.

Results

Between 1999 and 2005, 48% of recently approved medicines (N=122) had been studied in comparison with existing medicines at the moment of market authorization. About one-third of these trials were published and publicly available at that moment.

Conclusion

For most new medicines evidence-based assessment of the (added) therapeutic value is hardly possible at the moment of market authorization.

Introduction

For optimal therapy with a new medicine, especially with a new active substance, it is important to know how the new compound compares with existing medicines [1,2]. This information is necessary to assess the added therapeutic value. For this purpose the optimal study design would be a randomized controlled trial of the new product with an active medicine already used in clinical practice as control group, a so-called randomized active control trial (RaCT).
Prescribers and reimbursement authorities, faced with a new medicine at the moment of market introduction, need comparative information in order to make decisions on prescribing or reimbursing. This means that ideally an RaCT should be conducted in the premarketing phase of drug development and published before market entry. The absence of RaCTs is generally regarded as an important problem [3,4]. However, there is a lack of quantitative information about the extent of this problem.
The aim of this study is to investigate the availability of information about premarketing randomized active-control trials involving medicines with a new active substance at the moment of market authorization via the centralized procedure in the European Union and to determine which characteristics of the new medicine are associated with the availability of an RaCT.

Methods

Source of information

For information about premarketing trials we used the European Public Assessment Reports (EPAR) as they give a good overview of clinical trials submitted by the industry for market approval and the scientific discussion in the Committee for Medicinal Products for Human Use (CHMP) [5]. We selected products with a new active substance authorized by the European Commission between 1999 and 2005. Diagnostics and vaccines were excluded. New active substances were those substances that had not previously been authorized as a medicinal product in the European Union [6]. We used the initial version of the EPAR which was retrieved from the EMEA website [5] at the moment the product was granted market authorization. From the EPARs, we extracted data about the authorization procedure, therapeutic characteristics (indications, mechanism of action, orphan drug designation, biotechnological product) and the clinical studies conducted. To identify relevant RaCTs, we selected all studies that were labelled in the EPAR as “main/pivotal

active-control studies". An active control trial was defined as a trial in which a drug under investigation is compared to a known active drug [7].

New mechanism of action

We defined a mechanism of action as new if the primary pharmacodynamic target (e.g., receptor, enzyme, ion channel or carrier molecule) and drug-target interaction differed from existing drugs [8]. When a medicine belonged to a new therapeutic class and the mechanism of action was unknown, we classified it as 'new'.

Literature search

MEDLINE and EMBASE databases using the drug's international nonproprietary name up until the first month after market authorization (actual search date: March 2006) were searched in order to identify which studies reported in the EPAR had been published. We retrieved the abstracts of RaCTs with the new drug and compared the study characteristics and outcomes of the published RaCTs to those reported in the EPAR. Meta-analyses were considered as a publication of a trial when not separately published.

Statistical analysis

In order to assess the association between drug characteristics and the availability of an RaCT, odds ratios with 95% confidence intervals were calculated using logistic regression analysis.

Results

We identified 122 medicines with a new active substance in the period 1999-2005. For 58 (48%), the initial EPAR reported one or more RaCTs. Table 1 gives an overview of these new substances and table 2 shows the associations between drug characteristics and the availability of an RaCT.

Table 1 - Randomized active control trials of new medicines in EU (1999-2005)

New medicines with premarketing RaCT	
New mechanism of action	**Similar mechanism of action**
aripiprazole, atosiban, bevacizumab (1), cetrorelix, darifenacin, enfuvirtide, fondaparinux, fulvestrant, ibritumomab tiuxetan (1), ivabradine, leflunomide, rasburicase (1), rosiglitazone, sirolimus, trastuzumab (1)	abacavir, amprenavir, atazanavir, bimatoprost, bivalirudin, brinzolamide, capecitabine, choriogonadotropin alpha (1), darbepoetin alpha (1), deferiprone, efavirenz, emedastine, emtricitabine, epoetin delta (1), ertapenem, fosamprenavir, ganirelix, insulin aspart (1), insulin detemir (1), insulin glargine (1), insulin glulisine (1), interferon alfacon-1 (1), lopinavir, nateglinide, norelgestromin, olopatadine, palonosetron, parecoxib, pegfilgrastim (1), peginterferon alpha-2a (1), peginterferon alpha-2b (1), pioglitazon, rasagiline, sevelamer, telithromycin, temozolomide, tenecteplase (1), tipranavir, travoprost, valdecoxib, voriconazole, zaleplon, zoledronic acid
New medicines without premarketing RaCT	
New mechanism of action	**Similar mechanism of action**
agalsidase alpha (1,2), agalsidase beta (1,2), alemtuzumab (1), anagrelide (2), anakinra (1), aprepitant, arsenic trioxide (2), becaplermin (1), bexarotene, bortezomib, bosentan (2), carglumic acid (2), caspofungin, cetuximab (1), cinacalcet, efalizumab (1), eflornithine, eptotermin alpha (1), erlotinib, human protein C (1), imatinib (2), infliximab (1), laronidase (1,2), levetiracetam, memantine, miglustat (2), mitotane (2), nitisone (2), nitric oxide, omalizumab (1), palifermin (1), palivizumab (1), pegvisomant (1,2), pre-gabalin, sodium oxybate (2), sodium phenylbutyrate, strontium ranelate, tasonermin (1), teriparatide (1), ziconotide (2), zonisamide	adalimumab (1), adefovir, alitretinoin, botulinum toxin b, calcitonin salmon (1), colesevelam, daclizumab (1), desloratadine, dibotermin alpha (1), drotrecogin alpha (1), duloxetine, eptifibatide, etanercept (1), human fibrinogen/thrombin (1), lutropin alpha (1), moroctocog alpha (1), oseltamivir, posaconazole, tadalafil, temoporfin, tenofovir, vardenafil, verteporfin

1 = biotechnological product; 2 = orphan drug; RaCT: randomized active control trial

Table 2 - Availability premarketing randomized active control trials of new medicines

Characteristics	without RaCT		with RaCT		crude odds ratio
Number of trials	64	52.5%	58	47.5%	
Year of authorization					
1999	9	14.1%	10	17.2%	1.00
2000	5	7.8%	10	17.2%	0.56 (0.14 – 2.26)
2001	13	20.3%	11	19.0%	1.31 (0.39 – 4.39)
2002	11	17.2%	10	17.2%	1.22 (0.35 – 4.26)
2003	7	10.9%	3	5.2%	2.59 (0.51 – 13.17)
2004	11	17.2%	9	15.5%	1.36 (0.39 – 4.79)
2005	8	12.5%	5	4.1%	1.78 (0.42 – 7.47)
Therapeutic indication					
Cancer	10	15.6%	6	10.3%	1.61 (0.54 – 4.73)
Diabetes mellitus	0		7	12.1%	NA
HIV-1 infections	1	1.6%	9	15.5%	0.09 (0.01 – 0.71)
Reumatoide arthritis	3	4.7%	2	3.4%	1.38 (0.22 – 8.55)
Orphan drug	14	21.9%	0		NA
Biotechnological product	26	40.6%	16	27.6%	1.80 (0.84 – 3.85)
New mechanism of action	41	64.1%	15	25.9%	5.11 (2.35 – 11.13)

RaCT: randomized active control trial

A new mechanism of action was shown to be a significant limiting factor in providing RaCT data (OR: 5.11; 95% CI: 2.35–11.13). There was no lack of RaCT data for medicines for the treatment of HIV-1 infections (OR: 0.09; 95% CI: 0.01–0.71). No significant association was found for the other main indications and biotechnological products; statistical analysis was not possible for antidiabetic drugs and orphan drugs due to zero-values. All the orphan drugs had a new mechanism of action; when these were

excluded from a stratified analysis, we still found an association between a new mechanism of action and the availability of an RaCT (OR: 3.37; 95% CI: 1.50–7.56).
In total 153 RaCTs were conducted in the premarketing period and mentioned in the EPAR. At the moment of market authorization, we found that 53 trials (35%) of 33 new medicines (27%) had been published.

Discussion

New medicines are studied extensively in the premarketing phase, but paradoxically enough, there are still important gaps in the knowledge needed to use them optimally after marketing authorization has been granted. Demonstrating efficacy and safety requires placebo-controlled trials, but for any differences with existing medicines, either positive or negative, we have to rely mainly on trial and error, clinical experience and such like. This study shows that 48% of the new medicines had been studied in an active control trial, but for only 27% the results were published at the moment of authorization.
We conclude that the lack of comparative data on new medicines, apart from the uncertainty about effectiveness and long-term safety, greatly hamper evidence-based assessment of the therapeutic value of these medicines. This constitutes an extra reason to be cautious about using new medicines during the first years following market introduction and about every claim of an added therapeutic value.

The lack of active control data is understandable in situations where no alternative active drug is available, as is the case with orphan drugs. However, when alternatives are available, the reasons for this lack of information are less clear. Companies may have methodological, economical and strategic reasons for deciding not to conduct an RaCT. For example, to prove clinically relevant differences between two active substances, trials have to be large and long, which brings added development costs. Furthermore, there is a risk that a new product will prove to be no better than an older and less costly, alternative. The fact that this risk weighs more heavily than the convincing evidence of an adequate active control trial, is revealing.

When an RaCT has been conducted, its value for the assessment of therapeutic value depends of the quality of the trial. As our study only focused on the availability of information we can not fully discuss this issue. Nevertheless, there is one important general finding. Only 35% of all trials were published at the moment of market authorization and

thereby freely available to review and to use as a reference for therapeutic decision-making. This means that EPARs are an important additional source of information, as they give insight into conducted trials and can lead to questioning the industry about their plans for publications. Moreover, they provide weighted information about the significance of the published data.

An important subject of discussion is what should happen in the future to fill in the gaps in comparative information assessed in this study. In view of the importance of comparative studies for pharmacoeconomic assessments and other patient outcome assessments, we had expected to see more RaCTs over the years. Our study does not suggest such a trend. However, we anticipate a change in this trend in the near future because the assessment of therapeutic value and cost-effectiveness requires a scientific basis including RaCT data. The present requirements for clinical trials seem to be sufficient for market authorization, but they are definitely not in the context of the wishes and needs of prescribers, formulary committees and reimbursement authorities.

Today's pharmaceutical market-place is under strong economical and regulatory pressure, and many business analysts are questioning whether the current model of pharmaceutical innovation is sustainable [9,10]. The costs of drug development are not in balance with the output and there is a strong voice for new scientific and regulatory models for making efficacious, safe and affordable drugs available to patients. In all our efforts to reduce costs, we have to make efficient use of current regulatory requirements. When designing clinical studies, companies should anticipate the need for comparative information. The future therefore probably lies not in more but in smarter and better-designed clinical development programs.

References

1. Henry D, Hill S. Comparing treatments. BMJ 1995;310:1279.
2. International Society of Drug Bulletins. ISDB declaration on therapeutic advance in the use of medicines. Paris: International Society of Drug Bulletins, 2001.
3. Kaplan W, Laing R. Priority medicines for Europe and the World. Geneva: World Health Organization, 2004.
4. Ray WA, Griffin MR, Avorn J. Evaluating drugs after their approval for clinical use. N Engl J Med 1993;329:2029-32.
5. The European Agency for the Evaluation of Medicinal Products. European Public Assessment Reports. 2009; Accessed in October 2009 via http://www.emea.europa.eu/htms/human/epar/eparintro.htm.
6. The European Agency for the Evaluation of Medicinal Products. Notice to applicants. Volume 2A: procedures for marketing authorisation appendix III. London: EMEA, 2004.
7. The European Agency for the Evaluation of Medicinal Products. Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96). London: EMEA, 2000.
8. Goodman and Gilman's the pharmacological basis of therapeutics. Eleventh. New York: McGraw-Hill, 2006.
9. Rawlins MD. Cutting the cost of drug development? Nat Rev Drug Discov 2004;3:360-4.
10. Ray WA, Stein CM. Reform of drug regulation--beyond an independent drug-safety board. N Engl J Med 2006;354:194-201.

Chapter 2.2

Superior efficacy of new medicines

Johan C.F. van Luijn
Frank W.J. Gribnau
Hubert G.M. Leufkens

Submitted

Abstract

Aims

To give an overview of and to discuss new authorized medicines with an improved efficacy.

Methods

Information on comparative efficacy of new medicines was obtained from the EMEA European Public Assessment Reports.

Results

Between 1999 and 2005 we identified 122 new medicines with a new active substance; for 13 (10%) medicines superiority was demonstrated.

Conclusions

A proven advantage in efficacy at an early stage of drug development is the exception rather than the rule. The absence of evidence for differences between medicines does not mean the absence of differences. Optimal pharmacotherapy would benefit from more comparative research in the development of new medicines. Results of comparative trials need a critical evaluation of their specific value to clinical practice. Prescription data may be helpful.

Introduction

The goal of developing new medicines should be an improvement in treatment: the new medicine should benefit patients when compared to previously existing options[1-4]. This added value might lie in different properties such as efficacy, safety, applicability, convenience of administration, etc., the first two of which are considered as the most important: a new, more efficacious and/or safer medicine.

Demonstrating any improvement is not an explicit condition for being granted marketing authorization. Data on quality, efficacy and safety are therefore needed in order to demonstrate a favourable benefit/risk ratio when treating a patient for the claimed therapeutic indication. For that purpose, placebo controlled trials provide robust evidence [5,6]. However, regulatory authorities also want to be sure that, for new medicines for which good alternatives are available, the possibility has been excluded that patients are treated with a product that is less efficacious or less safe [7]. Files submitted to the regulatory authorities can include studies that demonstrate efficacy by confirming the absence of a difference (equivalence trial), or by showing that the new medicine is no worse than an existing medicine (noninferiority trial). Besides this, efficacy can also be demonstrated by showing an improved efficacy compared with a medicine already used in practice for the same claimed therapeutic indication (superiority trial). It goes without saying that the results of these trials are particularly interesting as they inform us how new medicines, accurately estimated for their efficacy, contribute to an improvement in treatment for patients. Statistics on the extent of superior medicines as a result of the marketing authorization process are scarce.
The aim of this study is to give an overview of and to discuss new authorized medicines with an improved efficacy.

Methods

We did a further analysis of the data from a previous study about the availability of comparative information on new medicines at the moment of European market authorization [8]. We therefore analyzed the European Public Assessment Reports (EPARs) of the European Medicines Agency (EMEA) between 1999 and 2005 on new medicines with a new active substance [9]. Data about the trials extracted from the EPARs included therapeutic indication, objective, comparator, design, clinical endpoints, results and also the

conclusion of the Committee for Medicinal Products for Human Use (CHMP) on comparative efficacy.

Results

Between 1999 and 2005 we identified 122 new medicines with a new active substance, of which 58 (48%) had been studied in comparison with existing medicines. Of the main/pivotal active control trials (N=153), the objective of 15 (10%) was to show superiority: for 4 trials this objective failed. This was also the case for 13 noninferiority/equivalence trials, as the result was a statistically significant difference in efficacy. Superiority was demonstrated for 13 (10%) new medicines (see table 1). The medicines were considered as superior in case of a statistically significant difference in primary clinical endpoints.

Table 1 - New medicines (1999-2005) with an improved efficacy

New medicine	Indication	Comparator
Bimatoprost	Glaucoma	Timolol
Capecitabine	Colorectal cancer	5-FU/Folonic acid
Emtricitabine	HIV-infections (combination)	Stavudine
Fondaparinux	Prevention of venous thromboembolic events	Enoxaparine
Insulin aspart	Diabetes mellitus type 1	Insulin regular human
Insulin glulisine	Diabetes mellitus type 2	Insulin regular human
Lopinavir	HIV-infections (combination)	Nelfinavir
Peginterferon alfa 2a	Chronic hepatitis C	Interferon alfa 2b Interferon alfa 2a
Peginterferon alfa 2b	Chronic hepatitis C	Interferon alfa 2b
Tipranavir	HIV-infections (combination)	Protease inhibitors
Travoprost	Glaucoma	Timolol
Voriconazole	Invasive aspergillosis	Amfotericin B (conv)
Zoledronic acid	Hypercalcaemia (tumour-induced)	Pamidronate

Discussion

Ideally, claims regarding an added value of a new medicine should be based on the results of comparative trials [3,10]. In a previous study we found that nearly one out of two new medicines had been studied in a randomized active control trial [8]. Further analysis of the data on comparative efficacy shows that an improvement was demonstrated for only one out of ten new medicines. Despite this small number, the conclusion cannot simply be drawn that the advance in pharmacotherapy is restricted to these new medicines. Nevertheless, this means there is sufficient reason to adopt a critical attitude towards claims regarding an added value.

A number of observations can be made regarding this result. Firstly, our analysis excluded new medicines for which no alternative was available and for which, inevitably, a comparative trial was lacking. However, developed as the first medicinal therapy for life-threatening or serious diseases, such medicines – for example, orphan drugs - can rightfully be considered an improvement in the treatment of patients. Secondly, we only focused on differences in efficacy and not on properties such as safety, applicability or convenience of administration. The reason is that main/pivotal trials are used in particular for demonstrating efficacy. Nevertheless, new medicines whose efficacy is equivalent or noninferior may have advantages in safety. For example, tenecteplase used in the treatment of suspected myocardial infarction; based on a study in 17005 patients, although it shows equivalence compared to alteplase, the safety profile seems to be in favour of tenecteplase [11].

Another reason for the small number of innovations is that, for granting market authorization, demonstrating advantages is not an objective in itself. So there is no need or requirement to conduct a trial with such an objective. Moreover, pharmaceutical companies would be taking a substantial risk, as failure to demonstrate superiority over a less expensive existing drug could be a financial disaster. The fact that, on the other hand, a positive result could be expected to lead to substitution of the comparator, appears to carry less weight.

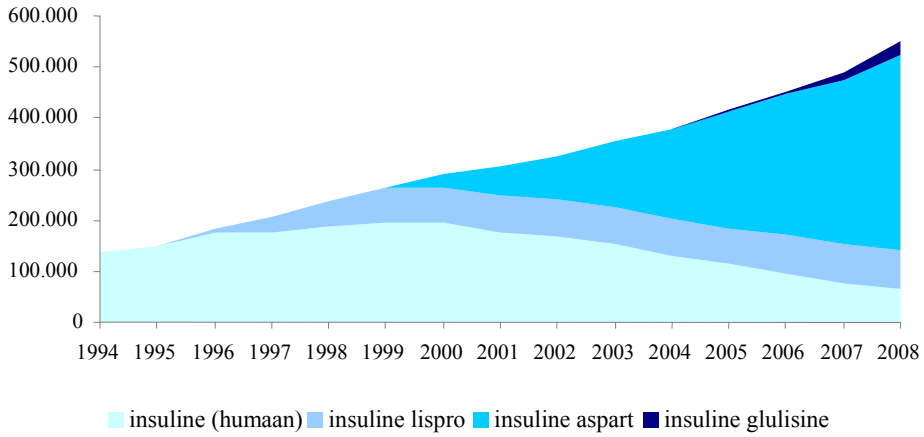
Furthermore, we should comment that whether the 13 medicines in our analysis really are an improvement in therapy depends on a sound review of all relevant properties. It is important always to weigh up the advantages and disadvantages meticulously. This also applies to the medicines in our study. According the EPAR, the efficacy of bimatoprost and travoprost is superior to timolol in the treatment of glaucoma, but their safety profile is

inferior due to a higher frequency of ocular side effects. The trial on tipranavir demonstrates a superior antiviral activity, but also a higher frequency of hepatic events and lipodystrophy. Moreover, comparative efficacy is always linked to a specific comparator, therapeutic indication and type of patients. Emtricitabine was more efficacious compared with stavudine in naive HIV-infected patients. However, its efficacy was inferior in comparison with lamivudine in the same type of patients; its efficacy was similar in a study that compared it with lamivudine in experienced patients.

Another issue in a critical evaluation of demonstrated superiority is the choice of the primary clinical endpoint. A composite endpoint was used for fondaparinux; analysis of all the endpoint events shows that the incidence of symptomatic venous thromboembolic events, including pulmonary embolism, was not significantly different between treatment groups [12,13].

Furthermore, we have to realise that drawing a conclusion of superiority based on a statistically significant difference says nothing about its practical significance. The absolute differences in change of glycated haemoglobin (HbA1c), demonstrated for insulin aspart and insulin glulisine compared to regular insulin, were, at best, of limited clinical relevance. Moreover, there was no relevant difference regarding the incidence of hypoglycaemic events. In this context it is interesting to follow developments in the prescription of fast-acting insulin in the treatment of diabetes, as the results of clinical studies may not always be reflected in practice [14,15]. For prescription data, we used the GIP database of the Health Care Insurance Board in the Netherlands. This database contains data on the prescription of extramural medicines, obtained from health insurance organisations and based on a sample of more than 12 million people. Graph 1 shows developments in the usage before and after the introduction of insulin aspart. The degree to which insulin aspart is used cannot be completely explained on the results of the premarketing trials. The more rapid onset and shorter duration of action of the insulin analogue is thought to facilitate a more flexible life style in comparison with the use of soluble human insulins [16]. However, this should also apply to insulin lispro, which can be regarded as being comparable to insulin aspart [17].

Graph 1 - Development number prescriptions of fast-acting insulins



After the introduction of insulin aspart in 1999 there was a decrease in the number of prescriptions of soluble human insulin, however the use was already decreasing since the introduction of insulin lispro in 1996. Since 2004 insulin aspart is the most prescribed fast-acting insulin. The introduction of insulin glulisine in 2005 had little impact on the number of prescriptions of the other insulins.

Finally, significant advantages as well as disadvantages of new medicines may only become evident during the course of time, on the basis of further study and experience. This means that assessing the added value of a new medicine is not a one-off incident but a continual process, supported by monitoring usage by means of prescription data.
This study shows and discusses how proven superiority, in the sense of well-demonstrated advantages in efficacy at an early stage of drug development, is the exception rather than the rule. The absence of evidence for differences between medicines does not mean the absence of differences. Insight into differences and similarities between medicines, however small they may be, is important in order to make the right choice for the right patient in clinical practice. Therefore, optimal pharmacotherapy would benefit from more comparative research in the development of new medicines. This study also shows that the results of comparative trials need a critical evaluation of their specific value to clinical practice. Prescription data may be helpful.

References

1. Dent TH, Hawke S. Too soon to market. BMJ 1997;315:1248-9.
2. Gale EA, Clark A. A drug on the market. Lancet 2000;355:61-3.
3. Henry D, Hill S. Comparing treatments. BMJ 1995;310:1279.
4. International Society of Drug Bulletins. ISDB declaration on therapeutic advance in the use of medicines. Paris: International Society of Drug Bulletins, 2001.
5. Lewis JA, Jonsson B, Kreutz G, Sampaio C, van Zwieten-Boot B. Placebo-controlled trials and the Declaration of Helsinki. Lancet 2002;359:1337-40.
6. The European Agency for the Evaluation of Medicinal Products. Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96). London: EMEA, 2000.
7. Koopmans PP, de Graeff PA, Zwieten-Boot BJ, Lekkerkerker JF, Broekmans AW. Clinical evaluation of efficacy and adverse effects in the (European) registration of drugs: what does it mean for the doctor and the patient? (in dutch). Ned Tijdschr Geneeskd 2000;144:756-61.
8. van Luijn JCF, Gribnau FW, Leufkens HG. Availability of comparative trials for the assessment of new medicines in the European Union at the moment of market authorization. Br J Clin Pharmacol 2007;63:159-62.
9. The European Agency for the Evaluation of Medicinal Products. European Public Assessment Reports. 2009; Accessed in October 2009 via http://www.emea.europa.eu/htms/human/epar/eparintro.htm.
10. Kaplan W. Comparative effectiveness of medicines and use of head-to-head comparative trials. In: Priority medicines for Europe and the world. Den Haag: Ministry of Health, Welfare and Sport, 2004:
11. Van De Werf F, Adgey J, Ardissino D, Armstrong PW, Aylward P, Barbash G, et al. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. Lancet 1999;354:716-22.
12. Heit JA. The potential role of fondaparinux as venous thromboembolism prophylaxis after total hip or knee replacement or hip fracture surgery. Arch Intern Med 2002;162:1806-8.
13. Turpie AGG, Bauer KA, Eriksson BI, Lassen MR. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. Arch Intern Med 2002;162:1833-40.
14. Heerdink ER, Urquhart J, Leufkens HG. Changes in prescribed drug doses after market introduction. Pharmacoepidemiol Drug Saf 2002;11:447-53.
15. Wathen B, Dean T. An evaluation of the impact of NICE guidance on GP prescribing. Br J Gen Pract 2004;54:103-7.
16. Raskin P, Guthrie RA, Leiter L, Riis A, Jovanovic L. Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. Diabetes Care 2000;23:583-8.
17. Plank J, Wutte A, Brunner G, Siebenhofer A, Semlitsch B, Sommer R, et al. A direct comparison of insulin aspart and insulin lispro in patients with type 1 diabetes. Diabetes Care 2002;25:2053-7.

Chapter 2.3

Postapproval trials of new medicines: widening use or deepening knowledge? Analysis of ten years of etanercept

Johan C.F. van Luijn ,
Marjan Danz,
Johannes W.J. Bijlsma,
Frank W.J. Gribnau,
Hubert G.M. Leufkens

Submitted

Abstract

Aims

To investigate the main aims of the postapproval randomized controlled trials on etanercept and the extent to which they were designed to gain more comparative information.

Methods

A search of the literature (MEDLINE, EMBASE), trial registries (Clinical Trials.gov, Controlled Trials.com) and market authorization reports (FDA , EMEA) was carried out in order to identify all RCTs. A comparison of trial data identified unpublished trials and multiple publications relating to the same study. All RCTs completed and/or published after initial market approval were regarded as postapproval.

Results

Up until 2008, we found 84 postapproval trials, 11 (13%) trials on approved extensions of indication, another 30 (36%) trials on the approved indications and 43 (51%) trials on indications not (yet) approved. After the initial approval of etanercept, 6 head-to-head trials were conducted on the approved indications. Overall, the main objectives of postapproval trials with etanercept were found to confirm efficacy and safety in new indications, and to gather additional information for optimal use on the approved indications.

Conclusion

Postapproval RCTs on etanercept focus more on studies searching for new indications than on deepening knowledge about use. Ten years after the market entry of etanercept, one of the reasonable demands of clinical practice for more comparative information , still remains unanswered.

Introduction

Marketing approval puts a significant mark on the clinical research program into the lifecycle of a new medicine. Trials are conducted to comply with the requirements of regulatory authorities by demonstrating a favorable benefit/risk ratio [1]. After marketing approval, studies are conducted to gain more in-depth knowledge about the new medicine. Studies on additional health outcomes, comparative information, long-term safety, refining dose recommendations, etc., are conducted to optimize use in clinical practice. Thus, knowledge on the benefits and risks of new medicines grows over time as a result of industry priorities, regulatory requirements and experience in clinical practice, the dynamics of reinvention, also seen in other medical technologies [2,3].

At market entry, knowledge on optimal use of the new medicine is limited, for obvious reasons, so there is a strong need of further investments in continuous – life cycle driven – knowledge gain. One of the identified knowledge gaps in positioning new medicines is the need of comparative efficacy and safety information in order to assess adequately the added therapeutic value. This was further highlighted in recent discussions in the US and elsewhere on reforming market authorization and expanding funding for comparative effectiveness research [4-6]. In a previous study we found that, in the pre-approval phase of the development of new medicines, one out of every two has been studied in comparison with another medicine for the same indication [7]. After market approval, new clinical trials could compensate for this lack of comparative information.

Etanercept is a pivotal learning case illustrating the dynamics of postapproval knowledge gain. It was the first tumor necrosis factor (TNF) inhibitor that the Food and Drug Administration (FDA) authorized, on 2nd November 1998, for the treatment of rheumatoid arthritis [8]. This introduction onto the market was discussed in an editorial to the first publication as a new and exciting – though costly – option in the treatment of these patients, and one that brought with it the urgency of more studies, such as comparisons with infliximab, another TNF-inhibitor available at that time, and (combinations of) the traditional disease-modifying antirheumatic drugs (DMARDs) [9]. A recent review of all DMARDs, inclusive the TNF-inhibitors, shows that even after more than a decade after marketing-approval, limited comparative evidence is available to support one therapy above another [10]. This raises questions on the dynamics, gaps and priorities in clinical follow-up research of etanercept after its introduction into clinical practice. The aim of this case study is to investigate the main objectives of postapproval randomized controlled trials on

etanercept and the extent to which they were designed to gain more comparative information.

Methods

Postapproval randomized controlled trials

Based on the marketing approval process, trials can be classified as pre- or postapproval trials, depending on whether they are conducted before or after the initial moment a new medicine is allowed onto the market. As initial approval by the Food and Drug Administration (FDA) and by the European Medicines Agency (EMEA) differ with respect to both date and parts of the indication, we chose the most widely approved initial indication, namely the EU market authorization on 2nd February 2000. We considered RCTs completed and/or published after that date as postapproval trials.

Data search and selection

In order to identify RCTs on etanercept, we consulted different sources of information, as there is no single public database on all clinical research. Publications, though very informative, are not representative of all the studies conducted, as some studies remain unpublished and some have multiple publications about different study results (multiple output).

Using a systematic literature search in the MEDLINE and EMBASE databases, clinical studies were identified using “fc fusion protein”, “etanercept” and “random”, with the limitation to RCTs written in English and published before 1st January 2009. To identify unpublished trials a search was carried out in two clinical trial registries [11,12]. All trials involving etanercept were selected if the study had been completed on 1st January 2009. In addition to this, all main/pivotal trials on etanercept were selected from the public reports/reviews by the EMEA and FDA [8,13].

The selection of RCTs involving etanercept, published and unpublished, and according to their main objectives, was carried out independently by two researchers (JvL, MD). Differing selection results were discussed and solved by consensus. All trial information was reviewed on items such as type of study and objectives. Excluded were all non-randomized studies, reviews, studies involving healthy subjects and studies that did not focus on investigating the effect of etanercept. Open label extension studies of RCTs were excluded as they are regarded as a form of observational study [14,15]. Separate

publications on interim results, secondary end-points and/or subgroups of patients were regarded as multiple output of the same study and analyzed as a single study.
To determine publication status, characteristics of the trials in the registries were compared with the publications found in the literature search. Finally, the company was asked about the publication status of the unpublished trials we found.

Table 1 - Characteristics approved therapeutic indications etanercept

Target disease	Severity Disease	Target patient population	Application	Line treatment
Active rheumatoid arthtritis	Moderate to severe	Adults	Mono Combination	First[1]
Active juvenile idiopathic arthritis	Moderate to severe	Children ≥ 2 yr[2]	Mono	First[3]
Psoriatic arthrits	Not specified	Adults	Mono Combination[4]	First[3]
Active ankylosing spondylitis	Not specified[5]	Adults	Mono	First[3]
Plaque psoriasis	Moderate to severe	Adults Children ≥ 8 yr[6]	Mono	First[3]

[1] First line only for severe and progressive rheumatoid arthritis (EMEA)
[2] Children aged 4 - 17 years (EMEA)
[3] Second line treatment (EMEA)
[4] Combination with methrotrexaat not labelled (EMEA)
[5] Severe ankylosing spondylitis (EMEA)
[6] Only adult patients, 18 years or older (FDA)

Data analysis
Two outlines were distinguished for the main objectives of postapproval RCTs: trials directed at to confirm efficacy and safety in new indications, and trials that gather additional information on the medicine's safety, efficacy, or optimal use for the approved indications. Therefore, at a certain moment in time, all postapproval trials were classified

into three categories: (1) efficacy/safety studies on approved extensions of the indication; (2) other trials on approved indications; (3) trials on indications not (yet) approved. As reference for the approved indications, we selected the indications most widely approved by the FDA and EMEA on 1st January 2009. Table 1 contains a summary of the main characteristics of a combination of the indications approved at that moment. For studies of comparative information on etanercept we selected the active control trials in which etanercept was compared directly with another medicine, the so-called head-to-head trials.

Results

Up until 2008, 93 RCTs have been conducted on etanercept. Figure 1 depicts a flow chart of the studies selected from all publications and trial registries. We found 84 postapproval trials, 11 (13%) trials on approved extensions of indication, another 30 (36%) trials on approved indications and 43 (51%) trials on indications not (yet) approved. Table 2 provides an overview of characteristics of the various types of RCTs.
Etanercept's initial market authorization was for the treatment of active rheumatoid arthritis where the response to DMARDs had been inadequate, and the treatment of active polyarticular juvenile chronic arthritis. Approval was based on 5 studies, one still unpublished [16-19]. Furthermore, at that time four studies were published on indications not yet approved [20-23].

After initial approval, trials on rheumatoid arthritis were subsequently submitted to the regulatory authorities for extensions of the indications, such as, for example, use in early rheumatoid arthritis and in combination with methotrexate, based on the interim results [24-26] of research that has now been completed [27,28]. Following rheumatoid arthritis, various postapproval trials were conducted to extend the approved indications to include psoriatic arthritis (in 2002) [29,30], ankylosing spondylitis (in 2003) [31-33] and plaque psoriasis (in 2004) [34-37]. In all cases FDA authorization preceded that of the EMEA, with the exception of pediatric plaque psoriasis. Moreover, exploratory studies were being conducted searching for new therapeutic applications, particularly new target diseases [38-66], but also in new applications such as intra-articular application [67] and combination therapy for psoriasis [68]. These trials on indications that have not (yet) been approved (table 2) differ from other postapproval trials. Patient numbers are much smaller (mean 41 patients), and in some cases (44% of studies) the trials were funded by independent sponsors.

Figure 1 – Flow chart selection randomized controlled trials on etanercept from publications and trial registries

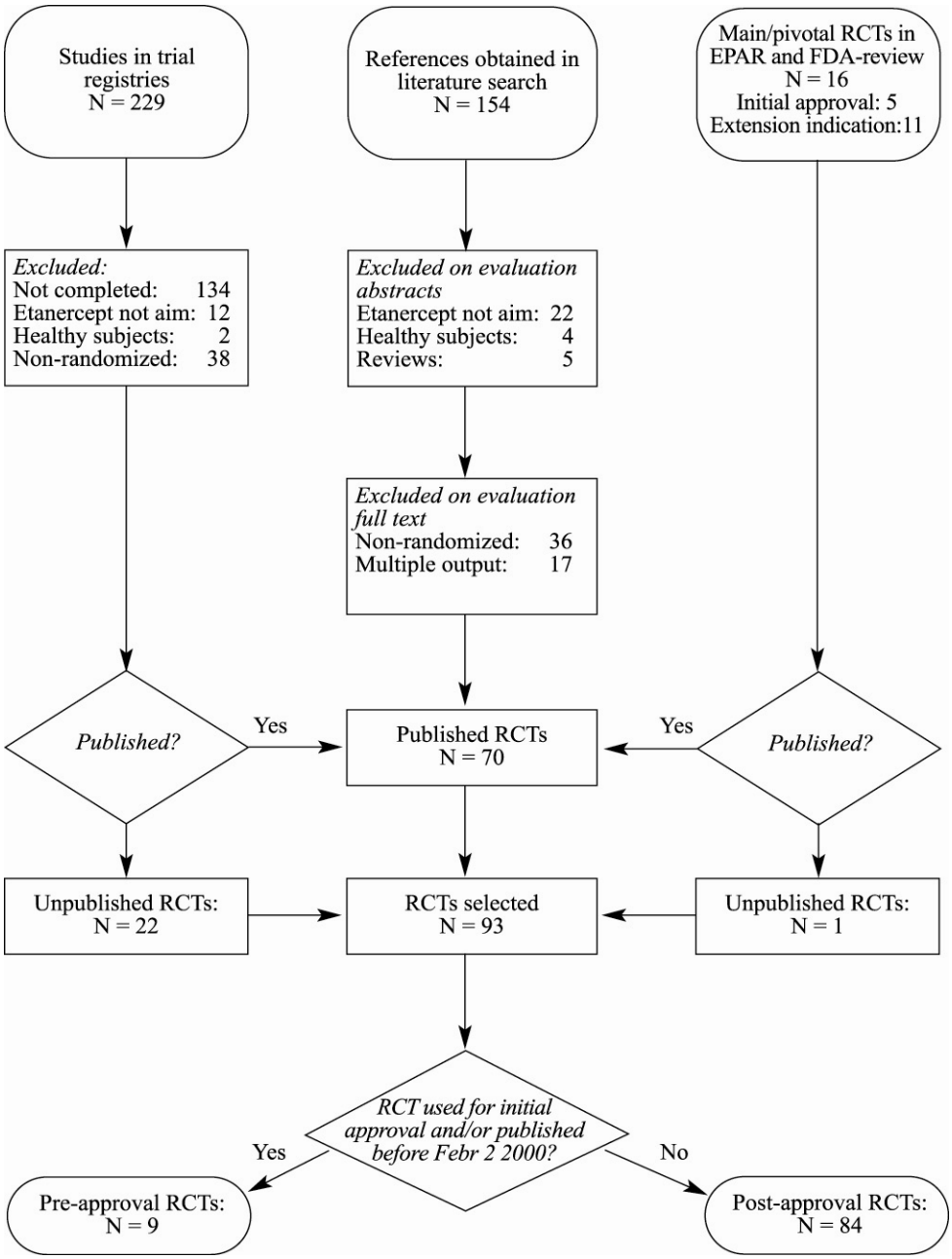


Table 2 - Post-approval randomized controlled trials etanercept 2000 – 2008

	Approved indications[1]		Not (yet) approved indications[2]	Total
	Pivotal RCTs	Other RCTs		
	N = 11 (13%)	N = 30 (36%)	N = 43 (51%)	N = 84
Comparative information				
Head-to-head trial	2 (18%)	4 (13%)	5 (12%)	11 (13%)
No direct comparison	9 (82%)	26 (87%)	38 (88%)	73 (87%)
Number patients				
< 100	3 (27%)	9 (30%)	39 (91%)	51 (61%)
100 – 250	3 (27%)	8 (27%)	4 (9%)	15 (18%)
> 250	5 (46%)	13 (43%)	0	18 (21%)
Mean number patients	315	341	41	
Duration trial				
< 12 wks	3 (27%)	12 (40%)	21 (49%)	36 (43%)
12 – 52 wks	7 (64%)	16 (50%)	21 (49%)	43 (51%)
> 52 wks	1 (9%)	3 (10%)	1 (2%)	5 (6%)
Mean number weeks	32	22	19	
Funding trials				
Industry	10 (91%)	23 (89%)	14 (34%)	47 (60%)
Government/independent	0	1 (4%)	18 (44%)	19 (24%)
Both	1 (9%)	2 (8%)	9 (22%)	12 (16%)
Unknown		4	2	6

[1] rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis

[2] alcoholic hepatitis, astma, autoimmune inner ear disease, Behcet's disease, cachexia, adjuvans chronic hepatitis C, Crohn's disease, diabetes mellitus, early inflammatoire arthritis, giant cell arteritis, heart failure, pulmonary fibrosis, keloids, low back pain, metaboloc syndrome, palmoplantar pustulosis, pemphigus vulgaris, postmenopausal osteoporosis, psoriasis combinationtherapy, heel enthesitis, Sjogren's syndrome, synovitis, temporomandibular disorder, uveitis, Wegener's granulomatosis

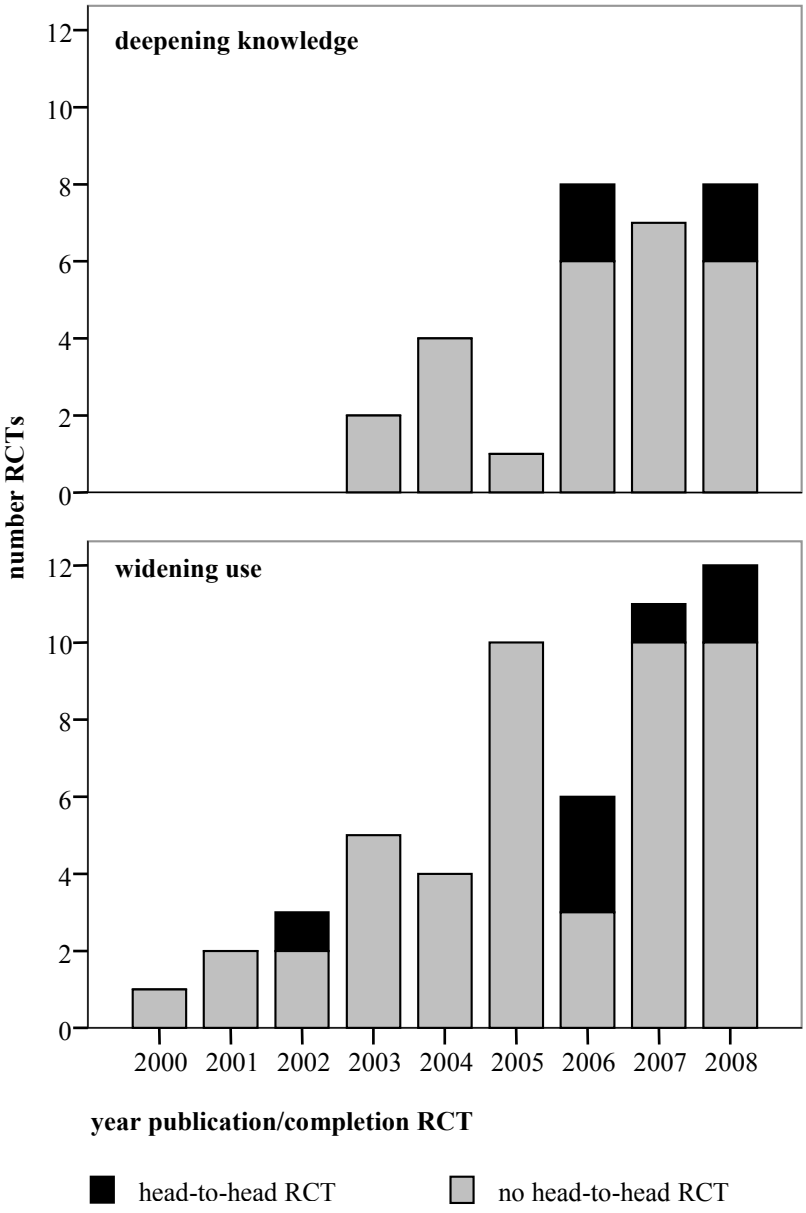
After the initial approval of etanercept, 11 (13%) head-to-head trials were conducted, six of which involved approved indications - rheumatoid arthritis (5) and ankylosing spondylitis (1) - and indications (5) not (yet) approved. In studies on the approved indications, etanercept was compared with methotrexate [27,28], sulphasalazine[69] (one unpublished), infliximab [70] and a combination of DMARDs (unpublished).

Discussion

In this analysis of ten years of etanercept, we found that nearly two-thirds of the postapproval trials focused on new applications. With respect to the comparative information on etanercept, we found 6 head-to-head trials involving the approved indication. The comparative study with infliximab was too small to draw firm conclusions and the results of a comparison with a combination of traditional DMARDs are still unknown. This demonstrates that one of the clinically relevant demands on comparative information around and after market entry is still unanswered.
The conclusion can be drawn that postapproval RCTs on etanercept prioritized more on studies searching for new indications than on deepening (comparative) knowledge about optimal use on approved indications, especially during the first years after introduction. This difference is illustrated by the two main objectives, based on the number of trials during the period 2000-2008 (figure 2).

An important explanation for this priority in clinical research is formed by etanercept itself. Due to its pharmacological properties, searching for new therapeutic indications is a realistic and promising option. Etanercept is a competitive inhibitor of tumour necrosis factor (TNF)-binding to its cell surface receptors, which results in inhibition of the biological activity of TNF. TNF is a dominant cytokine in inflammatory processes. This means that etanercept could potentially be used for all diseases in which this cytokine plays a role, such as autoimmune diseases [71,72]. Widening the use of etanercept as soon as possible within the period of patent protection is therefore commercially attractive. However, the pharmaceutical industry was not the only initiator of these studies. Nearly half of the studies on indications not yet approved were initiated and funded by independent sponsors. Though these were often small pilot studies, this illustrates the need to improve the pharmacotherapy of other diseases, especially those with insufficient possibilities for treating patients adequately. Moreover, new indications also present a scientifically more exciting challenge for clinical researchers than studies on existing indications.

Figure 2. Main objectives postapproval RCTs on etanercept 2000-2008



Our analysis is a case study of etanercept, a medicine for which the market authorization conditions have been adjusted regularly on the basis of new postapproval studies. This makes it an illustrating example for other immunomodulators. This type of medicine has led to a significant change during recent years in the diffusion of new medicines into clinical practice. It has led to the regulatory model gradually evolving from a one-off marketing authorization to a life cycle approach [2]. The development of medicines is a continuous and dynamic process in which new knowledge has consequences for the conditions of marketing authorization. Extensions in indications as well as new safety information, lead to a continuous evaluation of the benefit/risk profile. This analysis of how etanercept evolved over time is a clear example of the needed development of continuous evaluation of new and existing medicines in terms of new applications, safety profile, improving optimal use, building comparative evidence and ensuring benefit/risk throughout the whole life cycle of medicinal products.

If the results of specific trials are considered as crucial for the optimal use of a new medicine, then more initiatives are required to stimulate orphaned comparative postapproval research. The comment made in the EPAR when etanercept was registered, that "unfortunately no comparative research had been carried out with other medicines", should not remain a mere statement. Based on the recommendations in the guidelines of rheumatologists, comparative trials of etanercept with DMARDs alone or in combination are still relevant [73,74]. The results of a recent study comparing intensive methotrexate treatment with conventional treatment in early rheumatoid arthritis, raises the question of a new comparison of etanercept with this tight control treatment [75,76]. The question is whether such comparative studies will still be conducted throughout the years after introduction. Scientific interest will decrease, as it will in clinical practice, because of the lack of head-to-head trials; implicitly and explicitly an assessment has already been made based on experience or indirect comparisons. Applied to TNF-inhibitors, adjusted indirect comparisons show that they have a similar efficacy in the treatment of patients with rheumatoid arthritis [77,78]. However, the strength of this evidence is lower than that of a randomized active control trial [79,80].

Two measures may be important if this situation is to improve: clear postapproval commitments and more independent clinical research. Firstly, registration authorities and the industry should make postapproval commitments to conduct special studies. However, so far the completion of such studies has proven not to be very successful [81]. More than half of the postapproval studies agreed with the FDA have not yet been started or are

behind schedule [82]. In order to exert pressure on those undertaking these studies, we propose that any uncertainties surrounding a new medicine that are solved by postapproval studies should be communicated more clearly in a separate section of the label information and package leaflet. More label information about the lack of knowledge about a new medicine will enable prescribers to take such limitations into account and the pharmaceutical industry will be stimulated to fill this gap.

Obviously, the fact that clinical research is very expensive also plays a role. We found that the companies Amgen and Wyeth were involved as a sponsor in 76% of all postapproval studies of etanercept, and in 60% as sole sponsor; only one postapproval study on the approved indications was funded through non-industry sources. Sponsoring and prioritizing research objectives go hand-in-hand and this could mean that scientifically and clinically relevant questions remain unanswered [83]. Therefore, once on the market, other stakeholders should also have an obligation to stimulate the optimal use of new medicines. This might in the first place involve the well-organized international scientific platforms of health care professionals, e.g., the European League against Rheumatism (EULAR) or the American College of Rheumatology (ACR). However, more initiatives are needed in order to initiate and fund postapproval studies. Good examples are US proposals on expanding the federal role in funding comparative effectiveness research, and independent medicinal research by the Italian Medicines Agency [84,85]. International cooperation between funders and reimbursement authorities could also facilitate studies that deepen our knowledge of new medicines with a reduced dependency on the pharmaceutical industry with its commercial interests.

A possible objection to our study set-up is that we distinguished between postapproval studies that widen the use of a new medicine and those that deepen our knowledge of that new medicine. This classification does not mean they are mutually exclusive. Efficacy and safety studies can also play an important additional role in gaining more in-depth knowledge about the new medicine. The TEMPO trial was important not only for approving the combination therapy with methotrexate, but also for demonstrating inhibition in the progression of structural joint damage by the combination [25,86]. Furthermore, the results of a number of premarketing trials on an indication that is not (yet) approved led to important warnings and precautions relating to the use of etanercept, for example its combined use with anakinra [87] and the use of etanercept in patients with congestive heart failure [20]. Furthermore, the multiple output of trials has also supplied important

additional data, such as the effect of etanercept on quality of life and on the consequences of vaccinating patients [26,88-95].

An important limitation of our study is the restriction to RCTs. We chose this type of research as it is the gold standard for evaluating therapeutic interventions. This is also the optimal design for comparative information on medicines as both medicines are studied under the same conditions. Nevertheless, research data provided via observational studies, especially when based on disease registries, also plays an important role in the postapproval phase, by revealing sound data on the benefit/risk balance when using a medicinal product in daily clinical practice [96].

Our research shows that differences exist between the FDA and the EMEA in the indications for which etanercept may be prescribed, in spite of the fact that the same studies were used for the assessment (table 1). For the EMEA, in many cases treatment with etanercept can be used when the response to previous conventional therapy has been inadequate, whilst the FDA sees a role in primary care treatment. In our analysis, we opted for the widest indication, without actually expressing a value judgment about the restrictions applied by the EMEA. We are intrigued by this difference between the FDA and the EMEA: an issue that warrants further study stimulating cross-system learning.

In conclusion, developing medicines is a continuous and dynamic process, in which marketing approval puts a significant mark on the clinical research program. Nevertheless, this is not the end, but rather the beginning of deepening and broadening our knowledge of the medicine involved. This case study on etanercept shows that postapproval RCTs on etanercept focused more on studies searching for new indications than on deepening knowledge about the optimal use in indications already approved, especially during the first years after introduction. Of course, there should be no competition between the two, as patients may benefit from both methods of investing in the life cycle of a new medicine. However, ten years after the market entry of etanercept, one of the reasonable demands of clinical practice, i.e., for more comparative information, still remains unanswered. New initiatives are needed to improve comparative effectiveness information. Clear commitments on postapproval studies, exploring new models for encouraging the industry to invest more in comparative information and increasing independent funding of comparative effectiveness research, should all be considered in order to fuel the life cycle of a medicine, new and old, with research addressing those questions that concern prescribers and patients most.

References

1. U.S.Food and Drug Administration. ICH-E8 General Considerations for Clinical Trials. Federal Register 1997;62:66113-9.
2. Eichler HG, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. Nat Rev Drug Discov 2008;7:818-26.
3. Shih C, Berliner E. Diffusion of new technology and payment policies: coronary stents. Health Aff (Millwood) 2008;27:1566-76.
4. Avorn J. Debate about funding comparative-effectiveness research. N Engl J Med 2009;360:1927-9.
5. Ray WA, Stein CM. Reform of drug regulation--beyond an independent drug-safety board. N Engl J Med 2006;354:194-201.
6. Wilensky GR. Developing a center for comparative effectiveness information. Health Aff (Millwood) 2006;25:w572-85.
7. van Luijn JC, Gribnau FW, Leufkens HG. Availability of comparative trials for the assessment of new medicines in the European Union at the moment of market authorization. Br J Clin Pharmacol 2007;63:159-62.
8. U.S.Food and Drug Administration. Drug details Enbrel. Accessed in January 2009 via www.accessdata.fda.gov/scripts/cder/drugsatfda/.
9. O'Dell JR. Anticytokine therapy--a new era in the treatment of rheumatoid arthritis? N Engl J Med 1999;340:310-2.
10. Donahue KE, Gartlehner G, Jonas DE, Lux LJ, Thieda P, Jonas BL, et al. Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. Ann Intern Med 2008;148:124-34.
11. Current Controlled Trials. ISRCTN Register. 2009; Accessed in January 2009 via www.controlled-trials.com.
12. US National Institute of Health. ClinicalTrials.gov. 2009; Accessed in January 2009 via www.ClinicalTrials.gov.
13. The European Medicines Agency. European Public Assessment Report Enbrel. 2009; Accessed in January 2009 via http://www.emea.europa.eu/humandocs/Humans/EPAR/enbrel/enbrel.htm.
14. Taylor GJ, Wainwright P. Open label extension studies: research or marketing? BMJ 2005;331:572-4.
15. Wainwright P. Consent to open label extension studies: some ethical issues. J Med Ethics 2002;28:373-6.
16. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med 2000;342:763-9.
17. Moreland LW, Baumgartner SW, Schiff MH, Tindall EA, Fleischmann RM, Weaver AL, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N Engl J Med 1997;337:141-7.
18. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med 1999;130:478-86.
19. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999;340:253-9.

20. Deswal A, Bozkurt B, Seta Y, Parilti-Eiswirth S, Hayes FA, Blosch C, et al. Safety and efficacy of a soluble P75 tumor necrosis factor receptor (Enbrel, etanercept) in patients with advanced heart failure. Circulation 1999;99:3224-6.
21. Du Bois JS, Trehu EG, Mier JW, Shapiro L, Epstein M, Klempner M, et al. Randomized placebo-controlled clinical trial of high-dose interleukin-2 in combination with a soluble p75 tumor necrosis factor receptor immunoglobulin G chimera in patients with advanced melanoma and renal cell carcinoma. J Clin Oncol 1997;15:1052-62.
22. Fisher CJJ, Agosti JM, Opal SM, Lowry SF, Balk RA, Sadoff JC, et al. Treatment of septic shock with the tumor necrosis factor receptor:Fc fusion protein. The Soluble TNF Receptor Sepsis Study Group. N Engl J Med 1996;334:1697-702.
23. Novak EJ, Blosch CM, Perkins JD, Davis CL, Barr D, McVicar JP, et al. Recombinant human tumor necrosis factor receptor Fc fusion protein therapy in kidney transplant recipients undergoing OKT3 induction therapy. Transplantation 1998;66:1732-5.
24. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000;343:1586-93.
25. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363:675-81.
26. van der Heijde D, Klareskog L, Singh A, Tornero J, Melo-Gomes J, Codreanu C, et al. Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. Ann Rheum Dis 2006;65:328-34.
27. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum 2002;46:1443-50.
28. van der Heijde D, Klareskog L, Landewe R, Bruyn GAW, Cantagrel A, Durez P, et al. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. Arthritis Rheum 2007;56:3928-39.
29. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet 2000;356:385-90.
30. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. Arthritis Rheum 2004;50:2264-72.
31. Calin A, Dijkmans BAC, Emery P, Hakala M, Kalden J, Leirisalo-Repo M, et al. Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis. Ann Rheum Dis 2004;63:1594-600.
32. Davis JCJ, van der Heijde D, Braun J, Dougados M, Cush J, Clegg DO, et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis Rheum 2003;48:3230-6.
33. Gorman JD, Sack KE, Davis JCJ. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. N Engl J Med 2002;346:1349-56.
34. Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, et al. A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol 2003;139:1627-32.
35. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, et al. Etanercept as monotherapy in patients with psoriasis. N Engl J Med 2003;349:2014-22.
36. Paller AS, Siegfried EC, Langley RG, Gottlieb AB, Pariser D, Landells I, et al. Etanercept treatment for children and adolescents with plaque psoriasis. N Engl J Med 2008;358:241-51.

37. Papp KA, Tyring S, Lahfa M, Prinz J, Griffiths CEM, Nakanishi AM, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol 2005;152:1304-12.
38. Etanercept plus standard therapy for Wegener's granulomatosis.
N Engl J Med 2005;352:351-61.
39. Baughman RP, Lower EE, Bradley DA, Raymond LA, Kaufman A. Etanercept for refractory ocular sarcoidosis: results of a double-blind randomized trial. Chest 2005;128:1062-47.
40. Berman B, Patel JK, Perez OA, Viera MH, Amini S, Block S, et al. Evaluating the tolerability and efficacy of etanercept compared to triamcinolone acetonide for the intralesional treatment of keloids. J Drugs Dermatol 2008;7:757-61.
41. Bernstein LE, Berry J, Kim S, Canavan B, Grinspoon SK. Effects of etanercept in patients with the metabolic syndrome. Arch Intern Med 2006;166:902-8.
42. Berry MA, Hargadon B, Shelley M, Parker D, Shaw DE, Green RH, et al. Evidence of a role of tumor necrosis factor alpha in refractory asthma. N Engl J Med 2006;354:697-708.
43. Bissonnette R, Poulin Y, Bolduc C, Maari C, Provost N, Syrotuik J, et al. Etanercept in the treatment of palmoplantar pustulosis. J Drugs Dermatol 2008;7:940-6.
44. Boetticher NC, Peine CJ, Kwo P, Abrams GA, Patel T, Aqel B, et al. A randomized, double-blinded, placebo-controlled multicenter trial of etanercept in the treatment of alcoholic hepatitis. Gastroenterology 2008;135:1953-60.
45. Bozkurt B, Torre-Amione G, Warren MS, Whitmore J, Soran OZ, Feldman AM, et al. Results of targeted anti-tumor necrosis factor therapy with etanercept (ENBREL) in patients with advanced heart failure. Circulation 2001;103:1044-7.
46. Charatcharoenwitthaya N, Khosla S, Atkinson EJ, McCready LK, Riggs BL. Effect of blockade of TNF-alpha and interleukin-1 action on bone resorption in early postmenopausal women. J Bone Miner Res 2007;22:724-9.
47. Cohen S, Shoup A, Weisman MH, Harris J. Etanercept treatment for autoimmune inner ear disease: results of a pilot placebo-controlled study. Otol Neurotol 2005;26:903-7.
48. Cohen SP, Wenzell D, Hurley RW, Kurihara C, Buckenmaier CC, Griffith S, et al. A double-blind, placebo-controlled, dose-response pilot study evaluating intradiscal etanercept in patients with chronic discogenic low back pain or lumbosacral radiculopathy. Anesthesiology 2007;107:99-105.
49. Dominguez H, Storgaard H, Rask-Madsen C, Steffen Hermann T, Ihlemann N, Baunbjerg Nielsen D, et al. Metabolic and vascular effects of tumor necrosis factor-alpha blockade with etanercept in obese patients with type 2 diabetes. J Vasc Res 2005;42:517-25.
50. Foster CS, Tufail F, Waheed NK, Chu D, Miserocchi E, Baltatzis S, et al. Efficacy of etanercept in preventing relapse of uveitis controlled by methotrexate. Arch Ophthalmol 2003;121:437-40.
51. Jatoi A, Dakhil SR, Nguyen PL, Sloan JA, Kugler JW, Rowland KMJ, et al. A placebo-controlled double blind trial of etanercept for the cancer anorexia/weight loss syndrome: results from N00C1 from the North Central Cancer Treatment Group.
Cancer 2007;110:1396-403.
52. Marcora SM, Chester KR, Mittal G, Lemmey AB, Maddison PJ. Randomized phase 2 trial of anti-tumor necrosis factor therapy for cachexia in patients with early rheumatoid arthritis. Am J Clin Nutr 2006;84:1463-72.
53. Martinez-Abundis E, Reynoso-von Drateln C, Hernandez-Salazar E, Gonzalez-Ortiz M. Effect of etanercept on insulin secretion and insulin sensitivity in a randomized trial with psoriatic patients at risk for developing type 2 diabetes mellitus. Arch Dermatol Res 2007;299:461-5.

54. Martinez-Taboada VM, Rodriguez-Valverde V, Carreno L, Lopez-Longo J, Figueroa M, Belzunegui J, et al. A double-blind placebo controlled trial of etanercept in patients with giant cell arteritis and corticosteroid side effects. Ann Rheum Dis 2008;67:625-30.
55. Melikoglu M, Fresko I, Mat C, Ozyazgan Y, Gogus F, Yurdakul S, et al. Short-term trial of etanercept in Behcet's disease: a double blind, placebo controlled study. J Rheumatol 2005;32:98-105.
56. Monk JP, Phillips G, Waite R, Kuhn J, Schaaf LJ, Otterson GA, et al. Assessment of tumor necrosis factor alpha blockade as an intervention to improve tolerability of dose-intensive chemotherapy in cancer patients. J Clin Oncol 2006;24:1852-9.
57. Morjaria JB, Chauhan AJ, Babu KS, Polosa R, Davies DE, Holgate ST. The role of a soluble TNFalpha receptor fusion protein (etanercept) in corticosteroid refractory asthma: a double blind, randomised, placebo controlled trial. Thorax 2008;63:584-91.
58. Raghu G, Brown KK, Costabel U, Cottin V, du Bois RM, Lasky JA, et al. Treatment of Idiopathic Pulmonary Fibrosis With Etanercept: An Exploratory, Placebo-Controlled Trial. Am J Respir Crit Care Med 2008;178:948-55.
59. Rouhani FN, Meitin CA, Kaler M, Miskinis-Hilligoss D, Stylianou M, Levine SJ. Effect of tumor necrosis factor antagonism on allergen-mediated asthmatic airway inflammation. Respir Med 2005;99:1175-82.
60. Sandborn WJ, Hanauer SB, Katz S, Safdi M, Wolf DG, Baerg RD, et al. Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. Gastroenterology 2001;121:1088-94.
61. Sankar V, Brennan MT, Kok MR, Leakan RA, Smith JA, Manny J, et al. Etanercept in Sjogren's syndrome: a twelve-week randomized, double-blind, placebo-controlled pilot clinical trial. Arthritis Rheum 2004;50:2240-5.
62. Schwarz EM, Campbell D, Totterman S, Boyd A, O'Keefe RJ, Looney RJ. Use of volumetric computerized tomography as a primary outcome measure to evaluate drug efficacy in the prevention of peri-prosthetic osteolysis: a 1-year clinical pilot of etanercept vs. placebo. J Orthop Res 2003;21:1049-55.
63. Sha BE, Valdez H, Gelman RS, Landay AL, Agosti J, Mitsuyasu R, et al. Effect of etanercept (Enbrel) on interleukin 6, tumor necrosis factor alpha, and markers of immune activation in HIV-infected subjects receiving interleukin 2. AIDS Res Hum Retroviruses 2002;18:661-5.
64. Smith JA, Thompson DJS, Whitcup SM, Suhler E, Clarke G, Smith S, et al. A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. Arthritis Rheum 2005;53:18-23.
65. Torre-Amione G, Wallace CK, Young JB, Koerner MM, Thohan V, McRee S, et al. The effect of etanercept on cardiac transplant recipients: a study of TNFalpha antagonism and cardiac allograft hypertrophy. Transplantation 2007;84:480-3.
66. Zein NN. Etanercept as an adjuvant to interferon and ribavirin in treatment-naive patients with chronic hepatitis C virus infection: a phase 2 randomized, double-blind, placebo-controlled study. J Hepatol 2005;42:315-22.
67. Bliddal H, Terslev L, Qvistgaard E, Konig M, Holm CC, Rogind H, et al. A randomized, controlled study of a single intra-articular injection of etanercept or glucocorticosteroids in patients with rheumatoid arthritis. Scand J Rheumatol 2006;35:341-5.
68. Gisondi P, Del Giglio M, Cotena C, Girolomoni G. Combining etanercept and acitretin in the therapy of chronic plaque psoriasis: a 24-week, randomized, controlled, investigator-blinded pilot trial. Br J Dermatol 2008;158:1345-9.
69. Combe B, Codreanu C, Fiocco U, Gaubitz M, Geusens PP, Kvien TK, et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. Ann Rheum Dis 2006;65:1357-62.

70. De Filippis L, Caliri A, Anghelone S, Scibilia G, Lo Gullo R, Bagnato G. Improving outcomes in tumour necrosis factor a treatment: comparison of the efficacy of the tumour necrosis factor a blocking agents etanercept and infliximab in patients with active rheumatoid arthritis. Panminerva Med 2006;48:129-35.
71. Furst DE, Keystone EC, Kirkham B, Kavanaugh A, Fleischmann R, Mease P, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2008. Ann Rheum Dis 2008;67 Suppl 3:iii2-25.
72. Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. Pharmacol Ther 2008;117:244-79.
73. Furst DE, Breedveld FC, Kalden JR, Smolen JS, Burmester GR, Bijlsma JWJ, et al. Updated consensus statement on biological agents, specifically tumour necrosis factor alpha (TNFalpha) blocking agents and interleukin-1 receptor antagonist (IL-1ra), for the treatment of rheumatic diseases, 2005. Ann Rheum Dis 2005;64 Suppl 4:iv2-14.
74. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008;59:762-84.
75. Bijlsma JWJ, Weinblatt ME. Optimal use of methotrexate: the advantages of tight control. Ann Rheum Dis 2007;66:1409-10.
76. Verstappen SMM, Jacobs JWG, van der Veen MJ, Heurkens AHM, Schenk Y, ter Borg EJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis 2007;66:1443-9.
77. Hochberg MC, Tracy JK, Hawkins-Holt M, Flores RH. Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis 2003;62 Suppl 2:ii13-ii16.
78. Nixon R, Bansback N, Brennan A. The efficacy of inhibiting tumour necrosis factor alpha and interleukin 1 in patients with rheumatoid arthritis: a meta-analysis and adjusted indirect comparisons. Rheumatology (Oxford) 2007;46:1140-7.
79. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997;50:683-91.
80. Gartlehner G, Moore CG. Direct versus indirect comparisons: a summary of the evidence. Int J Technol Assess Health Care 2008;24:170-7.
81. Meyer RJ. Regulatory considerations for determining postmarketing study commitments. Clin Pharmacol Ther 2007;82:228-30.
82. Avorn J. Paying for drug approvals--who's using whom? N Engl J Med 2007;356:1697-700.
83. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ 2003;326:1167-70.
84. Congressional Budget Office. Research on the comparative effectiveness of medical treatments: issues and options for an expanded federal role. 2007; Accessed in May 2009 via http://www.cbo.gov/ftpdocs/88xx/doc8891/12-18-ComparativeEffectiveness.pdf.
85. Agenzia Italiana del Farmaco. Independent research on drugs funded by the Italian Medicines Agency. Rome: AIFA, 2007.
86. van der Heijde D, Landewe R, Klareskog L, Rodriguez-Valverde V, Settas L, Pedersen R, et al. Presentation and analysis of data on radiographic outcome in clinical trials: experience from the TEMPO study. Arthritis Rheum 2005;52:49-60.

87. Genovese MC, Cohen S, Moreland L, Lium D, Robbins S, Newmark R, et al. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. Arthritis Rheum 2004;50:1412-9.
88. Braun J, McHugh N, Singh A, Wajdula JS, Sato R. Improvement in patient-reported outcomes for patients with ankylosing spondylitis treated with etanercept 50 mg once-weekly and 25 mg twice-weekly. Rheumatology (Oxford) 2007;46:999-1004.
89. Feldman SR, Kimball AB, Krueger GG, Woolley JM, Lalla D, Jahreis A. Etanercept improves the health-related quality of life of patients with psoriasis: results of a phase III randomized clinical trial. J Am Acad Dermatol 2005;53:887-9.
90. Gelfand JM, Kimball AB, Mostow EN, Chiou CF, Patel V, Xia HA, et al. Patient-reported outcomes and health-care resource utilization in patients with psoriasis treated with etanercept: continuous versus interrupted treatment. Value Health 2008;11:400-7.
91. Kosinski M, Kujawski SC, Martin R, Wanke LA, Buatti MC, Ware JEJ, et al. Health-related quality of life in early rheumatoid arthritis: impact of disease and treatment response. Am J Manag Care 2002;8:231-40.
92. Krueger GG, Langley RG, Finlay AY, Griffiths CEM, Woolley JM, Lalla D, et al. Patient-reported outcomes of psoriasis improvement with etanercept therapy: results of a randomized phase III trial. Br J Dermatol 2005;153:1192-9.
93. Mathias SD, Colwell HH, Miller DP, Moreland LW, Buatti M, Wanke L. Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo. Clin Ther 2000;22:128-39.
94. Mease PJ, Ritchlin CT, Martin RW, Gottlieb AB, Baumgartner SW, Burge DJ, et al. Pneumococcal vaccine response in psoriatic arthritis patients during treatment with etanercept. J Rheumatol 2004;31:1356-61.
95. van Riel PLCM, Freundlich B, MacPeek D, Pedersen R, Foehl JR, Singh A. Patient-reported health outcomes in a trial of etanercept monotherapy versus combination therapy with etanercept and methotrexate for rheumatoid arthritis: the ADORE trial. Ann Rheum Dis 2008;67:1104-10.
96. Vandenbroucke JP. Observational research, randomised trials, and two views of medical science. PLoS Med 2008;5:e67.

Chapter 3

Quality of comparative information on new medicines

Chapter 3.1

Choice of comparator in active control trials of new medicines

Johan C.F. van Luijn,
Arie C. van Loenen,
Frank W.J. Gribnau,
Hubert G.M. Leufkens

Published: Ann Pharmacother 2008;42:1605-12

Abstract

Aims

To evaluate the choice of comparator in premarketing randomized active control trials (RaCTs) in comparison with recommendations for standard treatment.

Methods

New medicines are selected that were authorized for the European Union market between 1999 and 2005. Information on active comparators in RaCTs was extracted from the European Public Assessment Reports (EPAR), and information on recommendations regarding standard treatments from the annual editions of the Dutch reference book on pharmacotherapy. Data on prescribing and indications at the moment of authorization and 3 years before authorization were included. The comparator was considered to be in line with the standard treatment if there was a similarity in both active substance or therapeutic class and the dosage.

Results

For 58 new medications identified, treatment in the active control group was in line with the recommended standard treatment in 108 of 153 (71%) RaCTs at the moment of the drug's authorization; 47 (81%) of the new medicines had been compared with the recommended standard treatment in at least one trial. When dissimilarities occurred, none of the comparators had been recommended as standard treatment 3 years earlier (the supposed moment of defining the protocol of the trials)

Conclusion

Most comparators in the premarketing RaCTs of new medicines were in line with the recommended standard treatment at the moment of marketing authorization. In view of this similarity, most of these trials are also fit for postmarketing decision-making on prescribing and on inclusion in clinical guidelines and reimbursement systems.

Introduction

Randomized controlled trials are conducted with the objective of demonstrating the efficacy and safety of a new medicinal product in order to obtain marketing authorization. These trials are placebo controlled and/or active controlled. If the benefit/risk ratio is favourable, the new product is allowed to enter the market. Following authorization, other properties of the new medicine are subjected to debate, such as its added therapeutic value and cost-effectiveness. These parameters are necessary for decisions on prescribing and on inclusion in clinical guidelines and reimbursement systems [1-5]. Crucial for these assessments are direct comparisons (head-to-head trials) of the new medicine with other treatment options for the same indication, by preference the drug of first choice, the so-called standard treatment. In a previous study we found that about half of the new medicines were studied in a randomized active control trial (RaCT) before entering the market [6]. In the present study, we focused on the choice of comparator in the available RaCTs, because trials with the most suitable comparator as the active control group could be an important source of comparative information.

Regulatory authorities recommend that investigators adhere as closely as possible to the available standard treatment when choosing the active control group [7]. However, for internationally conducted studies, this is not simple, as recommendations on medicines of first choice vary depending on preferences on both a national and a local level, which are affected by differences in healthcare structure, medical practice and culture [8,9]. In addition, standard treatment can vary over time, because there are frequent signals for updating systematic reviews that are directly relevant to clinical practice [10]. As a consequence, clinical guidelines have to be revised regularly. What was considered the best choice of comparator at the start of a trial may, at the moment of market authorization, prove to be no longer the most suitable choice. Little is known about differences between the chosen comparators in clinical trials and recommendations on standard treatment.

The aim of this study was to evaluate the choice of comparator in premarketing randomized active control trials in comparison with recommendations on standard treatment.

Methods

Comparators in premarketing active control trials

We selected premarketing RaCTs that investigated new medicinal products with a new active substance that were authorized via the centralized procedures of the European Commission during the period 1999-2005. Diagnostics and vaccines were excluded. We used the European Public Assessment Reports (EPAR) of these new medicines for information on premarketing RaCTs [11]. These reports provide an overview of clinical trials that applicants have submitted to the European Medicines Agency for market approval and summarize the scientific discussion in the Committee for Medicinal Products for Human Use (CHMP).

All studies that were labeled in the EPAR as main/pivotal studies with an active control were included. Information about the date of marketing authorization was extracted from the EPAR and information on the therapeutic indication, the comparator, the name of the active substance and the dosage was obtained from each RaCT.

Recommendations on standard treatment

We searched for information about national recommendations on prescribing, including the standard treatment for all relevant indication(s), at 2 different moments: in the year of market authorization of a new medicine and three years earlier, the supposed moment of setting up the protocol for the RaCT. This meant that we required data sources of these national recommendations that are regularly updated (preferably annually). As case source of information we selected the Dutch reference book on pharmacotherapy, entitled the "Farmacotherapeutisch Kompas" (box) [12].

From the annual editions of the book, we extracted the different standard treatments for the therapeutic indications of all new medicines included in the study. All comparators in the RaCTs were classified into 1 of 4 categories on the basis of the recommendations regarding their place in therapy: (1) standard treatment; (2) alternative for the standard treatment if insufficiently effective; (3) limited use in special situations; and (4) prescription not recommended. The clinical point of view formed the basis for selecting recommended standard treatments; this means a preference based on therapeutic classification, as the drug of choice within a category is often chosen on the basis of experience or for economic reasons. To assess similarity, the dosage of the comparator used in the study was compared with the authorized maintenance dosage. The comparator in the RaCT was considered to be in line with recommended standard treatment if the 2 medicines were similar in both active substance or therapeutic class and the dosage.

Box. - Description of *Farmacotherapeutisch Kompas*

"*Farmacotherapeutisch Kompas*" is a reference book for medical practice and training in The Netherlands. It is published by the Health Care Insurance Board under the directions of the Committee on Pharmaceutical Aid.
This book is a guide providing practical information and recommendations on the prescription of medicines, and describing the treatment of all relevant therapeutic indications and medicines that are available. The basic principle is to recommend the pharmacotherapy that is optimal from a medical point of view and most economical for patients and insurance organizations.
The book is edited by an independent committee of experts with members from a variety of backgrounds, including physicians, pharmacists, and health economists, as well as advisers from different clinical specialialties. It was first published in 1982 and subsequently on an annual basis. Every edition is revised on the basis of new international peer-reviewed publications, new medicines, new information on product characteristics, and specific guidelines of Dutch healthcare professionals. The book is issued free of charge to all prescribers, pharmacists and medical and pharmacy students.
Since 2003 the content of the book is also published on the internet (http://www.fk.cvz.nl). As the same committee is also involved in assessing the reimbursement of new medicines, the recommendations on standard treatment in this book are also used in assessing the reimbursement of new medicines.

Results

We identified a total of 153 RaCTs for 58 new medicines used as main/pivotal trial in the Europian Union (EU) marketing authorization process between 1999 and 2005. The new medicines were intended for the treatment of 45 different therapeutic indications (appendix).
Table 1 shows the similarities between the active comparators and standard treatment.
At the moment of market authorization, in 108 (71%) RaCTs the active control group was the same as the recommended standard treatment; 47 (81%) of the new medicines were compared with the recommended standard treatment in at least one trial. In 45 (29%) trials there were dissimilarities; however, none of the comparators in these trials had been recommended as standard treatment three years earlier.
Compared with the situation 3 years prior to market authorization, the standard treatment had changed in 4 indications (HIV-infections, rheumatoid arthritis, urge incontinence, adjunctive treatment for glaucoma). In 6 trials, a different comparator should have been used based on the recommendations 3 years earlier; however, this had not be done. With respect to trials with a comparator not in line with the recommended standard treatment, we

could not find a relationship with a specific therapeutic indication or a trend over the years. The overview of the comparators (appendix) also illustrates that, for all indications, another choice for the most suitable comparator had been possible.

Table 1 - Similarity of comparators in randomized active control trials of new medicines to current standard treatment at two moments

Therapeutical characteristics comparator	**Supposed moment designing trial: T0 minus 3 yr**	**Moment of market authorization: T0**
	N = 153	N =153
Similar with standard treatment	102 (67%)	108 (71%)
Alternative for standard treatment	27 (18%)	19 (12%)
Limited use	8 (5%)	8 (5%)
Prescription not recommended	0 (0%)	1 (1%)
Different dosage	8 (5%)	8 (5%)
Off-label use	5 (3%)	5 (3%)
Not on market	3 (2%)	4 (3%)

Most of the comparators that were not classified as standard treatment, had a different place in therapy, for example, alternative treatment if standard treatment is insufficiently effective (e.g., aromatase inhibitors in breast cancer), or limited use (e.g., second- and third-generation cephalosporins in serious infections). Some comparators had no place at all, as their use was not recommended (third-generation oral contraceptives for young, first-time users), but also because their use was off-label (e.g., triptorelin in preventing premature

ovulation) or the medicine was not marketed in The Netherlands (e.g., trovafloxacin was withdrawn for safety reasons). For 5 comparators in 8 trials, the dosage differed from the authorized dosage. For example, in the EU, unlike in the US, lower dosages of diclofenac and naproxen are preferred for the treatment of osteoarthritis, rheumatoid arthritis and primary dysmenorrhoea.

Discussion

When a RaCT is conducted, there is a preference that the drug of first choice be used in the control group. Results of the our study show that in 71% of RaCTs, the active control group was receiving the recommended standard treatment and 81% of the new agents were compared with the recommended standard treatment in at least one trial. Our results imply that investigators are compliant with the regulatory authorities recommendation to adhere as closely as possible to the standard treatment when choosing comparators. Attempts to bridge the gap between the approval process and clinical practice are proving to be effective. Most of the selected standard treatments were in line with international insights in pharmacotherapy, which are used in designing premarketing trials intended for drug approval. An explanation for this could be the way the recommendations in the selected reference book on pharmacotherapy are realized, based on a regularly updated, comprehensive and critical evaluation of peer-reviewed international literature and (inter)national guidelines.

Our study did not confirm the assumption that the time-lag between the moment of selection of the comparator and actual market entry has a sizeable impact on differences between comparator and recommended standard treatment, as the consequence of a better standard treatment having been found in the interim. It may be that, in designing trials, pharmaceutical companies anticipate new insights into treatment options in good time, but there are also arguments that lead to the conclusion that guidelines are conservative in including new developments.

The question now is what impact these results will have on postmarketing decision-making with regard to prescribing and reimbursement. The choice of comparator is only one aspect (albeit an important one) of trial design that is relevant for decision-making. Other aspects of clinical trials, such as the patients included, the endpoints, sample size and the duration of the study, may also be important in considering whether the results are relevant to

clinical decision-making. Head-to-head trials are necessary in order to compare medicines directly. However, the inclusion of an active control does not always mean that a direct comparison has been made. In some trials the control group is an active treatment and the investigated drug is added to this treatment; this was the case in the studies of enfuvirtide (2), trastuzumab (1) and bevacizumab (1). In trials of rasagiline (1) and aripiprazole (2), an active control was included for the validation of comparison with the placebo group. When we exclude these active controls (4 standard treatments, 3 alternative treatments) from our analysis, most of the RaCTs are, in view of the similarity of the comparator with the recommended standard treatment, still fit for decision-making on prescribing and reimbursement.

Restricting ourselves to the use of only one national reference book on pharmacotherapy for the analysis of international studies could be regarded as a weakness of this study. We recommend using the data from this study to carry out the same analysis in other countries using their own national recommendations on standard treatment. Similarities but also, undoubtedly, differences will be revealed according to national characteristics with regard to drug therapy. An obvious example will be the position of antibacterial agents. In international comparative studies, the Netherlands has been shown to be amongst the lowest users of antibiotics and especially of cephalosporins [13,14]. This is the result of the policy to minimize the risk of developing antibiotic (cross-)resistance by avoiding unnecessary over-prescription and limiting the use of some antibacterial agents to the treatment of serious infections. Limited use is recommended for half of the antibacterial agents used in the trials in this study.
Another important limitation inherent to our study is the use of standard treatment. Just as clinical practice does not always adhere to clinical guidelines, neither is a comparison with standard treatment the only option for decisions on prescribing and reimbursement [15-17]. In spite of a dissimilarity with the recommended standard treatment, the chosen comparator could be relevant for decisions on prescribing and reimbursement. Comparison with the most frequently prescribed drug or the one most likely to be substituted, as recommended in some pharmacoeconomical guidelines, could be more informative [18]. For this reason, some trials in this analysis, with a comparator assessed as an alternative for the standard treatment, can certainly be regarded as useful in post-marketing decisions. For example, for the treatment of diabetes mellitus type 2, there was a preference for sulphonylureas and, within this class, for tolbutamide. However, in practice, metformin is the most commonly used medicine [19]. Acetaminophen is considered to be the initial drug of choice for pain management in the treatment of osteoarthritis; however, in clinical practice nonsteroidal

antiinflammatory drugs (NSAIDs) are often prescribed, as many patients have already used this over-the-counter agent and NSAIDs seem to be more effective in treatment of moderate-to-severe pain [20]. For clinical practice it is interesting to know how brinzolamide compares not only with timolol (the standard treatment for glaucoma), but also with dorzolamide, the first medicine in the same class of carbonic anhydrase-inhibitors. These examples demonstrate that the post-marketing decision-making process should involve not only recommended standard treatments, no matter how theoretically well-founded these are, but also data on patterns of drug usage.

This study confirms the results of earlier studies about the importance of choosing the right dose of the active comparator [21]. The suboptimal dose of glibenclamide has influenced the decision of regulatory authorities to initially reject the use of glitazones as monotherapy. Firm conclusions about the gastrointestinal safety of valdecoxib cannot be drawn using the highest recommended dose of diclofenac and naproxen, knowing that to prevent adverse events, it is important to prescribe the lowest possible effective dose. In this case, data on the prescribed dose from clinical practice could be helpful in determining the dose of the comparator. A substantial minority of medicines are known to undergo substantial changes at the prescribed dose, relative to initially recommended dosages [22]. The examples of diclofenac and naproxen also illustrate the problem of the differences in recommendations made by registration authorities in the US and in the EU. Where these differences exist, different dosage regimens in premarketing trials are in the interest of an effective discussion on comparative efficacy and safety. A good example can be seen from the active control trials conducted on fondaparinux, of which 2 were not in line with the recommended dosage. In addition, trials were conducted with a twice-daily dose of enoxaparin, which is authorized in the EU; 2 other trials used a once-daily dose, which is approved in North America.

In conclusion, most comparators in the premarketing RaCTs of new medicines as presented to European regulatory authorities are in line with the recommended standard treatment at the moment of marketing authorization. In view of this similarity, most of these trials are also fit for postmarketing decision-making on prescribing and on inclusion in clinical guidelines and reimbursement systems. In case of dissimilarities, none of the comparators had been recommended as standard treatment 3 years earlier, the supposed moment of setting up the protocol for the trial. Moreover, this study may stimulate more analyses on the choice of comparators, which will be carried out using other national reference books on pharmacotherapy.

References

1. Dent TH, Hawke S. Too soon to market. BMJ 1997;315:1248-9.
2. Henry D, Hill S. Comparing treatments. BMJ 1995;310:1279.
3. International Society of Drug Bulletins. ISDB declaration on therapeutic advance in the use of medicines. Paris: International Society of Drug Bulletins, 2001.
4. Kaplan W. Comparative effectiveness of medicines and use of head-to-head comparative trials. In: Priority medicines for Europe and the world. Den Haag: Ministry of Health, Welfare and Sport, 2004:
5. Pearson SD, Rawlins MD. Quality, innovation, and value for money: NICE and the British National Health Service. JAMA 2005;294:2618-22.
6. van Luijn JCF, Gribnau FW, Leufkens HG. Availability of comparative trials for the assessment of new medicines in the European Union at the moment of market authorization. Br J Clin Pharmacol 2007;63:159-62.
7. The European Agency for the Evaluation of Medicinal Products. Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96). London: EMEA, 2000.
8. Sturm HB, van Gilst WH, Veeger N, Haaijer-Ruskamp FM. Prescribing for chronic heart failure in Europe: does the country make the difference? A European survey. Pharmacoepidemiol Drug Saf 2007;16:96-103.
9. Veninga CC, Lundborg CS, Lagerlov P, Hummers-Pradier E, Denig P, Haaijer-Ruskamp FM. Treatment of uncomplicated urinary tract infections: exploring differences in adherence to guidelines between three European countries. Drug Education Project Group. Ann Pharmacother 2000;34:19-26.
10. Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, Moher D. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med 2007;147:224-33.
11. The European Agency for the Evaluation of Medicinal Products. European Public Assessment Reports. 2009; Accessed in October 2009 via http://www.emea.europa.eu/htms/human/epar/eparintro.htm.
12. College voor Zorgverzekeringen. Farmacotherapeutisch Kompas. 1996-2005. Diemen: Health Care Insurance Board, 2005.
13. Cars O, Molstad S, Melander A. Variation in antibiotic use in the European Union. Lancet 2001;357:1851-3.
14. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 2005;365:579-87.
15. Stolk P, Van Wijk BLG, Leufkens HGM, Heerdink ER. Between-country variation in the utilization of antihypertensive agents: Guidelines and clinical practice. J Hum Hypertens 2006;20:917-22.
16. Turnbull F. Managing cardiovascular risk factors: the gap between evidence and practice. PLoS Med 2005;2:e131.
17. Wathen B, Dean T. An evaluation of the impact of NICE guidance on GP prescribing. Br J Gen Pract 2004;54:103-7.
18. Hjelmgren J, Berggren F, Andersson F. Health economic guidelines--similarities, differences and some implications. Value Health 2001;4:225-50.
19. Langendam MW, Hooijkaas C, Piepenbrink JF. Toenemend gebruik van geneesmiddelen voor diabetes mellitus in Nederland, 1998-2003. Ned Tijdschr Geneeskd 2006;150:1396-401.
20. Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev 2006;CD004257.
21. Hugenholtz GWK, Heerdink ER, Stolker JJ, Meijer WEE, Egberts ACG, Nolen WA. Haloperidol dose when used as active comparator in randomised controlled trials with atypical

antipsychotics in schizophrenia: comparison with officially recommended doses. J Clin Psychiatry 2006;67:897-903.
22. Heerdink ER, Urquhart J, Leufkens HG. Changes in prescribed drug doses after market introduction. Pharmacoepidemiol Drug Saf 2002;11:447-53.

Appendix - Overview comparators in main RaCTs of new medicines, 1999 – 2005

Therapeutic indication	New medicine	MA Year	RaCT n	Active control group	Place in therapy
acute hyperuricaemia (chemo induced)	rasburicase	2001	1	allopurinol 3.3 mg/kg tid	standard treatment
acute gynaecological infections	ertapenem	2002	1	*piperacillin 3 g/ tazobactam 375 mg iv qid*	limited use, serious infections
acute sinusitis	telithromycin	2001	1	*amoxicillin 500 mg / clavulanate 125 mg tid 10d*	limited use, serious infections
anaemia chronic renal failure	darbepoetin alfa	2001	1	epoetin alfa 50 U/kg iv biw	standard treatment
			3	epoetin alfa 50 U/kg iv tiw	standard treatment
	epoetin delta	2002	1	epoetin alfa 50 U/kg iv tiw	standard treatment
breast cancer	fulvestrant	2004	2	*anastrozole 1 mg od*	alternative for tamoxifen
	trastuzumab	2000	1	anthracycline/cyclophospha-mide or paclitaxel	standard treatment
chronic bronchitis (acute exacerbation)	telithromycin	2001	1	*amoxicillin 500 mg /clavulanate 125 mg ttd 10d*	limited use, serious infections
			1	*cefuroxim axetil 500 mg bid 10d*	limited use, serious infections

Therapeutic indication	New medicine	MA Year	RaCT n	Active control group	Place in therapy
chronic hepatitis C	interferon alfacon-1	1999	1	interferon alfa 2b 3MU sc tiw	standard treatment
	peginterferon alfa-2a	2002	3	interferon alfa 2a 3MIU/6MIU sc tiw	standard treatment
			1	interferon alfa 2b 3MIU sc tiw + ribavirin	standard treatment
	peginterferon alfa-2b	2000	1	interferon alfa 2b 3MIU sc tiw	standard treatment
chronic stable angina pectoris	ivabradine	2005	1	atenolol 100 mg od	standard treatment
			1	*amlodipine 10 mg od*	alternative for betablocker/ nitrates
colorectal cancer	capecitabine	2001	2	5-fluorouracil/folinic acid iv (Mayo regimen)	standard treatment
	bevacizumab	2005	1	*irinotecan* + 5-fluoroura-cil/folinic acid bolus iv	alternative for oxaliplatin
community-acquired pneumonia	ertapenem	2002	1	*ceftriaxone 1 g iv od*	limited use, serious infections
	telithromycin	2001	1	amoxicillin 1000 mg ttd 10d;	standard treatment
			1	clarithromycin 500 mg bid 10d	standard treatment
			1	*trovafloxacin 200 mg od 7-10d*	not marketed
compl urinary tract infections	ertapenem	2002	1	*ceftriaxone 1 g iv od*	limited use, serious infections

Therapeutic indication	New medicine	MA Year	RaCT n	Active control group	Place in therapy
delay imminent pre-term birth	atosiban	2000	1	ritodrine max 0.35 mg/min iv	standard treatment
			1	*salbutamol max 45 µg/min iv*	off label use
			1	*terbutaline max 25 µg/min iv*	off label use
diabetes mellitus type 1	insulin aspart	1999	2	regular insulin 30 min ac + basal bolus regimen	standard treatment
	insulin detemir	2004	5	NPH insulin od/bid + basal bolus regimen	standard treatment
	insulin glargine	2000	5	NPH insulin od/bid + regular insulin ac	standard treatment
	insulin glulisine	2004	2	insulin lispro 0-15 min ac + basal regimen	standard treatment
diabetes mellitus type 2	insulin aspart	1999	1	regular insulin 30 min ac + basal bolus regimen	standard treatment
	insulin detemir	2004	3	NPH insulin od/bid + basal bolus regimen	standard treatment
	insulin glargine	2000	5	NPH insulin od/bid + regular insulin ac	standard treatment
	insulin glulisine	2004	1	regular insulin 30-45 min ac + basal bolus regimen	standard treatment
	nateglinide	2001	1	*glibenclamide 10 mg od*	alternative for tolbutamide
			1	*metformin 500 mg tid*	alternative for tolbutamide
			1	*troglitazone 600 mg*	not marketed
	pioglitazone	2000	1	*glibenclamide 2.5 – 5 mg od*	different recommended dosage

Therapeutic indication	New medicine	MA Year	RaCT n	Active control group	Place in therapy
diabetes mellitus type 2 (continued)	rosiglitazone	2000	1	*glibenclamide 2.5 – 15 mg od*	alternative for tolbutamide
female contraception	norelgestromin (comb)	2002	1	*ethinylestradiol/desogestrel (monophasic)*	recommended not to prescribe
			1	*ethinylestradiol/levonor-gestrel (triphasic)*	alternative for monophasic contraceptive
glaucoma (mono/adjunctive)	bimatoprost	2002	2	timolol 0.5% bid	standard treatment
			1	latanoprost 0,005 qd + timolol	standard treatment
	brinzolamide	2000	2	timolol 0,5% bid	standard treatment
			1	*dorzolamide 2% tid*	alternative for betablocker
			1	dorzolamide 2% bid + timolol	standard treatment
	travoprost	2001	2	timolol 0.5% bid	standard treatment
			1	latanoprost 0.005% bid + timolol	standard treatment
glioblastoma multiforme	temozolomide	1999	1	procarbazine starting dose 125 or 150 mg/m2/day	standard treatment

Therapeutic indication	New medicine	MA Year	RaCT n	Active control group	Place in therapy
HIV-1 infections	abacavir	1999	1	indinavir 800mg tid + 2NRTIs	standard treatment
	amprenavir	2000	1	indinavir 800 mg tid + 2NRTIs	standard treatment
	atazanavir	2004	1	ritonavir 400mg + 2NRTIs;	standard treatment
			2	lopinavir/ritonavir + 2NRTIs	standard treatment
	efavirenz	1999	1	indinavir 800mg tid + 2NRTIs	standard treatment
	emtricitabine	2003	2	lamivudine 150mg bid + NRTI + NNRTI/PI	standard treatment
			1	stavudine 30/40mg bid + NRTI +NNRTI	standard treatment
	enfuvirtide	2003	2	individualised optimal background therapy	standard treatment
	fosamprenavir	2004	1	nelfinavir 1250mg bid + 2NRTIs	standard treatment
			1	lopinavir/ritonavir 400/100mg bid + 2 NRTIs	standard treatment
	lopinavir (comb)	2001	1	PI (investigator selected) + NNRTI + 2NRTIs	standard treatment
			1	nelfinavir 750mg tid + 2NRTIs	standard treatment
	tipranavir	2005	2	PI (genotype defined) + ritonavir/ background regimen	standard treatment
hypercalcaemia (tumour induced)	zoledronic acid	2001	2	pamidronate 90mg od iv	standard treatment

Therapeutic indication	New medicine	MA Year	RaCT n	Active control group	Place in therapy
hyperphospha-temie	sevelamer	2000	1	calcium acetate starting dose 667 mg – 2 g tid	standard treatment
infertility an/oligo-ovulatory	choriogonado-tropin alfa	2001	1	gonadotropin chorionicum 5000IU sc	standard treatment
insomnia	zaleplon	1999	1	*zolpidem 5 mg an*	alternative for short-acting benzodiaze-pines
			2	*zolpidem 10 mg an*	alternative for short-acting benzodiaze-pines
intra abdominal infections	ertapenem	2002	1	*piperacillin 3 g/tazobactam 375 mg iv qid*	limited use, serious infections
invasive aspergillosis	voriconazole	2002	1	amfotericin B deoxycholate 1-2 mg/kg iv	standard treatment
iron overload thalassemia major	deferiprone	1999	1	deferoxamine	standard treatment
nausea/vomiting (chemo induced)	palonosetron	2005	2	ondansetron 32 mg i.v.	standard treatment
			1	*dolasetron 100 mg i.v.*	not marketed
non-Hodgkin's lymphoma	ibritumomab tiuxetan	2004	1	*rituximab 375 mg/m2 iv qiw*	alternative for combination chemotherapy
oesophageal candidiasis	voriconazole	2002	1	fluconazole 200 – 400mg	standard treatment

Therapeutic indication	New medicine	MA Year	RaCT n	Active control group	Place in therapy
osteoarthritis	valdecoxib	2003	1	*diclofenac sr 75 mg bid*	alternative for acetamino-phen
			2	*naproxen 500 mg bid*	alternative for acetamino-phen
Parkinson's disease (adjunctive)	rasagiline	2005	1	*entacapone 200mg* + levodopa	alternative for dopamine-agonist
percutaneous coronary intervention	bivalirudin	2004	1	heparin (unfract) 60-70mg/kg iv bolus + GPIIb/IIIa inh	standard treatment
postoperative pain	parecoxib	2002	1	*keterolac 15mg iv*, morphine 4mg iv	not marketed/ standard treatment
			3	*keterolac 30mg iv*, morphine 4mg iv	not marketed/ standard treatment
			1	*keterolac 60mg iv*	not marketed
			1	*keterolac 15 mg iv,* valdecoxib 20mg o, ibuprofen 400mg o, tramadol 100mg o.	not marketed/ standard treatment
prevention premature ovulation	cetrorelix	1999	1	buserelin 0.15 mg i.n. 4 td	standard treatment
			1	*triptorelin depot 3.75 mg im*	off label use

Therapeutic indication	New medicine	MA Year	RaCTn	Active control group	Place in therapy
prevention premature ovulation (cont)	ganirelix	2000	1	buserelin 0.15 4td i.n. 26d	standard treatment
			1	*leuprolide 0.1 mg/day 21d*	off label use
			1	*triptorelin 0.1 mg sc od 14d*	off label use
prevention thromboembolic events	fondaparinux	2002	2	enoxaparin 40 mg od 5-9d	standard treatment
			2	*enoxaparin 30 mg bid 5-9d*	different recommended dosage
primary dysmenorrhoe	valdecoxib	2003	2	*naproxen sodium 550 mg bid 3d*	different recommended dosage
prophylaxis renal rejection	sirolimus	2001	1	azathioprine 2-3 mg/kg/d + cyclosporin/corticosteroid	standard treatment
reduction duration neutropenia	pegfilgrastim	2002	2	filgrastim 5 mg/kg/day sc	standard treatment
rheumatoid arthritis	leflunomide	1999	2	methotrexate 7.5-15 mg/weekly	standard treatment
			1	sulfasalazine 2 g/day	standard treatment
	valdecoxib	2003	2	*naproxen 500 mg bid*	different recommended dosage
			1	*diclofenac sr 75 mg bid*	different recommended dosage

Therapeutic indication	New medicine	MA Year	RaCT n	Active control group	Place in therapy
schizophrenia	aripiprazole	2004	3	haloperidol 10 mg/day	standard treatment
			1	*risperidone 6 mg*	alternative for haloperidol
seasonal allergic conjunctivitis	emedastine	1999	2	levocabastine 0.05% bid	standard treatment
	olopatadine	2002	1	levocabastine 0.05% bid	standard treatment
			1	*cromolyn sodium 2% qid*	alternative for antihistamines
skin/skin structure infections	ertapenem	2002	1	*piperacillin 3 g/tazobactam 375 mg iv qid*	limited use, serious infections
superovulation prior to IVF	choriogonadotropin alfa	2001	3	uHCG 10000IU im; uHCG 5000IU sc/im	standard treatment
suspected myocardial infarction	tenecteplase	2001	1	alteplase <=100mg iv + acetylsalicylic acid/heparin	standard treatment
tonsilitis/ pharyngitis	telithromycin	2001	1	phenoxymethylpenicillin V 500 mg ttd 10d	standard treatment
			1	clarithromycin 250 mg bid 10d	standard treatment
urge incontinence	darifenacin	2004	1	tolterodine 2 mg bid	standard treatment

cursive: comparator not in line with recommended standard treatment in "Farmacotherapeutisch Kompas"

RaCT: randomized active control trial

Information based on the European Public Assessment Reports of the new medicines.

Chapter 3.2

More transparency needed on additional information about comparators in noninferiority and equivalence trials on new medicines

Johan C.F. van Luijn

Submitted

Abstract

In an open letter to the regulatory authorities problems are discussed in interpreting the existing public data on noninferiority and equivalence trials. The purpose is to make a joint effort to improve premarketing comparative research.
In a previous study European Public Assessment Reports of new medicines marketed in the EU between 1999–2005 were analyzed for the availability of premarketing randomized active control trials. A further analysis was conducted on the noninferiority and equivalence trials.

The conclusion is that crucial additional information on the comparator used in these studies of new medicines is insufficiently reported in public sources of information to be able to verify the conclusions on (comparative) efficacy. Additional information on previous superiority trials of the comparator is needed for choosing the margin and establishing the constancy assumption.

The question is whether strict methodological requirements on the design and conduct of noninferiority and equivalence trials can be met in a case of an optimal choice of comparator based on therapeutic reasons. This highlights the need of more insight into reflections of the regulatory authorities on making decisions regarding efficacy based on these trials. If previous superiority studies on the comparator are not particularly useful for establishing assay sensibility, a superiority trial should be required for demonstrating the (comparative) efficacy of the new medicine.

Dear colleagues,

We share a common interest: the assessment of medicines. However, our interests focus on different moments in the life cycle of a new medicine. Whilst you are involved in marketing authorization, we set about determining the place of a medicine once it has appeared on the market, with a view to providing reimbursement and information on prescribing. Once your task has pretty much come to an end, we take over the baton, thereby making grateful use of the public assessment reports and the knowledge of the studies on which you based your decisions on market authorization. This material, together with the publications of premarketing trials, forms the point of departure for our assessment process, whereby our interest goes out in particular to information about comparisons of the new medicine with existing products: pivotal randomized active control trials (RaCTs).

Premarketing RaCTs have clearly become increasingly useful for this subsequent stretch of the road. In particular it is a question of availability and quality. You prefer placebo controlled trials as the most reliable evidence of efficacy of new medicines, but you recognise and agree that in some circumstances active control trials are necessary or desirable without sacrificing the reliability of the conclusions with respect to efficacy [1-3]. Placebo-controlled trials that are designed to show a reduction in irreversible harm are unacceptable if good alternatives are available and acceptable. You regard comparative information as desirable for certain new medicines for which good alternatives are available, in order to avoid the possibility that patients are treated with a product that is less efficacious or less safe. A good example are the new antihypertensives, for which, according to your guidelines, “controlled trials with reference therapy should be performed, aiming at demonstration of (at least) a similar efficacy/safety ratio of the drug under investigation in comparison to an acknowledged standard antihypertensive agent in the same and other therapeutic classes” [4]. Furthermore, premarketing comparative trials are often in line with your recommendations to adhere as closely as possible to the standard treatment when choosing the active control group [5].

In addition to your efforts to facilitate the decision-making process after market authorization, we see a potential for enlarging the usefulness of these premarketing RaCTs for our activities, on condition that the information on these studies is improved. Especially, we would emphasise, information on comparative studies the aim of which is to prove that the new product is equal to (equivalence trial) or at least not worse than (noninferiority trial) an existing product. The purpose of this letter is to draw your attention to problems we

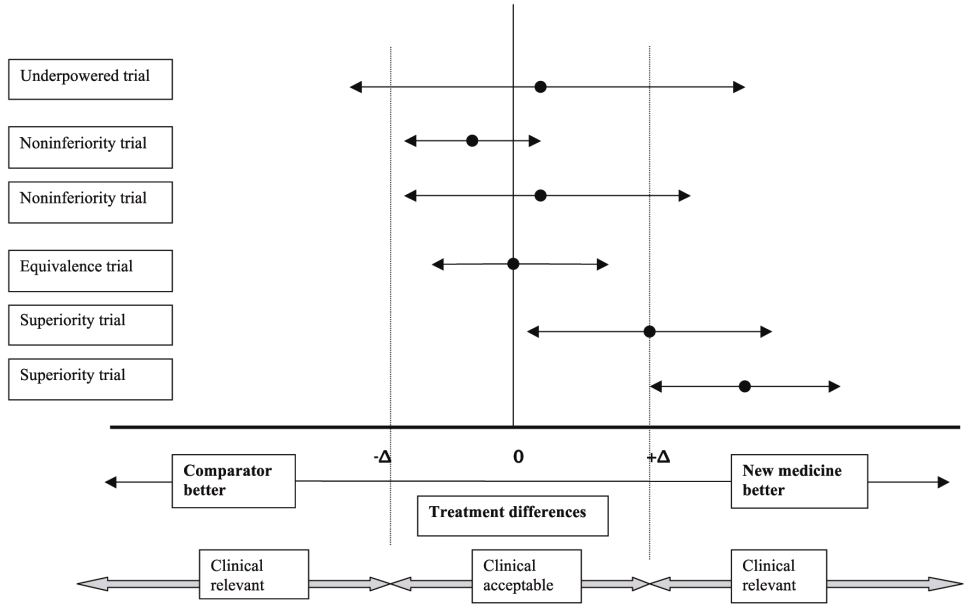
experienced in interpreting the existing public data on these studies with the purpose of making a joint effort to improve premarketing comparative research.

General conditions for noninferiority and equivalence trials

Noninferiority trials and equivalence trials present particular difficulties in design, conduct, analysis and interpretation. Therefore technical guidelines were drawn up for dealing with these problems properly and to ensure fairness of comparison [6,7]. The results of noninferiority trials and equivalence trials can only be accepted as evidence of efficacy on the assumption that the comparator is effective under the conditions of the trial. These trials must have assay sensitivity: the ability to distinguish an effective treatment from an ineffective or less effective treatment. One method of realising this is to add a placebo-arm to the study. A three-arm study is necessary when an existing, established efficacious medicines do not consistently demonstrate superiority to placebo, for example antidepressants, anxiolytics, drugs on allergic rhinitis etc. However, where a placebo-arm is not plausible, additional information on previous trials with the comparator is needed for designing and conducting a noninferiority or equivalence trial in order to realise assay sensitivity. This additional information is also needed for a correct interpretation of the results of these trials.
One of the topics in active control trials is the choice of comparator. Therapeutically, there is a preference for “a widely used therapy”, interpreted in practice as the standard treatment, and/or for the most prescribed drug within the same therapeutic class. Methodologically, there are additional requirements on a comparator in noninferiority and equivalence trials: the efficacy in the same indication must be “clearly established and quantified in well-designed and well-documented superiority trial(s)” [7,8]. There are two main reasons for these specific requirements. Firstly, the so-called constancy assumption. This is the assumption that the superiority of the comparator demonstrated in these previous trials holds up in the setting of the noninferiority or equivalence trial. To realize this situation the new trial should be designed in a manner consistent with the superiority trials of the comparator. The trials should be as similar as possible with respect to critical design characteristics such as patient selection, intervention and endpoints. The second reason is the margin: a quantitative specification of a clinically irrelevant difference between two treatments. This is the largest difference that can be judged as being clinically acceptable and it should be smaller than the differences observed in the superiority trials of the comparator. For an equivalence trial, both upper and lower margins are needed, whilst only

the lower margin is needed for a noninferiority trial (figure 1). Altogether this means that additional information on the previous superiority trials of the comparator is needed for choosing the margin and establishing the constancy assumption.

Figure 1 - Overview design comparative trials, treatment differences (point estimate, confidence interval) and margin (Δ)



In order to verify your decisions on (comparative) efficacy and safety based on noninferiority or equivalence trials, we were interested in the availability of this additional information in public sources of information on these trials, such as publications and your assessment reports. With respect to publications, we are aware that they reveal important deficiencies, such as the absence of justification for the margin chosen [9]. For this reason we focused on your assessment reports.

Tabel 1. Noninferiority and equivalence trials of new medicines between 1999-2005

New medicines	Therapeutic indication	Comparators	N trials	Published at MA
abacavir	HIV-1 infection	indinavir	1	
amprenavir	HIV-1 infection	indinavir	1	
atazanavir	HIV-1 infection	lopinavir/ritonavir , ritonavir	3	[18]
bivalirudin	Percutaneous coronary intervention	heparin	1	
brinzolamide	Glaucoma	dorzalamide, timolol	4	[22,26,27]
capecitabine	Colorectal cancer	fluorouracil/folinic acid	2	
Choriogonado-tropin alfa	Infertility an/oligo-ovulatory	gonadotropin chrionicum	1	
	Superovulation prior to IVF	gonadotropin chrionicum	3	[13,37]
darbepoetin alfa	Anaemia by chronic renal failure	epoetin alfa	2	
deferiprone	Iron overload thalassemia major	desferoxamine	1	
efavirenz	HIV-1 infection	indinavir	1	
emedastine	Seasonal allergic conjunctivitis	levocabastine	2	
emtricitabine	HIV-1 infection	lamivudine, stavudine	3	
epoetin delta	Anaemia by chronic renal failure	epoetin alfa	1	
ertapenem	Bacterial infections	piperacillin/tazobactam, ceftriaxone	5	[24]
fosamprenavir	HIV-1 infection	lopinavir, nelfinavir	2	[15]
fulvestrant	Breast cancer	anastrozole	2	
ganirelix	Prevention of premature ovulation	buserelin, leuprorelin, triptorelin	3	
ibritumomab tiuxetan	Non-Hodgkin's lymphoma	rituximab	1	[32]

insulin aspart	Diabetes mellitus type 1	insulin regular human	2	
insulin aspart	Diabetes mellitus type 2	insulin regular human	1	
insulin detemir	Diabetes mellitus type 1	insulin NPH human	5	[20,25,28, 30]
insulin detemir	Diabetes mellitus type 2	insulin NPH human	3	
insulin glulisine	Diabetes mellitus type 1	insulin regular human, insulin lispro	2	
insulin glulisine	Diabetes mellitus type 2	insulin regular human	1	[12]
ivabradine	Chronic stable angina pectoris	amlodipine, atenolol	2	[29]
lopinavir (comb)	HIV-1 infection	nelfinavir, diff protease inhibitors	2	
olopatadine	Seasonal allergic conjunctivitis	cromolyn	1	
palonosetron	Nausea/vomiting (by chemother.)	ondansetron, dolasetron	3	[14,17]
pegfilgrastim	Reduction duration neutropenia	filgrastim	2	[19]
peginterferon alfa-2a	Chronic hepatitis C	interferon alfa 2a	1	[33]
rosiglitazone	Diabetes mellitus type 5	Glibenclamide	1	
telithromycin	Bacterial infections	amoxicillin,amoxicillin/ clavulanate, cefuroxim, clarithromycin,pheno-xymethylpenicillin , trovafloxacin	8	
temozolomide	Glioblastoma multiforme	procarbazine	1	
tenecteplase	Suspected myocardial infarction	alteplase	1	[31]
travoprost	Glaucoma	latanoprost, timolol	3	[16,23]
valdecoxib	Osteoarthritis	Diclofenac	1	
	Rheumatoid arthritis	Diclofenac	1	
voriconazole	Invasive aspergillosis	amphotericin B	1	
zoledronic acid	Hypercalcaemia (tumour induced)	pamidronate	2	[21]

MA: market authorization

Analysis of noninferiority and equivalence trials

We did a further analysis of the data from a previous study about the availability of comparative information on new medicines at the moment of European market authorization. We therefore analyzed the European Public Assessment Reports (EPAR) of the EMEA between 1999 and 2005 on new medicines with a new active substance [10]. In that period 58 (48%) of the approved medicines (N=122) had been studied in comparison with existing medicines [11]. Of these main/pivotal active controlled trials (N=153), 26 (17%) had also a placebo-arm to establish assay sensitivity. We found that 83 (54%) trials had the objective to show noninferiority or equivalence; at the moment of market authorization 24 (29%) of these trials had been published (table 1)[12-33]. For 15 (10%) RaCTs, the objective was to demonstrate superiority and information on the objective was lacking for 55 (36%) of the trials.

For most of the trials it was clear in publications as well as EPARs which margin was used to demonstrate noninferiority or equivalence. However, there was a lack of reporting on the rationale for the choice of margin. In the EPARs of three new medicines there was a reference to published studies (fulvestrant), FDA guidance (ertapenum) and a systematic review (palonosetron), however, without a concrete reference to the literature. With respect to establishing constancy assumption, two trials contained a description of similarity in patient populations between the fulvestrant trials and two previous studies of the comparator anastrozole compared with megestrol acetate.
We found two publications on a noninferiority and equivalence trial on ivabradine and tenecteplase with a rationale for the choice of the comparator, however, with insufficient additional information on the similarity in patients, interventions and outcomes to establish constancy assumption [29,31].

Discussion

Efficacy of a new medicine can be demonstrated either by showing superiority to a control treatment (placebo or active treatment) or by demonstrating a predefined margin of equivalency or noninferiority in comparison with an existing efficacious therapy. Each method can be valid, but each requires a different approach to conduct the trials. Trials showing superiority provide their own internal validity check. The validity of trials

demonstrating equivalence or noninferiority without the use of a placebo-arm relies solely on external information on previous superiority trials of the comparator used. On the basis of our analysis, we conclude that this crucial additional information on the comparator used in noninferiority and equivalence studies of new medicines is insufficiently reported in public sources of information to be able to verify the conclusions on (comparative) efficacy. The underreporting of this information in peer-reviewed publications was known [9] and has resulted in an extension of the CONSORT statement [34].

Although this additional information is not provided, we assume that it was clearly specified in the protocol of the studies; however, publicly it is unclear to what degree this information has been taken into consideration when interpreting the results of these studies as evidence of efficacy. In view of the various guidelines, you clearly recognize the importance of properly designing and conducting these trials, but it would be helpful to clarify the degree to which these guidelines have been followed.

The importance of more transparency can be illustrated by two examples. One of the new medicines in our analysis, lopinavir combined with ritonavir, was also used as comparator in the noninferiority trials of two other new medicines for the treatment of HIV-infections, fosamprenavir and atazanavir. The superior antiviral activity of lopinavir was demonstrated in a well-designed study involving a comparison with nelfinavir in combination with stavudine and lamivudine in antiretroviral-naïve patients [35]. Data on the benefits to experienced patients are too limited to draw a conclusion on superiority. However, the noninferiority studies on fosamprenavir and atazanavir were conducted in experienced patients and with different combinations of two nucleosides. This raises the question of whether the limited data on the efficacy of lopinavir in experienced patients were sufficient to justify the choice of this comparator in these noninferiority studies and to establish assay sensitivity. In all studies on new insulins in our analysis, the same margin of 0.4% glycated haemoglobin (HbA1c) was used independently of the comparator (regular human insulin, insulin lispro) and type of patients (type 1 as well as type 2 diabetes). This raises questions as to how this margin was established. Superiority studies are lacking, because comparing insulin with placebo would be unethical and the introduction of human insulin onto the market in the early 1980s was without scientific proof of advantage over purified animal insulins [36].

We realize that in planning noninferiority and equivalence trials, it is not always easy for investigators to meet not only therapeutic requirements, but also specific methodological

requirements. Occasionally these may even be in conflict with each other. Therapeutically there is a preference to choose as comparator the standard treatment and/or the most widely used drug within the same therapeutic class. This first choice in clinical practice is often based not only on the results of clinical trials but also on years of positive experience using the medicine on many patients. However, it is possible that previous superiority trials no longer serve as a study design for new clinical trials because clinical and methodological insights may have changed substantially over time. In that case, holding the constancy assumption would be scientifically questionable. In order to illustrate this problem, we analyzed the different combinations of a new medicine versus its comparator in these trials according to differences in therapeutic class and experience. We considered the combination as belonging to the same therapeutic class if there was a level four similarity (pharmacological/chemical subgroup) in the ATC-code. Experience with the comparator was calculated as the difference between the year of market authorization of the new medicine and the year of market entry of the comparator. Table 2 gives an overview of the results.

Table 2 - Differences in experience and therapeutic class in combinations of a new medicine and its comparator

Experience with comparator	**Therapeutic class new medicine compared with comparator**					
	Same		**Different**		total	
< 3 yrs	0	0	3	13%	3	6%
3 – 10 yrs	14	52%	3	13%	17	33%
10 – 25 yrs	8	30%	7	29%	15	30%
> 25 yrs	5	18%	11	46%	16	31%
total	27		24			
	53%		47%			

We found 51 different combinations in 83 noninferiority and equivalence trials. There were almost as many combinations of the same therapeutic class as of a different one. In 61% of the combinations, a comparator was chosen with broad experience in clinical practice, even longer than 25 years for 31% of the combinations.
In the case of a comparator with shorter experience, a choice was often made within the same class. The assumption in practice, which may be implicit on the basis of broad experience and/or a similar mechanism of action, is that the comparator is also efficacious in the setting of the new trial, but crucial to this is which treatment difference/ratio should be taken as a margin, based on the size of effect in previous superiority trials.

The question is whether strict methodological requirements can be met in a case of an optimal choice of comparator based on therapeutic reasons. On the other hand, this highlights the need of more insight into your reflections on making decisions regarding efficacy based on noninferiority and equivalence trials, especially when comparators are used with a long and good record in pharmacotherapy. If previous superiority studies on the comparator were not particularly useful for establishing assay sensibility, a superiority trial should be required for demonstrating a new medicine's (comparative) efficacy.

References

1. Koopmans PP, de Graeff PA, Zwieten-Boot BJ, Lekkerkerker JF, Broekmans AW. Clinical evaluation of efficacy and adverse effects in the (European) registration of drugs: what does it mean for the doctor and the patient? (in dutch). Ned Tijdschr Geneeskd 2000;144:756-61.
2. Lewis JA, Jonsson B, Kreutz G, Sampaio C, van Zwieten-Boot B. Placebo-controlled trials and the Declaration of Helsinki. Lancet 2002;359:1337-40.
3. Temple R, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: ethical and scientific issues. Ann Intern Med 2000;133:455-63.
4. The European Agency for the Evaluation of Medicinal Products. Note for guidance on clinical investigation of medicinal products in the treatment of hypertension. London: EMEA, 2004.
5. van Luijn JCF, van Loenen AC, Gribnau FWJ, Leufkens HGM. Choice of comparator in active control trials of new drugs. Ann Pharmacother 2008;42:1605-12.
6. The European Agency for the Evaluation of Medicinal Products. Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96). London: EMEA, 2000.
7. The European Agency for the Evaluation of Medicinal Products. Guideline on the choice of the non-inferiority margin (EMEA/CPMP/EWP/2158/99). 2006; Accessed in October 2009 via http://www.emea.europa.eu/pdfs/human/ewp/215899en.pdf.
8. Lange S, Freitag G. Choice of delta: requirements and reality--results of a systematic review. Biom J 2005;47:12-27.
9. Le Henanff A, Giraudeau B, Baron G, Ravaud P. Quality of reporting of noninferiority and equivalence randomized trials. JAMA 2006;295:1147-51.
10. The European Agency for the Evaluation of Medicinal Products. European Public Assessment Reports. 2009; Accessed in October 2009 via http://www.emea.europa.eu/htms/human/epar/eparintro.htm.
11. van Luijn JCF, Gribnau FW, Leufkens HG. Availability of comparative trials for the assessment of new medicines in the European Union at the moment of market authorization. Br J Clin Pharmacol 2007;63:159-62.
12. Dailey G, Rosenstock J, Moses RG, Ways K. Insulin glulisine provides improved glycemic control in patients with type 2 diabetes. Diabetes Care 2004;27:2363-8.
13. Driscoll GL, Tyler JP, Hangan JT, Fisher PR, Birdsall MA, Knight DC. A prospective, randomized, controlled, double-blind, double-dummy comparison of recombinant and urinary HCG for inducing oocyte maturation and follicular luteinization in ovarian stimulation. Hum Reprod 2000;15:1305-10.
14. Eisenberg P, Figueroa-Vadillo J, Zamora R, Charu V, Hajdenberg J, Cartmell A, et al. Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT3 receptor antagonist: results of a phase III, single-dose trial versus dolasetron. Cancer 2003;98:2473-82.
15. Gathe JCJ, Ive P, Wood R, Schurmann D, Bellos NC, DeJesus E, et al. SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir /ritonavir versus twice-daily nelfinavir in naive HIV-1-infected patients. AIDS 2004;18:1529-37.
16. Goldberg I, Cunha-Vaz J, Jakobsen JE, Nordmann JP, Trost E, Sullivan EK. Comparison of topical travoprost eye drops given once daily and timolol 0.5% given twice daily in patients with open-angle glaucoma or ocular hypertension. J Glaucoma 2001;10:414-22.
17. Gralla R, Lichinitser M, Van Der Vegt S, Sleeboom H, Mezger J, Peschel C, et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately

emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Ann Oncol 2003;14:1570-7.
18. Haas DW, Zala C, Schrader S, Piliero P, Jaeger H, Nunes D, et al. Therapy with atazanavir plus saquinavir in patients failing highly active antiretroviral therapy: a randomized comparative pilot trial. AIDS 2003;17:1339-49.
19. Holmes FA, O'Shaughnessy JA, Vukelja S, Jones SE, Shogan J, Savin M, et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. J Clin Oncol 2002;20:727-31.
20. Home P, Bartley P, Russell-Jones D, Hanaire-Broutin H, Heeg JE, Abrams P, et al. Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial. Diabetes Care 2004;27:1081-7.
21. Major P, Lortholary A, Hon J, Abdi E, Mills G, Menssen HD, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. J Clin Oncol 2001;19:558-67.
22. March WF, Ochsner KI. The long-term safety and efficacy of brinzolamide 1.0% (azopt) in patients with primary open-angle glaucoma or ocular hypertension. The Brinzolamide Long-Term Therapy Study Group. Am J Ophthalmol 2000;129:136-43.
23. Netland PA, Landry T, Sullivan EK, Andrew R, Silver L, Weiner A, et al. Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. Am J Ophthalmol 2001;132:472-84.
24. Ortiz-Ruiz G, Caballero-Lopez J, Friedland IR, Woods GL, Carides A. A study evaluating the efficacy, safety, and tolerability of ertapenem versus ceftriaxone for the treatment of community-acquired pneumonia in adults. Clin Infect Dis 2002;34:1076-83.
25. Russell-Jones D, Simpson R, Hylleberg B, Draeger E, Bolinder J. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal-bolus regimen. Clin Ther 2004;26:724-36.
26. Sall K. The efficacy and safety of brinzolamide 1% ophthalmic suspension (Azopt) as a primary therapy in patients with open-angle glaucoma or ocular hypertension. Brinzolamide Primary Therapy Study Group. Surv Ophthalmol 2000;44 Suppl 2:S155-S162.
27. Silver LH. Clinical efficacy and safety of brinzolamide (Azopt), a new topical carbonic anhydrase inhibitor for primary open-angle glaucoma and ocular hypertension. Brinzolamide Primary Therapy Study Group. Am J Ophthalmol 1998;126:400-8.
28. Standl E, Lang H, Roberts A. The 12-month efficacy and safety of insulin detemir and NPH insulin in basal-bolus therapy for the treatment of type 1 diabetes. Diabetes Technol Ther 2004;6:579-88.
29. Tardif JC, Ford I, Tendera M, Bourassa MG, Fox K. Efficacy of ivabradine, a new selective I(f) inhibitor, compared with atenolol in patients with chronic stable angina. Eur Heart J 2005;26:2529-36.
30. Vague P, Selam JL, Skeie S, De Leeuw I, Elte JWF, Haahr H, et al. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. Diabetes Care 2003;26:590-6.
31. Van De Werf F, Adgey J, Ardissino D, Armstrong PW, Aylward P, Barbash G, et al. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. Lancet 1999;354:716-22.
32. Witzig TE, Flinn IW, Gordon LI, Emmanouilides C, Czuczman MS, Saleh MN, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. J Clin Oncol 2002;20:3262-9.

33. Zeuzem S, Feinman SV, Rasenack J, Heathcote EJ, Lai MY, Gane E, et al. Peginterferon alfa-2a in patients with chronic hepatitis C. N Engl J Med 2000;343:1666-72.
34. Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJW. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. JAMA 2006;295:1152-60.
35. Walmsley S, Bernstein B, King M, Arribas J, Beall G, Ruane P, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. N Engl J Med 2002;346:2039-46.
36. Richter B, Neises G. 'Human' insulin versus animal insulin in people with diabetes mellitus. Cochrane Database Syst Rev 2005;CD003816.
37. Induction of final follicular maturation and early luteinization in women undergoing ovulation induction for assisted reproduction treatment--recombinant HCG versus urinary HCG. The European Recombinant Human Chorionic Gonadotrophin Study Group. Hum Reprod 2000;15:1446-51.

Chapter 4

Usage of comparative information in decision-making on new medicines

Chapter 4.1

Gap in publication of comparative information on new medicines

Johan C.F. van Luijn,
Pieter Stolk,
Frank W.J. Gribnau,
Hubert G.M. Leufkens

Published: Br J Clin Pharmacol 2008; 65:716-722

Abstract

Aims

To determine the time-lag between the EU authorization of new medicines and the publications of the main randomized active control trials (RaCTs) used in the authorization process; to compare unpublished to published RaCTs of the same medicine.

Methods

All RaCTs for new medicines with a new active substance, authorized between 1999 and 2003, were extracted from the European Public Assessment Reports (EPAR). Information about the publication status of RaCTs was obtained from the MEDLINE and EMBASE databases.

Results

We identified 116 RaCTs for 42 new medicines; 28% of the RaCTs had been published at the moment of market authorization, 59% after one year, 78% after two and 83% after three years. Most of the rest of the studies remain unpublished after three years of follow-up. Unpublished RaCTs differed from published trials of the same medicine especially regarding therapeutic use and/or comparator. In some cases unpublished trials have influenced the benefit/risk assessment of the registration authorities.

Conclusion

Most of the main RaCTs, relevant for assessing the added value of a new medicine, are published subsequent to market entry; a part of these trials remain unpublished. We argue for a standardised public registration of the results of the main premarketing clinical trials as a condition for market authorization.

Introduction

When a new medicine is marketed, it is important to know how it compares with existing medicines for the same indication [1,2]. Prescribers, pharmacists, formulary committees and regulators all require this information soon after market authorization in order to make a therapy decisions on individual patients, to develop prescribing guidelines and to set reimbursement levels.
Evaluating how a new medicine compares to an existing medicine for the same indication on certain outcomes under the same conditions, can best be studied in a randomized controlled trial with the existing medicine as the active control group (RaCT).
In the premarketing period clinical trials are conducted with the objective to show efficacy and safety in order to obtain a marketing authorization. For the EU market these studies are evaluated through the European Medicines Agency (EMEA) and for the US market by the Food and Drug Administration (FDA). Placebo controlled trials are commonly used; active control trials are not compulsory, only desirable, and sometimes necessary when a placebo controlled trial would be unethical [3-6]. Trials designed to confirm the preliminary evidence on safety and efficacy, are called the main or pivotal trials. Efficacy can be demonstrated by detecting a difference with an placebo or an active control group (superiority trial), by confirming the absence of a difference with an active control group (equivalence trial) or by showing that the new medicine is no worse than the active control group (non-inferiority trial) [6].

At the moment of market entry, the main clinical trials with an active control group are the primary source of information for learning more about the comparative efficacy and safety of the new medicine. To assess the usefulness of these studies for prescribing and reimbursement decisions, the full data of these trials should be publicly available, preferably in the form of peer-reviewed publications. Failing to publish the results of clinical trials substantially limits the possibility of making an evidence-based assessment of a new medicine and conducting systematic reviews [7]. For this reason, there should be a scientific and moral obligation upon conductors of the studies to publish the results [8,9]. This view is echoed in the Good Publication Practice guideline for pharmaceutical companies, which points out the responsibility of companies to make an effort to publish the results of all studies [10].
Currently little is known about the publication rates of RaCTs that are used in the authorization process or about the time-lag between market authorization and publication as

an article in a journal. Furthermore, it is unknown which comparative information used in the market authorization process remains unpublished.
The aim of this study is to determine the time-lag between the authorization of a new medicine in the European Union (EU) and the publication of RaCTs used in the authorization process in the period 1999-2003 and to compare unpublished with published main RaCTs in terms of relevant therapeutic characteristics.

Methods

Source of information

We selected products with a new active substance that were authorized through the European Commission's centralized procedure in the period 1999-2003. Diagnostics and vaccines were excluded. For information about the premarketing RaCTs we used the European Public Assessment Reports (EPAR). These reports give an overview of the clinical trials that applicants have submitted to the EMEA for market approval and summarize the scientific discussion in the Committee for Medicinal Products for Human Use (CHMP) [11]. The initial version of the EPAR, which was retrieved from the EMEA website, was used. All studies were included that were labelled as main/pivotal studies in the EPAR and in which the medicine under investigation was compared directly to a known active medicine [12]. We extracted information about the date of marketing authorization and characteristics (indication, study design, number of patients) of each RaCT. In order to compare, the EU authorization date with the authorization date in the USA, we retrieved this date from the website of the FDA [13].

Literature search

To determine which of the RaCTs that were reported in the EPAR had been published as an article in a journal, we searched the MEDLINE and EMBASE databases using the new medicine's international non-proprietary name and the keywords "randomized controlled trial". The search date was January 1, 2007.
One investigator [JvL] assessed the publication status of all RaCTs by comparing the study design, number of patients and study-results of the published RaCTs with those reported in the EPAR. A second investigator [PS] assessed whether a study was correctly identified as not published. Meta-analyses were regarded as publications of a RaCT when not separately published. The date of publication, both on-line or in print, was extracted and the latter date was used for the analysis.

Therapeutic analysis

To analyze possible useful comparative information on efficacy and safety in unpublished studies, relevant therapeutic characteristics of unpublished main RaCTs were compared with the published trials of the same medicine. We made this comparison at two different moments, the moment of market authorization and three years later.

We classified these therapeutic characteristics into six categories: 1) unpublished RaCT is the only source of information on comparative efficacy and safety used in the authorization process; 2) different therapeutic use (studied in another indication or patient population than in published RaCTs); 3) different comparator (different substance or dose than in published RaCTs); 4) longer duration of treatment than in published RaCTs; 5) shorter duration of treatment than in published RaCTs; 6) same therapeutic use, comparator and duration as in published RaCTs.

If a medicine was compared with another comparator in case of different indication than in a published RaCT, it was classified as different therapeutic use (category 2).

Categories 1, 2, 3 and 4 were regarded as relevant additional information, categories 5 and 6 as less relevant.

Statistical analysis

We constructed Kaplan-Meyer curves depicting publication probability. Trials published before the moment of EU-authorization were analysed with a time to publication of 0.01 months.

Results

Between 1999 and 2003 we identified 116 randomized active control trials for 42 medicines with a new active substance. Table 1 gives an overview of relevant characteristics of these RaCTs and their publication status. At the moment of market authorization 33 (28%) RaCTs had been published, one year after market authorization 68 (59%), after two years 90 (78%) and after three years 96 (83%). The annual number of publications two and three years after authorization, is reasonably constant. In view of the small number of new medicines with a RaCT in 2003, it is not possible to assess whether a trend towards prompter publication of trials at the moment of authorization exists.

Table 1. Publication status of premarketing randomized active control trials .

Characteristics	Med	RaCT	Number of published trials (%) At MA	After 1 yr	After 2 yrs	After 3 yrs
Year of authorization						
1999	10 [a]	18	2 (11%)	9 (50%)	15 (83%)	15 (83%)
2000	9 [b]	25	5 (20%)	12 (48%)	17 (68%)	18 (72%)
2001	11 [c]	31	10 (32%)	18 (58%)	27 (87%)	29 (94%)
2002	10 [d]	31	12 (39%)	22 (71%)	23 (74%)	25 (81%)
2003	2 [e]	11	4 (36%)	7 (64%)	8 (73%)	9 (82%)
All years	42	116	33 (28%)	68 (59%)	90 (78%)	96 (83%)
Therapeutic indication						
Bacterial infections	2	13	1 (8%)	5 (39%)	11 (85%)	13 (100%)
Diabetes mellitus	5	18	4 (22%)	8 (44%)	10 (56%)	11 (61%)
Glaucoma	3	10	7 (70%)	8 (80%)	9 (90%)	9 (90%)
HIV-1 infections	5	8	0	3 (38%)	5 (63%)	5 (63%)
Other (n=25)	27	67	21 (31%)	44 (66%)	55 (82%)	58 (87%)
Study design RaCT						
Noninferiority	17 □	32	7 (22%)	19 (59%)	26 (81%)	27 (85%)
Equivalence	10 □	23	6 (26%)	11 (48%)	19 (83%)	20 (87%)
Superiority	5 □	10	4 (40%)	8 (80%)	8 (80%)	9 (90%)
No information	20 □	51	16 (31%)	30 (59%)	37 (73%)	40 (79%)

Market authorization						
EU first	16	41	7 (17%)	19 (46%)	32 (78%)	35 (85%)
FDA first	26	75	26 (35%)	49 (65%)	58 (77%)	61 (81%)

Medicines with new active substance (number of trials)

[a] abacavir (1), cetrorelix (2), deferiprone (1), efavirenz (1), emedastine (2), insulin aspart (3), interferon alfacon-1(1), leflunomide (3), temozolomide (1), zaleplon (3)

[b] amprenavir (1), atosiban (3), brinzolamide (4), ganirelix (3), insulin glargine (10), peginterferon alfa -2b (1), pioglitazone (1), rosiglitazone (1), sevelamer (1)

[c] capecitabine (2), choriogonadotrophin alfa (4), darbepoetin alfa (4), lopinavir (2), nateglinide (3), rasburicase (1), sirolimus (1), telithromycin (8), tenecteplase (1), travoprost (3), zoledronic acid (2)

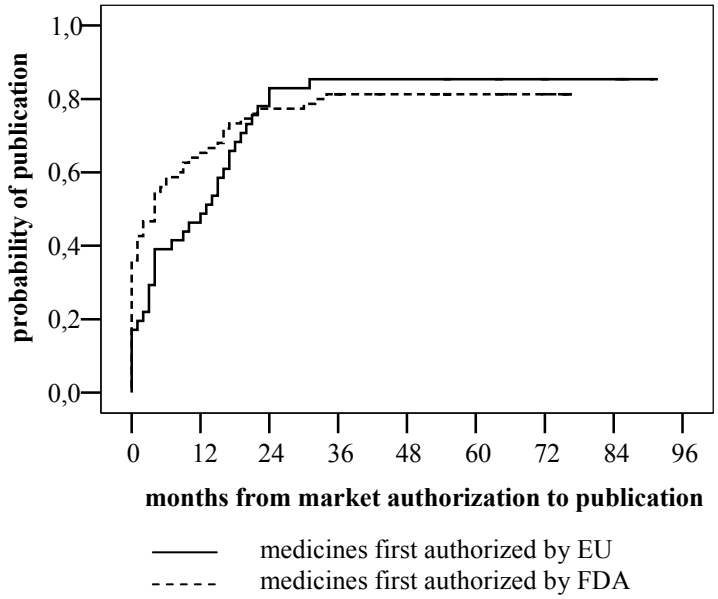
[d] bimatoprost (3), epoetin delta (1), ertapenem (5), fondaparinux (4), norelgestromin (2), olopatadine (2), parecoxib (6), pegfilgrastim (2), peginterferon alfa-2a (4), voriconazole (2)

[e] emtricitabine (3), valdecoxib (8); valdecoxib: suspension in marketing authorisation Oktober 13, 2005

 different study designs per medicine

The new medicines were intended to treat a number of different indications. Indications with 8 or more studies are bacterial infections, HIV-1 infections, diabetes mellitus and glaucoma. For new antiretroviral and antidiabetic medicines the publication rates after three years were lower than for antibacterial and antiglaucoma agents. Looking at the design of the RaCTs, superiority trials have a comparatively higher publication rate than non-inferiority and equivalence trials during the first year after market authorization. For 51 (44%) trials there was a lack of information in the EPAR on the design of the trial; on the basis of the CHMP's opinion on the results of the studies, we assume that almost all studies were noninferiority or equivalence trials. This lack of clarity restricts a sound conclusion on differences in publication rate in relation to the study design. However, the results show that most of the studies are not designed to demonstrate superiority. We found 10 superiority trials for five new medicines: bimatoprost (2), fondaparinux (4), olopatadine (1), peginterferon alfa-2a (2) and voriconazole (1).
Figure 1 shows two Kaplan-Meyer curves depicting the publication probability of a RaCT after market authorization for medicines that were first authorized by the FDA and for those first authorized by the EMEA.

Figuur 1- Kaplan-Meyer curves depicting the publication probability of a randomized active control trial after market authorization



We found that 26 (62%) medicines were authorized by the FDA before they were authorized by the EMEA. In these cases, the US authorization date was, on average, 13 months earlier than the EU authorization date. At the moment of EU market authorization, there were more publications for medicines with a prior FDA authorization. Both curves show that after two or three years few additional RaCTs are published; at the end of the follow-up 18 (16%) of the premarketing RaCTs remain unpublished.

To evaluate the importance of the unpublished main clinical trials, we compared relevant therapeutic characteristics of these RaCTs with the characteristics of the trials published at that moment for the same medicine. Table 2 shows the results of this analysis at two different moments in the time.

Table 2 - Comparison of therapeutic characteristics of unpublished to published randomised active control trials of the same new medicine

Category therapeutic characteristics of premarketing unpublished vs published trials	Number of unpublished trials (medicines)	
	At moment of authorization	After three years
Only comparative information		
One RaCT/new medicine	11 (11)	5 (5)
More RaCTs/new medicine	37 (12)	0
Different therapeutic use		
Other therapeutic indication	12 (6)	2 (2)
Other patient population	5 (2)	3 (2)
Different comparator (same therapeutic use)		
Other active substance	9 (6)	6 (6)
Other dose	1 (1)	1 (1)
Longer duration of treatment	0	0
Shorter duration of treatment	3 (3)	2 (1)
Same therapeutic use, comparator and duration	5 (3)	1 (1)

RaCT: randomized active control trial

For 75 of the 83 (90%) RaCTs unpublished at the moment of market authorization it would be interesting to know the full data of the trial especially because of a different indication, patient population or comparator. After three years, 17 of the 20 (85%) unpublished RaCTs possibly contained relevant therapeutic information. For amprenavir, deferiprone, epoetin delta, pioglitazone and rosiglitazone the unpublished RaCT was the only RaCT used in the authorization process. Also not published were: 1) trials with a different comparator, namely for: darbepoetin alfa (comparator with another dose), emtricitabine, insuline glargine, lopinavir, olopatadine, parecoxib and valdecoxib; 2) trials in which medicines were studied in a different therapeutic indication, this was the case for bimatoprost in adjunctive therapy of glaucoma and insuline aspart in diabetes type II; 3) trials in which medicines were studied in a special population, this was found for zaleplon in elderly patients and parecoxib in patients with postorthopaedic surgery analgesia. Less interesting are the results of three studies on insuline glargine as they had the same design or a shorter duration as the published trials.

Discussion

Once market authorization for a new medicine has been obtained, there is considerable pressure on health care professionals and regulators to make the new medicine available so that it can be applied in clinical practice. At the same time there is a great need for information to make an evidence-based assessment of the therapeutic position of the new medicine in relation to products already on the market. In this study we found that less than one third of the main RaCTs used in the EU market authorization process, had been published at the moment of market authorization, and 78% after 2 years. About one in five RaCTs remain unpublished even after 3 years of follow-up.

Overall this is good news, it reflects a strong commitment by pharmaceutical companies to publish the main RaCTs. However, we found that for most of the unpublished RaCTs it was still relevant to take note of the results as a peer-reviewed publication. This conclusion is based on a comparison between published and unpublished RaCTs in terms of a different therapeutic use, comparator and duration. The usefulness of the results of these studies for prescribing and reimbursement decisions depends on the quality of the data. Therefore, the full data of the trial should be publicly available, to make a critical evaluation possible. For example, relating to the study design, assay sensitivity - the ability to distinguish active from inactive medicines - is a very critical issue in non-inferiority and equivalence trials for

a correct interpretation of the efficacy results [6,14]. We found much more RaCTs with this study design than to show superiority.

The finding that three years after market authorization less than one-fifth of the RaCTs remain unpublished, raises this question of whether trials with positive results are more likely to be published than trials with a negative result [15-17]. We could not study this problem as detailed information is needed on the statistical significance between the trial arms. For most studies the EPAR did not provide the basic details of trial design and results in a uniform fashion, as was mentioned earlier [18]. Therefore, we analyzed the results of some of the unpublished RaCTs qualitatively. We found that the superiority trial with olopatadine had failed to show a difference in efficacy to levocabastine.
Moreover, some unpublished studies have influenced the risk/benefit assessment of the registration authorities, resulting in a restrictive therapeutic indication. For amprenavir the results of the comparative study were reason to mention in the approved indication that in protease inhibitor naive HIV-patients, amprenavir is less effective than indinavir. The comparative studies of rosiglitazone and pioglitazone, compared to sub-optimal doses of glibenclamide, gave insufficient evidence of efficacy in mono-therapy in diabetes mellitus; only four years later, based on new comparative studies, this indication was accepted by the EMEA. It is interesting to note that, based on the same comparative study on rosiglitazone and placebo-controlled studies, in an earlier authorization the FDA, unlike the EMEA, accepted the use of both glitazones for the treatment of diabetes mellitus type II in mono-therapy [13,19]. These examples show that publication of all available data from RaCTs that were reviewed in the context of the authorization process, is important for an evidence-based assessment of the position of a new medicine in therapy.

When interpreting the results of this study, there are four limitations that have to be taken into account. Firstly, this analysis is restricted to new medicines studied during the premarketing period in randomized active control trials. In an earlier study we found that only 48% of the new medicines has been studied in the premarketing period in comparison with an existing medicine [20]. When the results of the present study are considered against this data, it means that for most new medicines very little comparative information is available at the moment of market authorization. Obviously, conducting RaCTs and making the results public through the scientific literature are two different systems.
Secondly, we only included medicines that were centrally authorized in the EU. This choice was made because the assessment reports of these products are available in the public

domain. Until October 2005, there was no obligation to provide a public assessment report under the decentralized procedure.
Thirdly, we were not able to evaluate whether the publicly available RaCT information was complete as the trials submitted for market approval are chosen by the applicant and all commercially confidential information is deleted from the EPAR [11]. However, pharmaceutical companies are likely to be the only sponsors for premarketing studies and they must incorporate all relevant studies into a marketing authorization application.
Finally, as this analysis was restricted to peer reviewed publications we excluded alternate methods for dissemination of trial results such as abstracts/posters at scientific meetings and databases sponsored by pharmaceutical companies.

The question is what needs to happen to improve, soon after market entry, the public availability of the information contained in main RaCTs. Firstly, improvements in the process of journal publication are an option, for example by reducing the duration of the peer-review process [21].
Secondly, time could also be gained by publishing articles electronically in advance. In our study, we found that only 5 % of the articles was published on-line prior to printed publication.
Thirdly, some suggest that registration authorities should be enabled to require publication of every clinical trial submitted [9]. However, although these possible solutions would improve the current situation, they still mean a delay in publication with the consequence of less data available to make a decision on prescribing, guideline review or reimbursement at the moment of market entry.
Therefore, in addition to peer reviewed publications and separated from the public clinical trial registry, we strongly support initiatives to make public the results of the main premarketing clinical trials in public trial results databases [22,23]. However, to ensure the usefulness as reference for evidence-based decision-making and conducting systematic reviews, we feel that trial results databases should have to meet the same requirements as stated by the International Committee of Medical Journal Editors for an acceptable clinical trial registry [24,25]. The database must be electronically searchable and accessible to the public at no charge; it should be open to all those who wish to register, it should be non-profit-making, and it should have a mechanism for ensuring the validity of the registration data. Moreover, the results should be reported in a comprehensive and uniform format. To give health care professionals and regulators the opportunity to use the same information as registration authorities, we argue for a standardized public registration of the results as a condition for market authorization.

Is the urge of acquiring comparative treatment information exclusively a European feature? Surely this is not the case. Within the US, Canada and other health care systems also, demands are being made for more comparative evidence when more than one treatment option is available in order to support prescribing guidelines and reimbursement decisions [26]. It is difficult to control health care costs and guarantee access to necessary treatment possibilities in daily practice, particularly when they are expensive, without comparing medicines in terms of added value for patients and society.

Although the added value of a new medicine may not be part of the formal market authorization process, either in Europe or in the US, there is no doubt about the great need to address both comparative safety and efficacy between medicinal products subsequent to market authorization [27-29]. Therefore, it is necessary to invest in studies that provide comparative evidence, but also to identify and develop incentives for building comparative information as soon as possible in the drug development process and to make the results of such comparisons as soon as possible available to the public domain.
This study shows that about four out of five of such main RaCTs are published within two or three years after market authorization. However, we need to evaluate the impact of the information gap due to the unpublished RaCTs. Moreover, we need also to study the quality of the comparative information, both with regard to the choice of comparator and study design.
Placebo controlled trials are commonly used in clinical drug development because they have important advantages; if patients are not harmed, such trials can ethically be carried out [3,5]. But that is not the end of the story. There is ample need for innovative and comparative learning on drug effects when the confirming route has already been paved in a significant way [30].

References

1. International Society of Drug Bulletins. ISDB declaration on therapeutic advance in the use of medicines. Paris: International Society of Drug Bulletins, 2001.
2. National Institute of Clinical Excellence. Guide to the methods of technology appraisal. London: NICE, 2004.
3. Ellenberg SS, Temple R. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 2: practical issues and specific cases. Ann Intern Med 2000;133:464-70.
4. Koopmans PP, de Graeff PA, Zwieten-Boot BJ, Lekkerkerker JF, Broekmans AW. Clinical evaluation of efficacy and adverse effects in the (European) registration of drugs: what does it mean for the doctor and the patient? (in dutch). Ned Tijdschr Geneeskd 2000;144:756-61.
5. Temple R, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: ethical and scientific issues. Ann Intern Med 2000;133:455-63.
6. The European Agency for the Evaluation of Medicinal Products. Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96). London: EMEA, 2000.
7. Reidenberg MM. Conflict of interest and medical publication. Sci Eng Ethics 2002;8:455-7.
8. Chalmers I. Underreporting research is scientific misconduct. JAMA 1990;263:1405-8.
9. Reidenberg MM. Improving how we evaluate the toxicity of approved drugs. Clin Pharmacol Ther 2006;80:1-6.
10. Wager E, Field EA, Grossman L. Good publication practice for pharmaceutical companies. Curr Med Res Opin 2003;19:149-54.
11. The European Agency for the Evaluation of Medicinal Products. European Public Assessment Reports. 2009; Accessed in October 2009 via http://www.emea.europa.eu/htms/human/epar/eparintro.htm.
12. The European Agency for the Evaluation of Medicinal Products. Notice to applicants. Volume 2A: procedures for marketing authorisation appendix III. London: EMEA, 2004.
13. U.S.Food and Drug Administration. Approved drug products. 2009; Accessed in October 2009 via www.accessdata.fda.gov/scripts/cder/drugsatfda/.
14. Temple R. Policy developments in regulatory approval. Stat Med 2002;21:2939-48.
15. Bardy AH. Bias in reporting clinical trials. Br J Clin Pharmacol 1998;46:147-50.
16. Hopewell S, Clark M, Stewart L, Tierney J. Time to publication for results of clinical trials. Cochrane Database Methodol Rev 2001;MR000011.
17. Ioannidis JP. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. JAMA 1998;279:281-6.
18. Wieringa NF, Vos R, de Graeff PA. Comparative trials in registration files of cardiovascular drugs: comparator drugs and dosing schemes. Pharm World Sci 2001;23:28-30.
19. Gale EA. Lessons from the glitazones: a story of drug development. Lancet 2001;357:1870-5.
20. van Luijn JCF, Gribnau FW, Leufkens HG. Availability of comparative trials for the assessment of new medicines in the European Union at the moment of market authorization. Br J Clin Pharmacol 2007;63:159-62.
21. Clark A, Singleton-Jackson J, Newsom R. Journal editing: managing the peer review process for timely publication of articles. Publishing Research Quarterly 2000;16:62-72.
22. Pharmaceutical Research and Manufactures of America. Clinical Study Results Database. 2009; Accessed in October 2009 via www.clinicalstudyresults.org.
23. Sim I, Detmer DE. Beyond trial registration: a global trial bank for clinical trial reporting. PLoS Med 2005;2:e365.

24. De Angelis C., Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med 2004;351:1250-1.
25. De Angelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Is this clinical trial fully registered?--A statement from the International Committee of Medical Journal Editors. N Engl J Med 2005;352:2436-8.
26. Morgan SG, McMahon M, Mitton C, Roughead E, Kirk R, Kanavos P, et al. Centralized drug review processes in Australia, Canada, New Zealand, and the United kingdom. Health Aff (Millwood) 2006;25:337-47.
27. Buckman S, Huang SM, Murphy S. Medical product development and regulatory science for the 21st century: the critical path vision and its impact on health care. Clin Pharmacol Ther 2007;81:141-4.
28. Ray WA, Stein CM. Reform of drug regulation--beyond an independent drug-safety board. N Engl J Med 2006;354:194-201.
29. Wood AJ. A proposal for radical changes in the drug-approval process. N Engl J Med 2006;355:618-23.
30. Sheiner LB. Learning versus confirming in clinical drug development. Clin Pharmacol Ther 1997;61:275-91.

Chapter 4.2

How strong are comparative efficacy data of new medicines at market entry?

Johan C.F. van Luijn
Nico Th Mes
Frank W.J. Gribnau
Hubert G.M. Leufkens

Submitted

Abstract

Aims

To evaluate the strength of comparative evidence of new medicines available at the moment of market authorization and used in a health technology assessment for advising clinical practice and supporting reimbursement decisions.

Methods

Information on comparative efficacy was obtained from public assessment reports on new medicines from the Health Care Insurance Board in the Netherlands. In order to analyse the strength of the evidence, evidence-based medicine (EBM) classifications for intervention studies were used, although these were adjusted for comparative research.

Results

For 19 (28%) of 69 new medicines it was not possible to form a clear opinion on comparative efficacy due the lack of data from clinical trials. In cases where an opinion was possible, for 8 (12%) medicines it was based on the highest evidence, a high-quality RaCT, and for 27 (39%) on the lowest evidence, the expert opinion.

Conclusions

More high-quality head-to-head trials, public access to all premarketing trials data and optimizing the use of adjusted indirect comparisons could ensure that assessments of comparative efficacy are based on a higher level of evidence.

Introduction

The development of new medicines has important consequences for the quality and the cost of health care. As resources for health care are limited, choices must be made and rational choices need to be informed on the basis of evidence. International developments in the use of methodologies like health technology assessment (HTA), evidence-based medicine (EBM) and grading the quality of evidence (GRADE) points to strong political and clinical support for a rational decision-making process [1-4]. The assessment of medicines is a clear example of this, given the marketing authorization process and the use of cost-effectiveness analyses.

New medicines are approved for entry onto the market if the benefit/risk profile has been shown to be favourable, i.e. the therapeutic efficacy has been sufficiently substantiated and the risks in terms of adverse effects are acceptable. Randomized controlled trials form the pivotal cornerstone for building evidence for assessing this balance. Placebo controlled trials are widely considered as the most robust evidence, as they measure the total pharmacological effect of the drug, the absolute efficacy [5]. However, faced with a new authorized medicine, health technology assessment organisations, doctors, formulary committees and reimbursement authorities are especially interested in the advantages and disadvantages of the new medicine compared with medicines already used in clinical practice for the same therapeutic indication [6]. For this purpose an optimal study design would be a randomized controlled trial of the new medicine with an existing medicine as control group, a so-called randomized active control trial (RaCT). Conducted as a premarketing trial to demonstrate the efficacy, RaCTs have the additional advantage of information about the comparative (relative) efficacy of the new medicine.

In a previous study we found that one out of two new medicines had been studied in a premarketing RaCT and one-third of these studies had been published at the moment of market authorization [7]. This lack of comparative data on new medicines at the moment of market authorization greatly hampers the assessment of comparative efficacy on the basis of the most robust evidence. Nevertheless an assessment has to be made in a case of a submission for reimbursement or where there is a wish – or pressure is being exerted – to prescribe the new medicine. The best available evidence is used in the absence of a better scenario. An important question is how strong the data are in terms of the likelihood of bias. The current model of evidence-based medicine categorizes different types of evidence and ranks these according to the likelihood of bias [8].

The aim of this study was to evaluate the strength of comparative evidence of new medicines available at the moment of market authorization and used in a health technology assessment for advising clinical practice and supporting reimbursement decisions.

Methods

Information about comparative efficacy

For information about the assessment of comparative efficacy we analyzed the public assessment reports on the therapeutic value of new medicines as used by the Health Care Insurance Board in the Netherlands, a national health technology organisation [9].
The evaluations are based on a comparison of drug properties (such as efficacy, safety, applicability, convenience and clinical experience) with other available and recommended treatment options [10]. Pharmaceutical manufacturers are invited to submit dossiers to support these evaluations. An independent committee of experts with members from a variety of backgrounds, including doctors, pharmacists, health economists, as well as advisers from different specific clinical specialisations, oversees the evaluations, resulting in opinions on the therapeutic value of a medicine to support reimbursement decisions and recommendations regarding drug prescribing.

We selected all assessment reports of new medicines with a new active substance for which an application was submitted for an HTA evaluation within two years after a European market authorization was granted between 1999 and 2005. In a previous study on the availability of premarketing randomized active control trials (RaCTs), we analyzed the same cohort of new drug applications [7]. From the assessment reports we extracted the conclusions on differences in efficacy (more, similar, less or unclear) and the substantiating evidence. For this analysis we classified the conclusions into two main outlines: a clear opinion (more, similar or less) or no clear opinion (differences are unclear). For the medicines we made a distinction between medicines which were or were not studied in premarketing RaCTs.

Hierarchy of evidence and analysis

For addressing the question of how strong the evidence was on which the expert committee had to rely, we used one of the available evidence-based medicine classifications [11]. These classifications categorize different types of evidence and rank them according to the likelihood of bias. Several systems exist, which generally differ in choice of subdivisions of

the main levels [2,8]. The main levels of evidence for intervention studies are: at the highest level systematic reviews and high-quality randomized controlled trials, then randomized control trials of a lower quality (greater likelihood of bias), non-randomized trials, with expert opinions having the lowest level of evidence. For our analysis we used the same main levels, although they were adjusted to the specific evidence needed for the assessment of comparative efficacy.

We therefore restricted the level of randomized trials to direct comparisons of the new medicine with the most appropriate comparator as the active control, and the level of non-randomized trials to indirect comparisons. All trials with methodological limitations, such as open studies, we considered as RaCTs of a lower quality, despite obvious and understandable reasons for this limitation. We restricted indirect comparisons to adjusted indirect comparisons because different methodological studies show that these comparisons should be used when making indirect comparisons [12-14]. In this approach the comparison of both medicines of interest is adjusted by the results of their direct comparison with a common control group. In this way the strength of the original RCTs is still partially used, unlike with a direct comparison of the relevant single arms of the trials (naive indirect comparison). We regard other types of comparisons as expert opinion: the lowest evidence. Based on these considerations, we used the following hierarchy of evidence for comparative research (box).

Box – Hierarchy of evidence for comparative research

A. High-quality randomized active control trial (RaCT) or a systematic review of RaCTs.
B. Lower quality RaCT.
C. Adjusted indirect comparison.
D. Expert opinion.

All studies including data on comparative efficacy were graded according to the above defined hierarchy of evidence for comparing treatments. The extraction of data on comparative efficacy and the grading of evidence were carried out independently by two members of the research team (JvL, NM). Differing results were discussed and solved by consensus.

Results

We could identify 82 new medicines, authorized for the EU-market between 1999 and 2005, for which an application was submitted for an HTA-evaluation within two years after authorization; 94% even within one year. For our analysis on comparative efficacy we excluded 13 new medicines as no eligible and labelled alternative medicine was available as comparative treatment. This was the case with most of the orphan drugs, but also medicines intended for diseases such as chronic diabetic ulcers or stress urinary incontinence which have few or no alternative pharmacological alternatives.
For 69 medicines we analyzed the conclusions on comparative efficacy and the substantiating evidence. Table 1 gives an overview of the medicines involved and the results of the analysis.

For 19 (28%) new medicines it was not possible to form an opinion on comparative efficacy due the lack of data from clinical trials. In cases where a clear opinion (more, similar or less) was possible, for 8 (12%) medicines it was based on the highest evidence, a high-quality RaCT, and for 27 (39%) on the lowest evidence, the expert opinion.
A premarketing comparative trial was available for 42 (61%) medicines; for 22 (52%) medicines the opinion on comparative efficacy was based on these studies. The comparative efficacy of one medicine was based on an adjusted indirect comparison.

Discussion

This analysis shows that in 70% of the studied cases it was possible to form a clear opinion on the comparative efficacy (more, similar or less) of the new medicine. However, only for a few (12%) could the strength of the comparative data be ranked as high-quality. Especially the open study design was reason to qualify RaCTs as lower quality. In about 40% of the evaluations the body of evidence was formed by only an expert opinion.

Given the fact that, in theory, for all the new medicines studied, an alternative treatment was available at the time of the evaluation, a key question remains why this did not result in a better body of comparative evidence. Different explanations can be given. The most important reason was that in the premarketing phase 27 new medicines were not studied in comparison with an alternative treatment that was already being used in clinical practice. However, this analysis also makes it clear that not only the availability of premarketing

RaCTs as such is important, but also the question of the accessibility to comparative data and the quality of the data. Given the fact that the assessments of the Health Care Insurance Board in the Netherlands, like other health technology organisations, have to rely on publicly available data, an important question is how accessible premarketing comparative information is [10]. Although public assessment reports, like the European Public Assessment Reports (EPARs), provide a very useful resource for acquiring summarized and extracted clinical information from the registration dossiers, access to the full data often remains limited for outside parties. Therefore, for 7 medicines (abacavir, amprenavir, emtricitabine, ivabradine, leflunomide, peginterferon alpha-2a, tipranavir) the evidence was classified as expert opinion, as the comparative studies with the right comparator were not accessible as a publication or an accepted manuscript. For seven other medicines an indirect comparison was made as the chosen comparator in the RaCT was not in line with the recommended standard treatment. Reasons for not conducting an indirect comparison are the preliminary data (this is frequently the case with market authorizations under exceptional circumstances [atazanavir, lopinavir]) and methodological limitations. As result it was not possible to form a clear opinion about comparative efficacy for 19 products (6 with and 13 without an RaCT).

In recent years various studies have shown that, in the absence of head-to-head trials, an adjusted indirect comparison is a welcome additional tool for the assessment of differences between medicines [15-17]. In our study we found that 21 (31%) of the assessments were based on indirect comparisons, only one of which was a publication of an adjusted indirect comparison[18]. The remainder of the indirect comparisons made by the expert committee were not carried out according to a fixed methodology. The significant importance of indirect comparisons in HTA evaluations would favour a more systematic approach. The further development of this methodology also provides possibilities for making these studies compulsory in relation to applying for inclusion in a reimbursement system. The increase in the number of systematic reviews of existing medicines and, in particular, of standard treatments, also presents the possibility of combining these results – in a follow-up study – with the results of the clinical studies of a new medicine in an indirect comparison. With respect to patient selection, clinical parameters, etc., the possibility of such a follow-up step could be taken into account when setting up a premarketing clinical study. This is an important condition as, even in our analysis, methodological problems made an indirect comparison impossible for about 30% of the new medicines studied. Due to the fact that an adjusted indirect comparison is in any case cheaper and less time-consuming than a head-to-head trial, it offers the possibility of bringing the assessment to a higher level.

Table 1 - Body of evidence in the assessment of comparative efficacy of new medicines (1999 – 2005) soon after market entry

Conclusion comparative efficacy	Level of evidence	Premarketing RaCTs available	Premarketing RaCTs not available	Total
		N = 42	N = 27	N = 69
Clear opinion	**A. Well designed RaCT/ systematisch reviews RaCTs**	bimatoprost, brinzolamide, choriogonadotropin alpha, fondaparinux, olopatadine, pegfilgrastim, travoprost, valdecoxib		8 12%)
	B. Less quality RaCT	aripiprazole, capecitabine, cetrorelix, darbepoetin alfa, fosamprenavir, ganirelix, ibritumomab tiuxetan, insulin aspart, insulin detemir, insulin glulisine, peginterferon alpha-2a, sevelamer, sirolimus, voriconazole		14 20%)

	C. Adjusted indirect comparison		adalimumab	1 (2%)
	D. Expert opinion	abacavir, amprenavir, bevacizumab, emtricita-bine, fulvestrant, ivabradine, leflunomide, norelgestromin comb, peginterferon alpha-2b pioglitazone, rasagiline, rosiglitazone, temozolo-mide, tipranavir	anakinra, bexarotene, efalizumab, erlotinib, etanercept, imatinib, levetiracetam, lutropin alfa. pregabalin, strontium ranelate, tadalafil, vardenafil, zonisamide	27 (39%)
No clear opinion		atazanavir , darifenacin efavirenz, lopinavir comb, nateglinide, zaleplon	adefovir, anagrelide, aprepitant, bosentan, botulinum toxin b, desloratidine, enfuvirtide, memantine, miglustat, pergvisomant, posaconazole, tenofovir, teriparatide	19 (28%)

RaCT: randomized active control trial

In our analysis we limited ourselves to comparative efficacy. Other properties, such as comparative safety, applicability, convenience, are also important for assessing the position of a new medicine in therapy. Efficacy was chosen as it was the primary objective of the pivotal premarketing trials and the calculation of the power of the study is often based on this objective.

The aim of the study was to provide a look at the way comparative efficacy has been assessed by a national HTA organisation at the moment a new medicine comes onto the market. Unlike upon market authorization, hardly any international requirements exist with respect to how manufacturers should provide data on comparative evidence. This study shows that, although at the time of the evaluation an alternative treatment was available for all the new medicines studied, the strength of the body of evidence on comparative efficacy thus far was rather limited. How can we get this situation to move in a better direction? In order to improve the quality of the assessment of comparative efficacy, manufacturers should have an interest in collecting comparative information during the development of a new medicine. Comparative data on a new medicine in a case where alternatives are available could be a condition for reimbursement. Results of head-to-head trials or at least of adjusted indirect comparisons should form part of a submission for reimbursement. In addition to this, we strongly support making the full data from all premarketing trials publicly available, and making this a condition to admission onto the market. Health technology organisations, doctors and reimbursement authorities should be given access to the same data as registration authorities in order to be able to properly assess the position of new medicines in therapy.

This analysis shows that in 70% of the new medicines studied, premarketing data were available for a conclusion about comparative efficacy. However, only for a few (12%) of the applications could the body of evidence be ranked on the highest level and for about 40% on the lowest level, the expert opinion. More high-quality head-to-head trials, public access to all premarketing trials data and optimizing the use of adjusted indirect comparisons could ensure that the assessment of comparative efficacy is based on a higher level of evidence.

References

1. Sackett DL, Straus SE, Richardson WS, et al. Evidence-based based medicine. How to practice and teach EBM. 2nd. Edinburgh: Churchill Livingstone, 2000.
2. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
3. Banta D. What is technology assessment? Int J Technol Assess Health Care 2009;25 Suppl 1:7-9.
4. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996;312:71-2.
5. Lewis JA, Jonsson B, Kreutz G, Sampaio C, van Zwieten-Boot B. Placebo-controlled trials and the Declaration of Helsinki. Lancet 2002;359:1337-40.
6. International Society of Drug Bulletins. ISDB declaration on therapeutic advance in the use of medicines. Paris: International Society of Drug Bulletins, 2001.
7. van Luijn JCF, Gribnau FW, Leufkens HG. Availability of comparative trials for the assessment of new medicines in the European Union at the moment of market authorization. Br J Clin Pharmacol 2007;63:159-62.
8. Oxford Centre for Evidence-based Medicine. Levels of Evidence. 2009; Accessed in September 2009 via http://www.cebm.net/index.aspx?o=1025.
9. Banta D, Oortwijn WJ. The Netherlands. Int J Technol Assess Health Care 2009;25 Suppl 1:143-7.
10. College voor Zorgverzekeringen. Procedure beoordeling extramurale geneesmiddelen. Diemen: CVZ, 2007.
11. CBO. Evidence-based Richtlijnontwikkeling. Handleiding voor werkgroepleden. 2007; Accessed in October 2009 via http://www.cbo.nl/Downloads/222/EBRO_handl_totaal.pdf.
12. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997;50:683-91.
13. Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ 2003;326:472.
14. Song F, Harvey I, Lilford R. Adjusted indirect comparison may be less biased than direct comparison for evaluating new pharmaceutical interventions. J Clin Epidemiol 2008;61:455-63.
15. Gartlehner G, Moore CG. Direct versus indirect comparisons: a summary of the evidence. Int J Technol Assess Health Care 2008;24:170-7.
16. Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, et al. Indirect comparisons of competing interventions. Health Technol Assess 2005;9:1-iv.
17. Song F, Loke YK, Walsh T, Glenny AM, Eastwood AJ, Altman DG. Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published systematic reviews. BMJ 2009;338:b1147.
18. Hochberg MC, Tracy JK, Hawkins-Holt M, Flores RH. Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis 2003;62 Suppl 2:ii13-ii16.

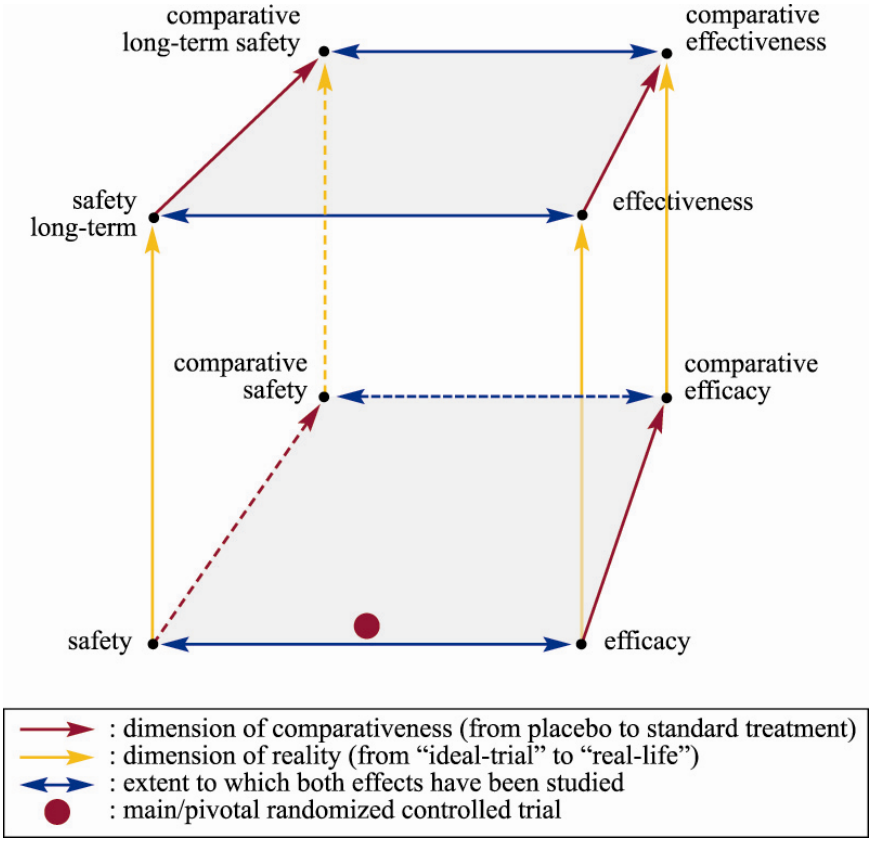
Chapter 5

General discussion

General discussion

We all are aware that most of our knowledge on the clinical effects of a new medicine at the moment of its market entry is limited. As no single study can answer all of the questions and insights relevant for therapy and as healthcare changes, the development of knowledge is at best termed as a continuous learning cycle [1,2].
Clinical research on the clinical effects of medicines was presented in Chapter 1 as the Box with Studies on Benefits and Risks. We distinguished two dimensions in the development of the clinical research about efficacy and safety: the basic properties of every medicine (figure 1).

Figure 1 - Box with Studies on Benefits and Risks



The dimension of reality gives more insight into the effects of use in daily practice (effectiveness, long-term safety) and the dimension of comparativeness provides insight into differences and similarities with other available treatments (comparative effectiveness and comparative long-term safety). During the life cycle of a medicine the Box gets filled with data of different types of clinical trials and registries. But what knowledge is needed and is available at market entry?

Pharmacotherapy is about the use of medicines in patients. The key questions are: what is the right medicine for a given patient, at what dose and with what form of guidance? In other words, pharmacotherapy is all about making choices with respect to medicines [3-5]. It is about the differences between medicines, and which product is the best one for a given patient. Knowledge on the absolute efficacy and safety is important, but on its own it is not enough to make an optimal choice.

This thesis focuses on comparative information of new medicines at the moment of market authorization: availability, quality and usage. Until now, the literature has lacked quantitative data and specific analyses. Our studies are an attempt to fill this gap. In other words, what kind of comparative information is available at the bottom of the Box. The main findings are therefore presented and discussed in the light of their significance and the consequences for the assessment of new medicines.

Combined findings thesis

Main results

For our analyses we selected new medicines with a new active substance that were authorized by the European Commission between 1999 and 2005, based on a positive opinion of the Committee for Medicinal Products for human Use (CHMP). For information about the premarketing main/pivotal randomized controlled trials (RaCTs), we used the European Public Assessment Reports (EPARs).
We identified 122 new medicines in that period, of which 58 (48%) had been studied in comparison with an existing medicine. A new mechanism of action was shown to be a limiting factor in providing comparative information (OR 3.37, 95% CI 1.50, 7.56). We found that 15 (10%) RaCTs were set up with the aim of demonstrating a difference

(superiority study). Of the 122 new medicines, 13 (10%) demonstrated a statistically significant difference in efficacy in comparison with an existing medicine.
In order to know whether new clinical trials after market approval could compensate for the lack of comparative information, we did a case-study on etanercept, one of the medicines without a premarketing RaCT. After ten years of etanercept use, we found 84 new randomized trials, 54 (64%) of which focussed on studies searching for new indications. The six head-to-head trials insufficiently answered the reasonable demands from clinical practice for more specific comparative information.

Two distinctive characteristics of premarketing RaCTs are the choice of comparator and the assay sensitivity of the trial. We studied both characteristics as typical quality aspects of comparative trials. Trials with the most suitable comparator could be an important source of comparative information. For the 58 new medicines with RaCTs, we found that 47 (81%) were compared with the recommended standard treatment in at least one trial; in 71% of all RaCTs, the comparator was the same as the recommended standard treatment.
Trials with the objective of demonstrating an equivalent or noninferior efficacy compared with the active control must have the ability to distinguish an effective medicine from an ineffective or less effective medicine (assay sensitivity); the comparator must therefore be effective in the setting of the comparative trial. Additional historical information on the superiority trial of the comparator is needed when designing and reporting a comparative trial. In an open letter to the regulatory authorities, we drew attention to the problems we experienced interpreting the public data of noninferiority and equivalence trials, as these trials provide insufficient additional information on the comparator in public sources of information on these trials, such as publications and your assessment reports.

Because most of the premarketing RaCTs were not published at the moment of market authorization, we determined the time-lag between market authorization and peer-reviewed publication. With a follow-up period of at least three years, this analysis was restricted to medicines authorized between 1999 and 2003. One year after market authorization, 59% had been published, after two years 78% and after three years 83%. After that period most of the RaCTs remained unpublished. In some cases these studies were of unmistakable public interest as they had influenced the benefit-risk assessment by the registration authorities. After market approval, decisions have to be made on reimbursement of the new medicines and their inclusion in clinical guidelines. For 50 (72%) of the new medicines studied, sufficient premarketing data were available for a conclusion about comparative

efficacy. However, for only a few (12%) of the applications the body of evidence could be ranked at the highest level and for about 40% at the lowest level: the "expert opinion".

Conclusions

Which conclusions can be drawn from the combined results of these studies?
First the good news. In the premarketing phase, about one out of two new medicines has been studied in a comparative clinical trial and for four out of five medicines a comparison has been made with the recommended standard treatment for the therapeutic indication for which the new medicine was studied. For most of these new medicines this is a good starting point for an assessment of their position in therapy. However, a relevant bottleneck will be accessibility to the full data of the study, either as a publication or at least as an accepted manuscript.
The bad news is that only about a third of the comparative trials had been published at the moment of market authorization. Over time, most of the trials are published subsequent to market entry, however, a delay of two or three years represents an obstacle to optimal decision-making on prescribing and reimbursement at the moment when the need is greatest.

The medicines without a randomized active control trial include most of the new products with a new mechanism of action. This is unfortunate because in clinical practice comparative information is badly needed for this type of new medicine. As a new working mechanism is involved, expectations are that these can be used to treat patients who – up till that moment in time – had responded insufficiently to existing medication or suffered too many side effects. Comparative studies could clarify new options for treatment. Furthermore, we conclude that in practice, in cases where there is a lack of (adequate) comparative trials, an attempt will be made to assess comparative efficacy on the basis of indirect comparison. However, most of these comparisons are not carried out according to a fixed methodology of adjusted indirect comparison.

Finally we note that generally most of the premarketing studies do not focus on profiling the new product. This is not to be expected of new medicines in this part of their life cycle, as the focus of the research is to demonstrate a favourable absolute efficacy and safety and a favourable benefit/risk ratio, and noninferiority or equivalence studies suffice for that objective. However, for this type of studies we found that information is lacking that verifies the quality of crucial topics such as assay sensitivity. Though the goal of developing new medicines should be to improve treatment, this is not always apparent from

the objectives and outcomes of premarketing research. Improved efficacy had been demonstrated for one out of ten new medicines only.
Summarised, at the moment of market entry, for about four out of ten medicines the bottom half of the Box is filled with the results of comparative trials, which generally make use of the right comparator, however, in most cases not with the objective of demonstrating differences, but of demonstrating efficacy.

Meaning of the results: comparisons needed

What is the meaning of these results for future premarketing clinical research on new medicines and their assessment with respect to prescription and reimbursement?.
Research into the development of new medicines focuses primarily on market authorization and therefore on the stipulated requirements presented in the official guidelines. However, in recent years market authorization no longer forms a guarantee that the product will actually be prescribed and used. Decisions on the prescription and reimbursement of new medicines depend increasingly on proven added value and decisions on their cost-effectiveness [6-9]. This means that comparative research will have to gain a more prominent position during the development of a new medicine. Above all it benefits the optimal use of new innovations in pharmacotherapy. More incentives are needed in order to obtain more adequate comparative information based on clinical research and to realize better access to the full data of premarketing trials. It clearly carries a good deal more weight when health authorities use economic arguments to achieve this goal. We therefore propose that the reimbursement of a new medicine should depend of the availability of adequate comparative information: a randomized active control trial with the right comparator or an indirect adjusted comparison if there are plausible and consequential reasons for not carrying out a direct comparison. An important condition to achieving regulatory pressure is close co-operation between the reimbursement authorities within the European Union for stipulating uniform requirements for their decisions.

Comparative research: hurdle or serving progress?

We are aware that such proposals will encounter resistance, as obligations are often perceived as a hurdle [6]. However, experience teaches us that we should also regard this as a way of improving the quality of decision-making. In this connection it is interesting to

take a backward glance at history and the development of market authorization [10]. In the nineteen-fifties there was a growing realisation in many Western countries that the marketing of medicines was in need of greater government control in order to protect public health. Up till then, every manufacturer could start marketing any product with a medical claim. An important trigger that brought this development into overdrive was the Softenon drama. Thousands of deformed children were born of mothers who had taken the sleeping pill thalidomide during pregnancy. This incident led to the creation of all sorts of national committees for assessing market authorization on the basis of the criteria quality, safety and efficacy. Many years later this led, among other things, to a growing centralisation of assessment within the EU in order to deal with internal trade barriers to commercial products, including medicines. The method of assessment used is essentially unaltered, though it has been adjusted according to scientific developments in research methodology, statistics, clinical pharmacology, pharmacotherapy, etc. The result of this process of development in market regulation is that nowadays we have high-quality, safe and effective medicines.

During recent decades, on national levels a development has been towards a greater role for government in the use of medicines for health care, though now based on the necessity of controlling costs. This is obviously imperative to guarantee proper health care for all citizens. This development was provoked in particular by the higher prices of new medicines. However, the increase in costs applies not only to medicines but also to other health care technologies. Improved insight into similarities and differences between health care technologies is of essential importance for health care policy in many Western countries. This also explains the development in these countries of health technology organisations, reimbursement systems, and, in practice, promotion or the compulsory made use of formularies and guidelines, etc.

Just as it was the need of a favourable benefit /risk ratio that triggered important alterations to the system in the past, the need of greater value for money has also triggered alterations in the system, so that greater account is being taken of cost-effectiveness. In order to improve the quality of assessments of new medicines for this purpose, carrying out premarketing comparative studies should be obligatory, just as in the past efficacy and safety studies were made obligatory for market authorization.

More and better premarketing comparative research

More new medicines studied in an randomized active control trial and more studies with the objective of demonstrating differences will increase the strengths of the evidence used for assessing the position of new medicines in therapy [11-15]. Comparative research in service of the progress in pharmacotherapy.
The results of our studies point to the interest in more and better studies on the quality of cost-effectiveness analyses. In many Western countries cost-effectiveness analyses play an important role in reimbursement decisions. As these economical analyses are always based on a comparison between different treatments, adequate comparative clinical data are crucial for the reliability of these studies [16-18]. The quality of cost-effectiveness analyses can only be as good as that of the trials on which they are based [19]. We doubt whether the strongest evidence of comparative information is always available for cost-effectiveness evaluations. In view of the importance of comparative studies for cost-effectiveness research, we would have expected our study to find more active controlled trials over the years. Our study did not disclose such a trend. Moreover, we found far fewer active control trials involving new medicines with a new mechanism of action. Because expectations regarding the therapeutic advantages of this type of medicines are high, as also are prices, one should expect precisely these medicines to be the subject of comparative studies underpinning the clinical data in a cost-effectiveness evaluation.

The need of comparative information plays also a role in the international discussion on reforming market authorization [20,21]. Some argue that failing to require comparative studies as part of the approval process leaves us with no means of ensuring that that they will ever be conducted; with the inevitable result that they are usually not [22]. Our case-study with etanercept supports this view. Ten years after first being expressed in the editorial of an authoritative medical journal, the desire from clinical practice for certain comparative studies remains unsatisfied. However, for the product in question, etanercept, the lack of such information has not prevented it from obtaining an important position in the treatment of rheumatoid arthritis. The significance of its new mechanism of action– not only for the treatment of rheumatic arthritis, but possibly also for other auto-immune diseases – resulted in research priorities going elsewhere. This inevitably leads to a reduced need of comparative research because where comparative trials are lacking, in clinical practice, implicitly and explicitly, assessments will be made based on experience or on indirect comparisons. However, the strength of this type of evidence is lower than that of a randomized active control trial.

Better access to full data of premarketing trials

A second proposal relates to the accessibility of data on premarketing research in order to get insight in the design and conduct of the trial and the quality of the results. To assess the usefulness of these studies for prescribing and reimbursement decisions, the full data of these trials should be publicly available. Failing to publish the results of clinical trials substantially limits the possibility of making an evidence-based assessment of a new medicine and conducting systematic reviews [23].

Given the fact that health technology assessment organisations, doctors and reimbursement authorities usually have to rely on publicly available data for their assessments and decision-making [7,24], an important question is how accessible such comparative information is. In our analysis we used the European Public Assessment Reports (EPARs) for information on main/pivotal trials. Although these public assessment reports provide a very useful resource for acquiring summarized and extracted clinical information from the registration dossiers, access to the full data often remains limited for outside parties. They have to rely on peer-reviewed publication of these premarketing trials. In general, scientific research should always be published [25,26], but research and publication are two separate entities, each with its own interests and rules. This partly explains the "publication gap" found in our study. For this reason we recommend that the results of all clinical studies that are part of procedures for market entry are included in a "trial results database", as a condition for granting market authorization. The significance of these studies for society is so great that all the data of these studies should be made accessible not only to registration authorities, but also to health care professionals, policy-makers and patients. The initiative for this could be taken by the FDA and the EMEA, united in the ICH. We feel that, in order to ensure the usefulness of trial results databases as a reference for evidence-based decision-making and conducting systematic reviews, they must be expected to meet the same requirements that are stipulated by the International Committee of Medical Journal Editors for an acceptable clinical trial registry [27,28]. The database must be open to electronic search and accessible to the public free of charge; it should be open to all who wish to register, it should be non-profit-making, and it should have a mechanism for ensuring the validity of the registration data. Moreover, the results should be reported in a comprehensive and uniform format. In order to give health care professionals, policy-makers and patients the opportunity of using the same information as regulatory authorities, we argue for a standardized public registration of the results of trials as a condition for market authorization.

Consequences of proposals

We are aware that proposing more and better comparative studies is easier said than done. However, these proposals are not a new phenomenon. During recent years there has been a great deal of discussion about the necessity of reforming the system of market authorization [20,21]. In this context, one of the limitations in the present system that is constantly referred to is the lack of data from comparative medicinal research [14,29]. Thoughts often go out to solutions involving the phased authorization of medicines with obligations for further research during this period. A follow-up to this are the discussions taking place regarding the desirability of linking phased authorization to conditional reimbursement [30]. Furthermore, as figure 1 illustrates extensive post-marketing studies are necessary in order to actually obtain insight into (comparative) effectiveness and safety [31-34]. The importance of developing our knowledge on this matter is clearly illustrated by recent initiatives in the USA on the $1.1 billion plan to support comparative effectiveness research [35-37]. The continually rising costs of developing new medicines, partly due to the requirements of the registration authorities, also demand that these requirements are subject to a critical analysis [38]. The extra studies we are currently proposing will not be regarded as a possibility for economising in this area.

However, the results of our study do raise a fundamental question that needs to be addressed within the framework of the above-mentioned discussions. Henceforth, in studies that focus on demonstrating the efficacy of a new medicine, why not make superiority studies with an active control, instead of with a placebo, the point of departure. Just as with a placebo-controlled study, internal validity is not open to dispute [39], in addition to which answers would be provided to the question of both efficacy and comparative efficacy. Placebo studies are only indicated if no alternative active product is available for the indication being studied. The need for more and better comparative research is important enough to be given serious consideration in discussions on reforming the requirements for market authorization.

Limitations of the thesis

It should be noted that our analysis is based on information available at the moment of market authorization of medicinal products regulated through the EU centralized procedure. In making this choice, we had to take certain limitations into account. We limited the

choice to new authorizations under the EU centralized procedure only because these assessment reports are public. Until October 2005, under the decentralized procedure there was no obligation to provide a public assessment report for new products. Marketing authorizations were also granted under the decentralized procedure during the same period in which our study was carried out; for example, in the Netherlands 49 medicines with a new active substance. Although the centralized procedure is compulsory for biotechnological products and orphan drugs, we expect the number of drugs with an RaCT to be lower under the centralized than under the decentralized procedure.
The most important source of information on premarketing trials were the EPARs of the various products. The EPAR provides insight into which clinical trials are submitted by the industry. The scientific discussion of the Committee for Medicinal Products for Human Use (CHMP) is informative as it provides not only a description of the design and the results of the studies, but also weighted information about the significance of the published data. Nevertheless, a disadvantage of the EPAR is the variable quality of the description of studies [40]. This applies in particular to the medicines at the start of our study. Uniformity has clearly improved over the course of time. However a further analysis of publication bias in the study regarding the publication gap was therefore not possible.

Finally

The studies in this thesis are about pharmacotherapy, the treatment of patients with medicines: the key questions what is therapeutically needed and justifiable in view of provisions in force and the choices that have been made. Costs can play a role in the final choice of a medicine, but this issue is not the field of attention of pharmacotherapy.
The purpose of the studies in this thesis is to shed light on the issue of adequate comparative information at a crucial moment in the life cycle of a new medicine: their entry into the dynamic world of clinical practice. Comparative information will help to guide newcomers, that per definition always will be unfinished upon entry in their life cycle, in finding their position in the treatment of patients, a privileged one if the evidence dictates so. We hope and advocate that this information will be in the future an integral part of the objectives of premarketing clinical research.

References

1. Sheiner LB. Learning versus confirming in clinical drug development. Clin Pharmacol Ther 1997;61:275-91.
2. Stolk P. From new molecules to leads for innovation. Studies on the post-innovation learning cycle for pharmaceuticals. 2008;
3. de Boer A. Farmacotherapie, eerste keuze? Oratie Universiteit Utrecht. Utrecht, 2002.
4. College voor Zorgverzekeringen. Farmacotherapeutisch Kompas. 2008. Diemen: Health Care Insurance Board, 2008.
5. Nelemans FA. De toekomst der farmacotherapie. Oratie Rijksuniversiteit Utrecht. Alphen aan den Rijn: Stafleu's Wetenschappelijke Uitgeversmaatschappij, 1984.
6. Cohen J, Stolk E, Niezen M. The increasingly complex fourth hurdle for pharmaceuticals. Pharmacoeconomics 2007;25:727-34.
7. Rawlins MD. 5 NICE years. Lancet 2005;365:904-8.
8. Schubert F. Health technology assessment. The pharmaceutical industry perspective. Int J Technol Assess Health Care 2002;18:184-91.
9. van Oostenbruggen MF, Jansen RB, Mur K, Kooijman H. Penny and pound wise: pharmacoeconomics from a governmental perspective. Pharmacoeconomics 2005;23:219-26.
10. van der Giesen WF, Hekster YA. De geneesmiddelenregistratie. In: Het geneesmiddel. 5e herz. dr. Maarssen: Elsevier Gezondheidszorg, 2009:
11. Dent TH, Hawke S. Too soon to market. BMJ 1997;315:1248-9.
12. Gale EA. Lessons from the glitazones: a story of drug development. Lancet 2001;357:1870-5.
13. Garattini S, Bertele' V. How can we regulate medicines better? BMJ 2007;335:803-5.
14. Henry D, Hill S. Comparing treatments. BMJ 1995;310:1279.
15. Kaplan W. Comparative effectiveness of medicines and use of head-to-head comparative trials. In: Priority medicines for Europe and the world. Den Haag: Ministry of Health, Welfare and Sport, 2004:
16. Cookson R, Hutton J. Regulating the economic evaluation of pharmaceuticals and medical devices: a European perspective. Health Policy 2003;63:167-78.
17. Drummond M, Jonsson B, Rutten F. The role of economic evaluation in the pricing and reimbursement of medicines. Health Policy 1997;40:199-215.
18. Hjelmgren J, Berggren F, Andersson F. Health economic guidelines--similarities, differences and some implications. Value Health 2001;4:225-50.
19. Rennie D, Luft HS. Pharmacoeconomic analyses: making them transparent, making them credible. JAMA 2000;283:2158-60.
20. Ray WA, Stein CM. Reform of drug regulation--beyond an independent drug-safety board. N Engl J Med 2006;354:194-201.
21. Wood AJ. A proposal for radical changes in the drug-approval process. N Engl J Med 2006;355:618-23.
22. Avorn J. Powerful medicines. The benefits, risks, and costs of prescription drugs. Revised and updated. New York: Vintage Books, 2005.
23. Reidenberg MM. Conflict of interest and medical publication. Sci Eng Ethics 2002;8:455-7.
24. College voor Zorgverzekeringen. Procedure beoordeling extramurale geneesmiddelen. Diemen: CVZ, 2007.
25. Chalmers I. Underreporting research is scientific misconduct. JAMA 1990;263:1405-8.
26. Wager E, Field EA, Grossman L. Good publication practice for pharmaceutical companies. Curr Med Res Opin 2003;19:149-54.

27. De Angelis C., Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med 2004;351:1250-1.
28. De Angelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Is this clinical trial fully registered?--A statement from the International Committee of Medical Journal Editors. N Engl J Med 2005;352:2436-8.
29. Comparative advantages of new drugs: French authorities are not sufficiently demanding. Prescrire Int 2005;14:75-8.
30. Niezen M, de Bont A, Stolk E, Eyck A, Niessen L, Stoevelaar H. Conditional reimbursement within the Dutch drug policy. Health Policy 2007;84:39-50.
31. Bombardier C, Maetzel A. Pharmacoeconomic evaluation of new treatments: efficacy versus effectiveness studies? Ann Rheum Dis 1999;58 Suppl 1:I82-I85.
32. Rawlins M. De testimonio: on the evidence for decisions about the use of therapeutic interventions. Lancet 2008;372:2152-61.
33. Schneeweiss S. Developments in post-marketing comparative effectiveness research. Clin Pharmacol Ther 2007;82:143-56.
34. Vandenbroucke JP. What is the best evidence for determining harms of medical treatment? CMAJ 2006;174:645-6.
35. Congressional Budget Office. Research on the Comparative Effectiveness of Medical Treatments: Issues and Options for an Expanded Federal Role. 2007; Accessed in September 2009 via http://www.cbo.gov/ftpdocs/88xx/doc8891/12-18-ComparativeEffectiveness.pdf.
36. Avorn J. Debate about funding comparative-effectiveness research. N Engl J Med 2009;360:1927-9.
37. Garber AM, Tunis SR. Does comparative-effectiveness research threaten personalized medicine? N Engl J Med 2009;360:1925-7.
38. Rawlins MD. Cutting the cost of drug development? Nat Rev Drug Discov 2004;3:360-4.
39. Lewis JA, Jonsson B, Kreutz G, Sampaio C, van Zwieten-Boot B. Placebo-controlled trials and the Declaration of Helsinki. Lancet 2002;359:1337-40.
40. Wieringa NF, Vos R, de Graeff PA. Comparative trials in registration files of cardiovascular drugs: comparator drugs and dosing schemes. Pharm World Sci 2001;23:28-30.

Summary

Samenvatting

Summary

In order to choose the right medicine when treating patients, the prescriber must have insight into the differences between medicines intended for treatment of the same disorder. That insight is obtained from studies in which these products have been compared with one another.
However, pharmaceutical companies are under no obligation to carry out comparative research with other medicines in order to obtain market authorization. All that is required is proof that the new product is efficacious and safe and that the benefit/risk profile has been shown to be favourable. The best evidence for this purpose is provided by studies in which the new product is compared with a placebo.
Nevertheless, there is a great need of results from comparative clinical research. There are many reasons for this. The range of products from which a choice has to be made is still increasing. Insight into added value is extra important due to the high prices of new medicines (value for money). In addition to this, during recent years the quality of the evidence in the process of making a choice (evidence-based medicine) is expected to meet stringent demands.

The lack of outcomes of comparative research upon the introduction of a new medicine is regarded as an important problem, and with good reason. However, statistics on the nature and extent of this problem are scarce.
The aim of this thesis is to shed light upon this problem by carrying out an evaluation of the availability, quality and the use of the comparative information on new medicines at the moment of market entry.

This thesis has five main chapters. In the first four we explain the problem and present our studies, which leads to the conclusion that is reached in chapter five. The following is a short explanation per section.

Chapter 1
In the first chapter we provide a general overview of the development of knowledge on the clinical effects of new medicines; we also explain the role played by comparative research and lastly we describe the objective and outline of this thesis.

Chapter 2
In the second chapter we focus on the availability of comparative information.

Chapter 2.1 describes our research into the number of new medicines studied, in the period prior to market entry, in a direct comparison with other medicines that were already available. For our research we selected all new medicines with a new active substance that were assessed for market authorization in the European Union (EU) between 1999 and 2005; new diagnostics and vaccines were excluded. For information on these medicines we used the public assessment reports (EPARs) of the Committee for Medicinal Products for Human Use (CHMP), the scientific committee of the European agency for the assessment of medicines (EMEA). We selected studies referred to in the EPAR as the most important randomized trials with an active control group (RaCT). During this period 122 medicines with a new active substance were granted market entry, 58 of which (48%) were studied in an RaCT. We found that 56 new medicines also had a new way of exerting their effect. This property turned out to be a limiting factor in the availability of RaCTs.

As the aim of developing new medicines is to improve the treatment of patients, we investigated for how many products sufficient information was available to be able to speak of improved efficacy. The study and the results are reproduced in chapter 2.2. This analysis reveals that 15 (10%) RaCTs of the new medicines authorized for marketing in the EU in the period 1999-2005 were set up with the aim of demonstrating a difference (superiority study). Of the 122 new medicines, 13 (10%) demonstrated a statistically significant difference in efficacy in comparison with an existing medicine. This does not necessarily mean that these medicines were actually an improvement for treatment. Apart from efficacy, the evaluation will always have to involved other properties, such as safety; furthermore, the improved efficacy must be seen within the contest of the study set-up (type of patient, choice of comparative product) and particularly, in the long run, the clinical relevance of the outcomes of the study. The analysis shows that a critical evaluation of the results of comparative research is required in order to determine the specific place of a medicine in treatment.

In chapter 2.3 we describe the study in which we examined whether the lack of comparative information at the moment of market entry is subsequently compensated with new research. This was studied for the medicine etanercept. The introduction of this product onto the market at the end of 1998 was discussed in the literature as an important new possibility for treating patients with rheumatoid arthritis. The emphatic comment was made regarding the

need of comparative research with other products (infliximab, combination DMARDs), as such studies were lacking at the time. In the 10-year period after its introduction, 84 randomized studies were conducted with etanercept, 6 of which were comparative studies involving the approved indications. However, this is insufficient to satisfy the specific requirement of comparative information. Furthermore, the study shows that 54 (64%) trials focused on widening the use of etanercept to include new therapeutic indications, both approved and not (yet) approved.

Chapter 3

The third chapter discusses the quality of the comparative information. Particular attention is given to two characteristic properties of comparative studies, the choice of comparative product and the assay sensitivity, the ability to distinguish an effective medicine from one that is less effective or ineffective.

Chapter 3.1 is a description of the study in which we examine the extent to which the choice of comparator is in line with the standard treatment recommended in practice for the indication for which the efficacy of the new product was being studied. The right choice is important not only for demonstrating efficacy and safety but also for determining the new product's place in treatment. However, making a choice is hampered because the standard treatment can vary depending on place and time. What was the best choice at the start of the study may have been superseded at the moment of market entry on the basis of new insights, which furthermore can differ per country and even locally.
For this study we used the RaCTs (N= 153) from the study described in chapter 2.1. For the choice of recommended standard treatments, use was made of the annual editions of the Farmacotherapeutisch Kompas, a Dutch pharmacotherapy reference manual. We compared the control groups in the RaCTs with the recommended standard treatment at two different moments, the year in which the product was granted market entry, and three years earlier, the supposed moment of setting up the comparative study. This analysis shows that at the moment of market entry, the active control group is in line (the same active substance/therapeutic class and dosage) with the recommended standard treatment in 108 (71%) of the RaCTs, and that 41 (81%) new medicines were subjected to such a comparison in at least one study. In cases where there was a difference, it did not involve a different recommended standard treatment three years earlier.

Chapter 3.2 takes the form of an open letter to the registration authorities, in which we asked for attention to be paid to greater transparency on the role played by superiority

studies carried out with the comparator in the past when setting up equivalence and non-inferiority studies of new medicines. In these studies the efficacy of the new medicine is demonstrated by proving – according to a fixed pre-determined margin – that it is equivalent to, or in any case not worse than, another effective medicine. One condition is that this comparator really is effective in the setting of the study with the new product. This can be realised by adding a placebo group or by setting up the new study based on the so-called constancy assumption. This is the assumption that the superiority of the comparator, as demonstrated in previous studies, is retained in the setting of the equivalence or non-inferiority study. This means that a number of critical design characteristics of the these studies must correspond with the superiority studies of the comparative product. The outcomes of these studies are also important for determining a clinically acceptable margin of equivalence or non-inferiority. The information over these studies in the EPARs and possible publications on the new medicines were analysed with this in mind, as described in Chapter 2.1. We found 83 (54%) RaCTs that were set up as equivalence or non-inferiority study; 24 (29%) RaCTs had actually been published at the moment of market entry. The size of the margin was described in most of the documentation. However, only five studies referred to a study that substantiated the choice. Furthermore, the description of the design and conduct of the studies pays almost no attention to the constancy assumption. In only two studies is attention given to the equivalence of the groups of patients. As this raises the question of whether the therapeutic and methodological requirements on the design and conduct of these studies can actually be realised in practice, a further analysis was done into the practical possibility of actually using the study design of the superiority studies with the comparator in order to be able to guarantee the constancy assumption. As 60% of the comparators used had been on the market for more than 10 years, half of them even for more than 25 years, it is possible that dated study designs would have to be used, and actually were used.

Chapter 4

The fourth chapter is about use of the results of comparative research in the assessment of medicines.

In chapter 4.1 we describe the study into the publication of the RaCTs used for market authorization. A publication in a peer-reviewed journal is important because it means that the full data of the study, tested according to scientific and ethical norms, are publicly available and can be verified, which means that they can be used in an evidence-based assessment of a product's place within therapy. We determined the time-lag between the

moment of market authorization and the moment of publication in order to investigate which RaCTs from the EPAR were published. We also drew a comparison between unpublished RaCTs and published RaCTs in relation to the therapeutic relevance of the study. Between 1999 and 2003, 42 new medicines were granted market entry partly on the basis of an RaCT. Less than one-third (28%) of the 116 RaCTs had been published at the moment of market entry, after one year 59%, after two years 78% and after three years 83%. Almost one-fifth of the RaCTs remained unpublished. 85% of the unpublished RaCTs contain therapeutic information that could be relevant. For example, for five products these were the only comparative studies.

In chapter 4.2 we analyse the assessments of the comparative efficacy of new medicines that were carried out in order to form an opinion on their prescription and reimbursement. We studied the robustness of the evidence according to the hierarchy of evidence, as used where "evidence-based medicine" is applied to intervention studies, but adjusted in keeping with the questions regarding comparative efficacy. This means that the most robust evidence is a properly conducted RaCT using the standard treatment for comparison, next in line are other RaCTs, then adjusted indirect comparisons and finally, the last category of evidence: the opinions of experts. For the assessments of the comparative efficacy of new medicines we used reports from the College voor zorgverzekeringen on medicines authorized during the period 1999-2004, for which inclusion in the reimbursement system was requested within two years after market authorization. 69 products were eligible for the analysis. For 19 (28%) products it was impossible to form a clear opinion over any difference in efficacy compared with the standard treatment. It was possible to form an opinion over more, less or equal efficacy, for 8 (12%) products, based on the highest level of evidence (RaCT in comparison with the standard treatment) and for 27 (39%) products, based on the least robust evidence (the opinions of experts). An adjusted indirect comparison was used for the assessment of one of the 27 new medicines without an RaCT.

Chapter 5

In the fifth chapter we draw conclusions about the outcomes of the various studies and discuss in detail the consequences for the assessment of new medicines

To summarize, we conclude that, during the period prior to market entry, about half of the new medicines were studied in comparison with an existing medicine; the recommended standard treatment was used for four out of every five new products. For most of these new medicines, this provides a good point of departure for assessing their place within

treatment. There are, however, a number of bottlenecks. Only one-third of the comparative studies had been published at the moment of market entry. This means that not all data are public and verifiable. Though the number of publications does increase over the course of time, a delay of two or three years does present a problem, because at the moment of market entry good decision-making is also needed on reimbursement and the place of a new medicine in treatment. Furthermore, we found that a great deal of comparative research does not focus on demonstrating differences, but on demonstrating a lack of differences. Only one in ten comparative studies was set up as a superiority study. Furthermore, in a case of equivalence or non-inferiority, additional information is required in order to be better able to assess the value of these studies.

More comparative research should also be carried out as well, certainly in the case of a new medicine with a new mechanism of action. Research shows a reduced probability that comparative studies will be done for this type of new medicine, whilst for these medicines there is a greater need of such information, because of the high expectations of an improvement in treatment and the pressure to get them reimbursed is enormous.
Lastly, we found that the lack of comparative research and the limitations of the existing research often force us, when determining the position of new medicines, to put up with a complete lack of evidence or with the lowest level of evidence. More adjusted indirect comparisons provide a possibility of improving the level of evidence where no direct comparison is available.

These bottlenecks and problems can partly be explained by the fact that all research in the period prior to market entry focuses on fulfilling the requirements for admission onto the market, which does not require compulsory comparative research. However, now that it has become clear that market authorization is no longer a guarantee for use in practice, research will increasingly have to focus on the studies that are needed for decision-making on prescribing and reimbursement. This will increase the desire – or dare we say demand – for more comparative research in order to substantiate the specific advantages of a new medicine. It is important that this research is not regarded as a new hurdle that needs to be cleared in order to obtain admission onto the market, but as a progress-serving tool in the better treatment of patients. Both health care workers and patients would vigorously emphasise this. In order to stimulate this research, there should be a financial incentive for companies to carry it out. There are proposals to allow the reimbursement of new medicines to depend on the availability of comparative research or an adjusted indirect comparison if there are weighty arguments for failing to conduct a direct comparison. An important

condition to this is close co-operation about such a joint requirement between the reimbursement authorities within the EU.
Furthermore, we suggest that, as a condition for market entry, all data on the registration research of new medicines should be available in public databases of trial results. The social and scientific importance of these studies for the use of new medicines is so great that all health care workers, patients and policy-makers should be given the opportunity of accessibility to the same data as the registration authorities.

Lastly: though new medicines have been subjected to extensive research when they are granted market entry, paradoxically enough, at that moment there are still significant gaps in our knowledge which hamper prescribing them properly. Research is necessary in order to demonstrate efficacy and safety, but for the moment we are forced to base our insight into differences with existing products on indirect comparisons, clinical experience and trial and error. When designing future premarketing studies, clinical research should better anticipate the demand for more comparative research at the moment of market entry, as this is in the interests of making the right choices in medicines when treating patients.

Samenvatting

Om goede geneesmiddelenkeuzes te maken bij de behandeling van patiënten is het noodzakelijk voor de voorschrijver om inzicht te hebben in de verschillen tussen geneesmiddelen bestemd voor de behandeling van dezelfde aandoening. Dat inzicht wordt verkregen uit onderzoeken waarbij deze middelen met elkaar worden vergeleken.
Om met een geneesmiddel tot de markt te worden toegelaten is er echter geen verplichting voor de geneesmiddelenfabrikant om vergelijkend onderzoek met andere geneesmiddelen uit te voeren. Daarvoor is enkel noodzakelijk dat het nieuwe middel werkzaam is en veilig en dat de voordelen groter zijn dan de risico's. Onderzoeken waarbij het nieuwe geneesmiddel wordt vergeleken met een placebo leveren daartoe in eerste aanleg het beste bewijs.

De behoefte aan resultaten van vergelijkend klinisch onderzoek is echter wel groot. Daarvoor zijn meerdere redenen. Het aantal middelen waaruit een keuze kan worden gemaakt neemt toe. Door de hoge prijzen van nieuwe geneesmiddelen wordt inzicht in de meerwaarde extra belangrijk ("value for money"). Daarnaast worden de afgelopen jaren hogere eisen gesteld aan de kwaliteit van de bewijslast in het keuzeproces ("evidence-based medicine").

Het ontbreken van uitkomsten van vergelijkend onderzoek bij de introductie van een nieuw geneesmiddel wordt met recht en reden beschouwd als een belangrijk probleem. Cijfers over de aard en de omvang van dit probleem zijn echter schaars.
Doel van dit proefschrift is dit probleem verhelderen door een evaluatie uit te voeren van de beschikbaarheid, kwaliteit en het gebruik van vergelijkende informatie over nieuwe geneesmiddelen op het moment van hun toelating tot de markt.

Dit proefschrift bestaat uit vijf hoofdstukken. In de eerste vier hoofdstukken zetten we de probleemstelling en de onderzoeken uiteen om in hoofdstuk vijf tot de conclusie te komen. Hieronder een korte toelichting per hoofdstuk.

Hoofdstuk 1
In het eerste hoofdstuk geven we een algemeen overzicht van de ontwikkeling van de kennis over de werking en bijwerking van nieuwe geneesmiddelen; verder lichten we de rol van het vergelijkende onderzoek daarbij toe en tot slot omschrijven we het doel en de opzet van dit proefschrift.

Hoofdstuk 2
Hoofdstuk twee bespreekt de beschikbaarheid van vergelijkende informatie.

In 2.1 beschrijven we het onderzoek naar de hoeveelheid nieuwe geneesmiddelen, die in de periode voor toelating tot de markt, zijn bestudeerd in een directe vergelijking met andere al beschikbare geneesmiddelen. Voor het onderzoek selecteerden we alle nieuwe geneesmiddelen met een nieuwe werkzame stof die tussen 1999 en 2005 zijn beoordeeld voor toelating tot de markt van de Europese Unie (EU); uitgezonderd nieuwe diagnostica en vaccins. Voor informatie over deze geneesmiddelen gebruikten we de openbare beoordelingsrapporten (EPARs) van de Committee for Medicinal Products for Human Use (CHMP), de wetenschappelijke commissie van het Europese agentschap voor de geneesmiddelenbeoordeling (EMEA). We selecteerden studies die in de EPAR werden aangeduid als de belangrijkste gerandomiseerde trials met een actieve controle groep (RaCT). Gedurende die periode zijn 122 geneesmiddelen met een nieuwe werkzame stof toegelaten tot de markt, waarvan er 58 (48%) waren onderzocht in een RaCT. We vonden dat 56 nieuwe middelen ook beschikten over een nieuwe manier waarop ze hun werking uitoefenen. De kans dat dan ook een RaCT beschikbaar is bleek geringer.

Omdat het doel van de ontwikkeling van nieuwe geneesmiddelen is ‘een verbetering van de behandeling van patiënten’, hebben we nader onderzocht bij hoeveel middelen voldoende informatie beschikbaar was om te kunnen spreken van een verbetering van de werkzaamheid. Het onderzoek en de resultaten hebben we opgenomen in 2.2. Uit deze analyse blijkt dat 15 (10%) RaCTs van de nieuwe middelen toegelaten tot de EU-markt in de periode 1999-2005, waren opgezet met als doel het aantonen van een verschil (superioriteit studie). Van de 122 nieuwe geneesmiddelen blijkt bij 13 (10%) sprake van een statistisch significant verschil in werkzaamheid in vergelijking met een ander geneesmiddel. Of deze middelen uiteindelijk ook een aanwinst zijn voor de behandeling staat niet bij voorbaat vast. Naast werkzaamheid zullen ook andere eigenschappen zoals veiligheid in de evaluatie moeten worden betrokken, bovendien moet de verbeterde werkzaamheid gezien worden in de context van de opzet van het onderzoek (type patiënt, keuze vergelijkend middel) en uiteindelijk vooral de klinische relevantie van de uitkomsten van het onderzoek. De analyse laat zien dat een kritische evaluatie van de resultaten van vergelijkend onderzoek noodzakelijk is om de specifieke plaats van het middel in de behandeling vast te stellen.

In 2.3 beschrijven we het onderzoek, waarin we nagaan of het gebrek aan vergelijkende informatie op het moment van toelating tot de markt, nog wordt goed gemaakt met nieuw onderzoek daarna. Dat onderzochten we voor het geneesmiddel etanercept. De introductie van dit middel op de markt eind 1998, werd in de literatuur besproken als een nieuwe belangrijke mogelijkheid om patiënten met reumatoïde artritis beter te behandelen. Daarbij werd nadrukkelijk aangetekend dat er behoefte was aan vergelijkend onderzoek met andere middelen (infliximab, combinatie DMARDs), omdat deze studies vooralsnog ontbraken. In de periode van 10 jaar na introductie, zijn er 84 gerandomiseerde studies uitgevoerd met etanercept, waarvan 6 vergelijkende studies bij de geregistreerde indicaties. Deze studies zijn echter onvoldoende om aan de gerichte behoefte aan vergelijkende informatie te voldoen. Uit het onderzoek blijkt voorts dat 54 (64%) van de trials waren gericht uitbreiding van de toepassing van etanercept bij nieuwe inmiddels geregistreerde of nog niet geregistreerde indicaties.

Hoofdstuk 3

Het derde hoofdstuk gaat over de kwaliteit van de vergelijkende informatie. Daarbij besteden we vooral aandacht aan twee kenmerkende eigenschappen van vergelijkende studies, de keuze van het vergelijkende middel en de assay sensitiviteit·.

In 3.1 beschrijven we het onderzoek, waarin we nagaan in hoeverre de keuze van het vergelijkende middel overeenkomt met de in de praktijk aanbevolen standaardbehandeling bij de indicatie waarvoor de werkzaamheid van het nieuwe geneesmiddel wordt onderzocht. De juiste keuze is belangrijk voor het aantonen van de werkzaamheid en veiligheid maar ook voor de plaatsbepaling van het nieuwe middel in de behandeling. De keuze is echter ook lastig omdat de standaardbehandeling kan variëren afhankelijk van plaats en tijd. Wat de beste keuze was bij de start van het onderzoek, kan op het moment van toelating tot de markt achterhaald zijn op basis van nieuwe inzichten, die bovendien nog per land en zelfs ook lokaal kunnen verschillen.
Voor dit onderzoek gebruikten we de RaCTs (N= 153) uit het onderzoek, zoals beschreven in hoofdstuk 2.1. Voor de keuze van de aanbevolen standaardbehandelingen is gebruik gemaakt van de jaarlijkse uitgaven van het Farmacotherapeutisch Kompas, een Nederlands naslagwerk voor de farmacotherapie. We vergeleken de controlegroepen in de RaCTs op twee verschillende momenten met de aanbevolen standaardbehandeling, het jaar van toelating van het middel tot de markt en drie jaar eerder, het veronderstelde moment van de opzet van het vergelijkend onderzoek. Uit deze analyse blijkt dat op het moment van markttoelating, in 108 (71%) RaCTs de actieve controlegroep overeenkomt (dezelfde

werkzame stof/therapeutische klasse en dosering) met de aanbevolen standaardbehandeling en dat 41 (81%) nieuwe geneesmiddelen in ten minste één studie hiermee zijn vergeleken. In geval van een verschil, was geen sprake van een andere aanbevolen standaardbehandeling drie jaar eerder.

Hoofdstuk 3.2 heeft de opzet van een open brief aan de registratieautoriteiten waarin aandacht wordt gevraagd voor meer transparantie over de rol van in het verleden uitgevoerde superioriteitsstudies van het vergelijkende middel bij de opzet van equivalentie- en non-inferioriteit studies van nieuwe geneesmiddelen. In deze studies wordt de werkzaamheid van het nieuwe middel aangetoond door te bewijzen dat het volgens een vooraf vastgestelde marge gelijkwaardig of in ieder geval niet slechter is dan een ander werkzaam geneesmiddel. Voorwaarde is dan wel dat dit vergelijkende middel inderdaad ook werkzaam moet zijn in de opzet van het onderzoek met het nieuwe middel. Dit kan worden gerealiseerd door toevoeging van een placebogroep of door bij de opzet van het nieuwe onderzoek uit te gaan van de zogenoemde aanname van constantheid ("constancy assumption"). Dit is de aanname dat de superioriteit van het vergelijkende middel, zoals aangetoond in eerdere studies, behouden blijft in de opzet van de equivalentie of non-inferioriteit studie. Dit houdt in dat de opzet van deze studies op een aantal cruciale kenmerken, zoals patiëntenselectie, interventie en eindpunten, overeen moet komen met de superioriteitstudies van het vergelijkende middel. De uitkomsten van deze studies zijn ook belangrijk voor het vaststellen van een klinisch aanvaarbare marge van gelijkwaardigheid of non-inferioriteit. De informatie over deze studies in de EPARs en eventuele publicaties van de nieuwe geneesmiddelen, zoals beschreven in hoofdstuk 2.1, zijn daarvoor geanalyseerd. We vonden 83 (54%) RaCTs die zijn opgezet als equivalentie of non-inferioriteit studie; 24 (29%) RaCTs waren ook gepubliceerd op het moment van markttoelating. In de meeste documentatie wordt de hoogte van de marge beschreven. Echter, voor slechts vijf studies wordt verwezen naar een onderzoek ter onderbouwing van de keuze. Ook de "constancy assumption" krijgt niet tot nauwelijks aandacht in de beschrijving van de opzet van de studies. Slechts in twee studies wordt aandacht besteed aan de gelijkwaardigheid van de patiëntengroepen. Omdat dit de vraag oproept of de therapeutische en methodologische eisen aan de opzet van deze studies in de praktijk wel kunnen worden gerealiseerd, is een verdere analyse uitgevoerd naar de praktische mogelijkheid om ook gebruik te maken van de studieopzet van de superioriteitsstudies van het vergelijkende middel om de "constancy assumption" te kunnen waarborgen. Omdat 60% van de gebruikte vergelijkende middelen al meer dan 10 jaar op de markt is waarvan

de helft zelfs meer dan 25 jaar, zou mogelijk gebruik moeten worden gemaakt, en de facto gebruik gemaakt zijn, van verouderde studiedesigns.

Hoofdstuk 4
Het vierde hoofdstuk gaat over het gebruik van resultaten van vergelijkend onderzoek bij de beoordeling van geneesmiddelen.

In 4.1 beschrijven we het onderzoek naar de publicatie van de bij de registratie gebruikte RaCTs. Een publicatie in een peer-reviewed tijdschrift is belangrijk, omdat daarmee de volledige gegevens van het onderzoek, getoetst aan wetenschappelijke en ethische normen, openbaar beschikbaar en controleerbaar zijn en daardoor verder gebruikt kunnen worden bij een “evidence-based” beoordeling van de plaats van het middel binnen de therapie. Om te onderzoeken welke RaCTs uit de EPAR zijn gepubliceerd hebben we het tijdsverloop vastgesteld tussen het moment van toelating tot de markt en het moment van publicatie. Verder maakten we een vergelijking tussen de ongepubliceerde RaCTs en de gepubliceerde RaCTs met betrekking tot therapeutische relevantie van de studie. Tussen 1999 en 2003 zijn 42 nieuwe geneesmiddelen op de markt toegelaten mede op basis van een RaCT. Van de 116 RaCTs was minder dan eenderde (28%) gepubliceerd op het moment van markttoelating, na één jaar was dat 59%, na twee jaar 78% en na drie jaar 83%. Bijna een vijfde van de RaCTs blijft ongepubliceerd. 85% van de niet gepubliceerde RaCTs bevat mogelijk wel belangrijke therapeutische informatie; voor vijf middelen bijvoorbeeld waren het de enige vergelijkende studies.

In 4.2 analyseren we de beoordelingen over de vergelijkende werkzaamheid van nieuwe geneesmiddelen ten behoeve van het opstellen van een advies over het voorschrijven en vergoeden ervan. We onderzochten de hardheid van de bewijzen, conform de hiërarchie van bewijsmateriaal, zoals die in “evidence-based medicine” wordt toegepast bij interventiestudies, maar dan aangepast aan de vraagstelling over vergelijkende werkzaamheid. Dit betekent dat het krachtigste bewijsmateriaal een goed uitgevoerde RaCT in vergelijking met de standaardbehandeling is, vervolgens in rangorde andere RaCTs, daarna gecorrigeerde indirecte vergelijkingen en tenslotte de als laatste geklasseerde bewijslast: de mening van deskundigen. Voor de beoordelingen van de vergelijkende werkzaamheid van nieuwe geneesmiddelen is gebruik gemaakt van de rapporten van het College voor zorgverzekeringen over geneesmiddelen, geregistreerd in periode 1999-2004, waarvoor binnen twee jaar na markttoelating een verzoek werd ingediend voor opname in het vergoedingssysteem. 69 middelen kwamen in aanmerking voor de analyse.

Voor 19 (28%) middelen was het niet mogelijk een duidelijk oordeel te geven over het verschil in werkzaamheid met de standaardbehandeling. Voor middelen waarover wel een oordeel over een grotere, mindere of gelijke werkzaamheid kon worden gegeven was dat voor 8 (12%) middelen gebaseerd op het krachtigste bewijsmateriaal (RaCT in vergelijking met de standaardbehandeling) en voor 27 (39%) op het minst zware bewijsmateriaal (de mening van deskundigen). Bij één van de 27 middelen zonder RaCT is bij de beoordeling gebruik gemaakt van een gecorrigeerde indirecte vergelijking.

Hoofdstuk 5
In hoofdstuk vijf trekken we gemeenschappelijke conclusies uit de uitkomsten van de verschillende studies en gaan we vervolgens in op de gevolgen daarvan voor de beoordeling van nieuwe geneesmiddelen.

Samengevat concluderen we dat ongeveer de helft van de nieuwe middelen, in de periode voor toelating tot de markt, is onderzocht in vergelijking met een ander geneesmiddel; voor vier van de vijf nieuwe middelen is daarbij de aanbevolen standaardbehandeling gebruikt. Voor het merendeel van deze nieuwe middelen betekent dit dus een goede uitgangspositie voor de beoordeling van de plaats binnen de behandeling. Echter daarbij doen zich wel een aantal knelpunten voor. Slechts eenderde van de vergelijkende onderzoeken zijn op het moment van toelating tot de markt gepubliceerd. Hierdoor zijn niet alle gegevens openbaar en controleerbaar. In de loop van de tijd neemt het aantal publicaties toe, maar een uitstel van twee á drie jaar is toch problematisch, omdat op het moment van markttoelating ook goede besluitvorming moet kunnen plaatsvinden over de vergoeding en de plaats van het nieuwe middel in de behandeling. Verder constateren we dat veel vergelijkend onderzoek niet gericht is op het aantonen van verschillen, maar op het aantonen dat die verschillen ontbreken. Slechts één op de tien vergelijkende studies was opgezet als een superioriteitstudie. Bovendien is er in geval van gelijkwaardigheid of non-inferioriteit behoefte aan additionele informatie om de waarde van uitkomsten van deze studies beter te kunnen beoordelen.

Daarnaast zou ook meer vergelijkend onderzoek moeten worden uitgevoerd, zeker indien sprake is van een nieuw geneesmiddel met een nieuw werkingsmechanisme. Uit het onderzoek blijkt dat vergelijkende studies over deze nieuwe geneesmiddel minder snel worden uitgevoerd. Echter, juist bij deze geneesmiddelen is de behoefte aan deze informatie het grootst, omdat de verwachtingen voor een verbetering van de behandeling hooggespannen zijn en de druk om ze te vergoeden het sterkst is.

Ten slotte wordt geconstateerd dat door het ontbreken van vergelijkend onderzoek en de beperkingen in het bestaande onderzoek, bij de plaatsbepaling van nieuwe geneesmiddelen vaak genoegen moet worden genomen met geen of onvoldoende robuust bewijsmateriaal. Meer gecorrigeerde indirecte vergelijkingen bieden de mogelijkheid om de bewijskracht te verbeteren bij het ontbreken van een directe vergelijking.

Deze knelpunten en problemen zijn deels verklaarbaar, omdat al het onderzoek in de periode voor toelating tot de markt gericht is op het voldoen aan de eisen voor toelating tot de markt en vergelijkend onderzoek daar geen verplicht onderdeel van uitmaakt. Echter, omdat inmiddels duidelijk is geworden dat markttoelating niet langer een garantie meer is voor het gebruik in de praktijk, zal het onderzoek zich ook meer moeten richten op studies nodig voor de besluitvorming over het voorschrijven en over de vergoeding. Dit betekent de vraag naar, beter gezegd de eis om, meer vergelijkend onderzoek om de specifieke voordelen van een nieuw geneesmiddel te onderbouwen. Het is belangrijk dat dit onderzoek door de fabrikant niet wordt gezien als een nieuwe horde voor toelating tot de markt, maar als een middel ten dienste van de verbetering van de behandeling van patiënten. Zowel gezondheidswerkers als patiënten zouden deze vraag krachtig kunnen benadrukken. Om dit onderzoek te stimuleren zullen fabrikanten een economisch belang moeten hebben bij het uitvoeren ervan. Voorgesteld wordt om de vergoeding van nieuwe geneesmiddelen te laten afhangen van de beschikbaarheid van vergelijkend onderzoek of een gecorrigeerde indirecte vergelijking als er zwaarwegende argumenten zijn om een directe vergelijking niet uit te kunnen voeren. Belangrijke voorwaarde hiervoor is een nauwe samenwerking tussen vergoedingsautoriteiten binnen de EU over een dergelijke gezamenlijke eis.
Verder stellen wij voor om alle gegevens over het registratieonderzoek van nieuwe geneesmiddelen op te nemen in een openbare databank, als voorwaarde voor toelating tot de markt. De maatschappelijke en wetenschappelijke betekenis van deze studies voor het gebruik van nieuwe geneesmiddelen is zo groot dat alle gezondheidswerkers, patiënten en beleidsmakers de gelegenheid moeten krijgen om te kunnen beschikken over dezelfde gegevens als de registratieautoriteiten.

Tot besluit: nieuwe geneesmiddelen zijn uitgebreid onderzocht wanneer ze tot de markt worden toegelaten, maar paradoxaal genoeg, zijn er dan toch nog belangrijke lacunes in onze kennis om ze op dat moment ook goed te kunnen voorschrijven. Om de werkzaamheid en veiligheid aan te tonen is onderzoek noodzakelijk, maar voor inzicht in de verschillen met bestaande middelen moeten we ons, vooralsnog noodgedwongen op dat moment, baseren op indirecte vergelijkingen, klinische ervaring en “trial and error”. De behoefte aan

meer vergelijkend onderzoek op het moment van markttoelating onderstreept de noodzaak om in de toekomst bij de opzet van het onderzoeksprogramma, hierop beter te anticiperen in het belang van goede geneesmiddelenkeuzes bij de behandeling van patiënten.

List of co-authors
List of publications
Dankwoord
About the author

List of co-authors

Affiliations during the conduct of the research

Johannes W.J. Bijlsma
Department of Rheumatology & Clinical Immunology, University Medical Centre Utrecht, The Netherlands

Marjan Danz
Health Care Insurance Board, Diemen, The Netherlands

Frank W.J. Gribnau
Department of Pharmacology and Toxicology, Section Clinical Pharmacology and Toxicology, Radboud University, Medical Centre, Nijmegen, the Netherlands

Hubert G.M. Leufkens
Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht, the Netherlands.

Arie C. van Loenen
Health Care Insurance Board, Diemen, The Netherlands

Nico Th. Mes
Health Care Insurance Board, Diemen, The Netherlands

Pieter Stolk
Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht, the Netherlands.

List of publications

Publications related to this thesis

Van Luijn JCF, Gribnau FWJ, Leufkens HGM. Availability of comparative trials for the assment of new medicines in the european union at the moment of market authorization. Br J Clin Pharmacol 2007;63:159-62

Van Luijn JCF, Stolk P, Gribnau FWJ, Leufkens HGM. Gap in publication of comparative information on new medicines. Br J Clin Pharmacol 2008;65:716-22

Van Luijn JCF, van Loenen AC, Gribnau FWJ, Leufkens HGM. Choice of comparator in active control trials of new drugs. Ann Pharmacother 2008;42:1605-12

Publications not related to this thesis

Van Luijn JC. Geneesmiddeleninformatie bij geneesmiddelenkeuze. Ziekenhuisfarmacie 1989;5:97-9

Van Luijn JC. De eigenbijdrage voor geneesmiddelen. De functie van de Commissie Vergoedingslimieten Geneesmiddelen. Medisch Contact 1992;47:889-92

Van Luijn JC. Meerwaarde van sumatriptan boven ergot-alkaloïden nog steeds niet aangetoond. Ned Tijdschr Geneeskd 1993;137:2554-8

Van Luijn JC, van Loenhout JWA, Riteco JA, Ripken ThMJ. Toetsing van het geneesmiddelenpakket. Medisch Contact 1995;50:1433-9

Riteco JA, Pipenbrink JF, van Luijn JC. Geneesmiddelenprijzen in Europa. Pharm Weekbl 1995;130:569-72

Van Luijn JC. Antidepressiva: nieuw is niet altijd beter. Patient Care 1995;22:19-26

Van Luijn JC, Schuurmans A. Op stofnaam voorschrijven en doelmatig afleveren. Geneesmiddelenbulletin 1996;30:39-44.

Van Luijn JC, Ripken ThMJ, Piepenbrink JF. Bij nader inzien aan aanwinst. Beoordeling van de wachtkamergeneesmiddelen. Pharm weekbl 1998;133:1902-6

Van Luijn JC. In het belang van “evidence-based”-farmacotherapie. Commissie Farmaceutische Hulp. Pharm Weekbl 1999;134:1292-4

Van Luijn JC. Oriënteer u op het Kompas. Informatie over niet-geregistreerde indicaties. Pharm Weekbl 2004;139:906-9

Dankwoord

Het was een voorrecht om de afgelopen jaren als buitenpromovendus te werken aan dit proefschrift. Mijn werkgever, het College voor zorgverzekering (CVZ) stelde mij daartoe in de gelegenheid en het Departement Farmaceutische Wetenschappen van de Utrecht Universiteit, bood mij daarvoor de gastvrijheid.
Grote dank ben ik verschuldigd aan dr Dik Hermans, algemeen directeur CVZ en mijn promotoren prof. dr. Frank Gribnau en prof. dr. Bert Leufkens. Zij gaven mij alle denkbare ruimte, vrijheid en vertrouwen om dit onderzoek uit te voeren en mijn ervaringen te toetsen aan de feiten. Ik hoop dat de resultaten een bijdrage leveren aan de verbetering van de kwaliteit van de geneesmiddelenbeoordeling en daarmee tevens aan de werkzaamheden van het CVZ.

De hernieuwde samenwerking met mijn promotoren heb ik als heel bijzonder ervaren, niet alleen op wetenschappelijk gebied, maar ook persoonlijk. Jullie eruditie, bevlogenheid en creativiteit maakten dat onze gesprekken altijd bijzonder levendig verliepen en mij inspireerden tot een verdere verdieping van het onderwerp. Daarbij bewaakten jullie heel scherp het onderscheid tussen mijn rol als onderzoeker/wetenschapper en CVZ medewerker.

Dit onderzoek gaat over farmacotherapie, de behandeling van patiënten met geneesmiddelen. Veel van mijn belangstelling en kennis voor dit onderdeel van het beroep van apotheker heb ik te danken aan mijn leermeester, wijlen prof. dr. Frans Nelemans.

Ik heb vanaf het begin gekozen om mijn promotie onderzoek om praktische redenen zoveel mogelijk uit te voeren vanuit de CVZ locatie. Het gevolg van deze keuze was dat ik niet zo heel vaak aanwezig ben geweest op de universiteit. Als ik wel aanwezig was dan trof ik er altijd een grote bereidheid om mij te helpen. Vooral de samenwerking de eerste jaren in het PILLs project was heel belangrijk om mij weer vertrouwd te maken met de academische wereld. Belangrijk waren ook de discussies over diverse onderwerpen op het gebied van “pharmaceutical policy analysis”.

Mijn mede auteurs, prof. dr. Hans Bijlsma, Marjan Danz, Arie van Loenen, Nico Mes en Pieter Stolk dank ik voor hun bereidheid mee te denken en voor hun concrete bijdragen aan de studies. Ik heb dankbaar gebruik mogen maken van jullie specifieke deskundigheid.

Marli van Amsterdam verdient mijn bijzondere dank, niet alleen voor de snelheid en de nauwkeurigheid waarmee zij voor mij literatuur verzamelde, maar vooral ook om de manier waarop, geïnteresseerd en betrokken. Chistene Beddow ben ik erkentelijk voor de bijzondere snelle en grondige wijze waarop ze de manuscripten steeds op het Engels heeft gecorrigeerd. Christa Hooijkaas dank ik voor de aanlevering van GIP-data.

De leden van de leescommissie, prof. dr. Jerry Avorn, prof. dr. Chiel Hekster, prof. dr. Jan Raaijmakers, prof. dr. Jan Schellens en dr. Barbara van Zwieten-Boot, wil ik bedanken voor hun bereidheid om mijn proefschrift te beoordelen.

Als tenslotte alles is opgeschreven en gecorrigeerd moet het nog wel worden opgemaakt, vormgeven en gedrukt. Marjolein Brink, Brian Mulder en Wim de Hertog dank ik voor hun hulp.

De morele steun van familie, vrienden en collega's was bij dit alles onmisbaar. Jullie belangstelling voor zowel inhoud als voortgang heb ik steeds als opbeurend ervaren. Speciale dank gaat uit naar mijn zwager Peter Wolters; jij gaf mij in onze gesprekken het laatste zetje om alsnog te gaan promoveren. Jouw doorzettingsvermogen en creativiteit stelde ik mij als voorbeeld, als ik het even niet meer zag zitten.

Paranimfen Rita van der Velde en Sietse van Luijn, ik ben blij dat jullie mij willen bijstaan bij de verdediging van mijn proefschrift. Jullie representeren wat voor mij belangrijk is aan het onderzoek, namelijk relevant voor de praktijk en toekomstgericht. Rita, samen hebben we eind jaren zeventig ons doctoraal examen farmacie en het apothekersexamen voorbereid. Ik ben blij dat je mij ook bij deze laatste stap in de afsluiting van mijn "studie" wilt bijstaan. Vanuit dezelfde idealen heb we ons op een verschillende manier beziggehouden met het vak van apotheker. Ik heb veel bewondering voor de wijze waarop jij de apotheker als zorgverlener vorm en inhoud hebt gegeven. Sietse, mijn zoon, jij staat voor de toekomst; hetzelfde geldt voor Renske, mijn dochter. Een toekomst die mij dierbaar is en hoopvol stemt.

Tenslotte. Als ik bepaalde personen vergeten ben persoonlijk te bedanken, dan hoop ik dat hij of zij mij dat vergeven.
Judith, een dankwoord voor jouw onvoorwaardelijke steun, is moeilijk uit te drukken in woorden, laat staan deze af te drukken. Dat gebeurt elders en anders.

About the author

Johan van Luijn was born on 28th April 1951 in the village of Bakel, in The Netherlands. In 1969 he completed secondary school at the St Willibrord Gymnasium in Deurne. Subsequently, he started his study in Pharmacy at the University of Utrecht. He obtained his M.Sc degree in 1977 and became a pharmacist in 1978.

In 1979 he worked as a teacher at Leergangen Algemene Gezondheidszorg in Amsterdam. Between 1980 and 1981 he was acting editor of the first edition of the Farmacotherapeutisch Kompas, a reference book for medical practice and training, published by the Ziekenfondsraad (Health Insurance Board), the predecessor of the current CVZ (Health Care Insurance Board). Since 1982 he has been working for CVZ. He started as editor and subsequently became coordinator of the annual edition of the Farmacotherapeutisch Kompas. In 1988 he became pharmaceutical adviser and secretary of the Central Medical Pharmaceutical Committee (CMPC) and in 1991 also of the Committee on Reimbursement Limits of Medicines (CVG). During 1998 he followed a course in Health Economics of Pharmaceuticals at the School of Economics in Stockholm. From 1999-2004 he was secretary of the Committee on Pharmaceutical Aid (CFH). In 2004 he was given the opportunity of starting a part-time PhD project at the Department of Pharmacoepidemiology and Pharmacotherapy of the Institute for Pharmaceutical Sciences of the University in Utrecht and started working on the studies described in this thesis.

Johan is married to Judith Verkerk and together they have a son Sietse and a daughter Renske.