Commentaries

Assessment of the Regulatory Dialogue Between Pharmaceutical Companies and the European Medicines Agency on the Choice of Noninferiority Margins

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ABSTRACT

Choosing a noninferiority margin is one of the main challenges when designing a noninferiority trial. The European Medicines Agency (EMA) published a guidance report on the choice of margins in 2005. Nonetheless, in 2008 and 2009 they did not accept 41% (35 of 86) of the noninferiority margins that were proposed by pharmaceutical companies in the context of scientific-advice letters. In this study, we focus on whether the EMA's recommendations were followed by pharmaceutical companies, and on a possible relationship with eventual drug approval. Five of the 35 unaccepted margins were equivalence margins; we considered only the 30 unaccepted noninferiority margins in our analysis. Twelve of these margins were defined based on clinical and statistical considerations (the approach recommended by the EMA) and were rejected due to unacceptable clinical considerations. The other 18 margins were rejected because they were considered too wide. The EMA's recommendations were followed in the cases of 10 of the 15 margins (67%) for which information on follow-through of recommendations was available. The main reason for ignoring the EMA's recommendation in the other 5 cases was that the margins had been accepted by the US Food and Drug Administration. The proportions of approved drugs for which recommendations were and were not followed were similar, yet numbers were too low for formal statistical testing. This study shows that the main concern of regulators with regard to noninferiority trials was the strictness of margins from a clinical perspective. Future studies using more recent data, including data on the US Food and Drug Administration, may help in assessing the impact of guideline recommendations on noninferiority margins used for drug approval and may assist in reaching consensus among regulators about the choice of margins. (*Clin Ther*. 2020;42:1588–1594)

Key words: Biostatistics, Clinical trials, Drug regulation, Methodology, Noninferiority, Randomized controlled trials.

INTRODUCTION

When designing a study on the efficacy of a new drug, a noninferiority design can be considered when it is anticipated that the test drug will not be more

Accepted for publication June 7, 2020
https://doi.org/10.1016/j.clinthera.2020.06.004
0149-2918/$ - see front matter

efficacious compared to an active comparator, but that it may offer advantages such as improved tolerability or a more convenient dosing schedule. To demonstrate noninferiority, a noninferiority margin needs to be determined.[1–9] For example, noninferiority is demonstrated when the 95% CI of the effect estimate of the test drug versus the active comparator does not include the noninferiority margin. Regulators recommend that noninferiority margins be based on clinical and statistical considerations. After the historical evidence (ie, from randomized, controlled trials) on the active comparator is reviewed and quantitatively summarized in a pooled estimate, a clinically relevant fraction of that estimate is chosen to be preserved by the new drug (ie, the *preserved fraction*). The *noninferiority margin* is the remaining clinically nonsignificant fraction of the pooled effect estimate.[1–9]

The European Medicines Agency (EMA) published a guideline on the choice of noninferiority margins in 2005. In a first study, Wangge et al[10] found, in the context of scientific advice, that the EMA in 2008 and 2009 rejected 41% (35 of 86) of the noninferiority margins proposed by pharmaceutical companies for use in the study of drugs intended to be marketed in Europe. Here, we describe an extension of their study, which focuses on the approaches used by pharmaceutical companies for defining these margins, the regulatory dialogue with the EMA about these margins, whether the EMA's recommendations on these margins were followed by pharmaceutical companies, and, if not, whether this had an impact on eventual drug approval.

COLLECTION OF DATA ON MARGINS

We collected information from the letters sent by the EMA in 2008 and 2009 to pharmaceutical companies in response to requests for scientific advice on developing drugs that are intended to be registered for marketing in Europe. Access to the dataset used in the present study was granted by the Dutch Medicines Evaluation Board. Although the present study is an extension of the study by Wangge et al,[10] complete details on these margins (ie, the methods used by pharmaceutical companies for defining the margins, and, in cases of rejected margins, alternative margins recommended by the EMA) were not provided in the published study by Wangge et al.[10] Of the 35 noninferiority margins discussed in that study, we excluded the 5 margins used for determining equivalence.

Information on whether a pharmaceutical company followed the EMA's recommendation was collected from the public domain of the EMA, registries of clinical trials (ClinicalTrials.gov and the EU Clinical Trials Register), and published trials. This information was also collected from centralized marketing-authorization applications (if such an application was submitted by a pharmaceutical company to the EMA), using the database of the Dutch Medicines Evaluation Board. Data on approval status were collected from the public domain of the EMA website.

COMMENTS AND DISCUSSION

How Margins Were Defined and Why They Were Rejected

Among the 30 margins included in the analysis, 12 (40%) were defined based on clinical and statistical considerations (Table I). There was no apparent concern from the EMA on the statistical approach used by the pharmaceutical companies for defining 11 of these 12 margins. The reason for the rejection of 1 margin was not due to the choice of the margin itself, but rather due to the choice of the active comparator. Eight of the 12 margins were based on information from historical randomized, controlled trials of the active comparator versus placebo. Among these 8, 7 were based on the pooled effect estimate of the active comparator, and 1 was based on the limit of the CI that was closer to the null effect. The other 4 margins were not based on information from historical trials, but rather on an indirect comparison with a historical placebo arm or noncomparative historical data. It seems that choosing the point estimate rather than the limit of its 95% CI for defining the margin was the main statistical approach that was accepted by the EMA (even though the EMA did not state a preference in the 2005 guidance). The US Food and Drug Administration (FDA), however, prefers a more conservative approach that is based on the limit of the 95% CI of the pooled effect estimate. The reason for this preference, as explained in the 2010 FDA guideline on noninferiority trials, which was finalized in 2016,[11] is the concern about the variability in the effect estimates of the active comparator from the historical controlled trials.[4] The impact of the FDA's

Table I. Approaches followed by pharmaceutical companies to define proposed non-inferiority margins (N = 30 margins).

Approach	No. of Margins
Clinical and statistical considerations	12
Based on the point-estimate from the historical data	7
Based on the limit of the confidence interval that is the closer to the null effect	1
Based on uncontrolled data from the historical evidence	4
Data not sufficient to classify the method or to identity the margin was actually derived from the historical evidence of the active comparator*	9
Not stated (although the approach was not stated for one margin, there was a mention of a discussion about the approach in previous meeting)	5
Used previously in similar trials	3
Regulatory guidance	1

* For some margins, the pharmaceutical company stated that the margin was also used previously in similar trials.

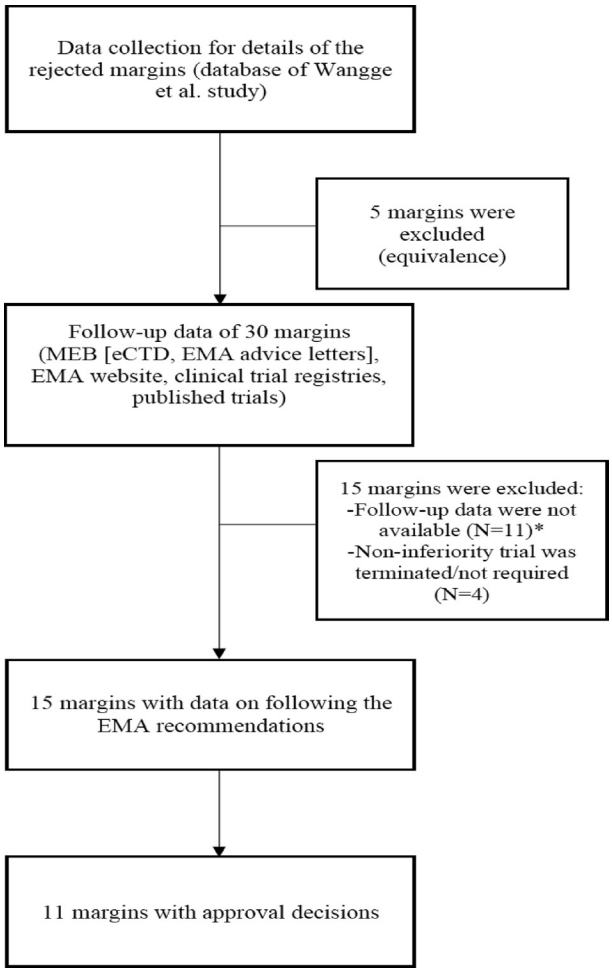

Figure 1. Collection of data on the details, the following of recommendations, and the approval decisions for drugs that were planned to be assessed using 35 noninferiority margins. EMA = European Medicines Agency; MEB = Dutch Medicines Evaluation Board; eCTD = Electronic Common Technical Document. *For some drugs, an application for marketing authorization was submitted to the EMA.

preference was noticed in a study that showed that the use of this approach increased substantially after the FDA's publication of the draft guidance on noninferiority trials in 2010.[16] It would be helpful for researchers to know whether the EMA shares the preference of the FDA.

The reason for the rejection by the EMA of the margins that were defined based on clinical and statistical considerations was the preserved fraction that was deemed unacceptable, except for the one that was rejected because of the unacceptable choice of the active comparator. The EMA recommended using stricter margins (ie, larger preserved fractions) in 9 cases. In the cases of 3 margins, the EMA concluded that a noninferiority trial was not feasible if stricter margins had been used. All 3 of these margins were based on noncomparative historical data. Among the rejected margins, the most commonly used preserved fraction was 50% (in 7 of 12 margins for which the preserved fraction was stated, the range was 42%–72%), which may suggest that the EMA does not consider a 50% preserved fraction clinically acceptable for most drug efficacy outcomes. The choice of the preserved

Table II. Details on pharmaceutical companies' refusal to follow the European Medicine Agency's (EMA) recommendation on rejected non-inferiority margins.

Drug	Comparator	Indication	Margin	Response From the EMA	Justification for Not Following the EMA's Recommendation	Approval by the EMA
Peginesatide (AF37702)[12]	Epoetin alfa	Treatment of anemia in dialysis and nondialysis patients with chronic kidney disease	Mean change in hemoglobin levels from the baseline of 1 g/dL	Margin was wide (0.5 g/dL was recommended)	No (trial was ongoing)	No
Menveo[13]	A/C/Y/W-135 meningococcal polysaccharide vaccine	Immunization of children aged >2 y to prevent invasive meningococcal disease	A difference in seroresponse of 10%	The margin was considered wide	No (the pharmaceutical company was expecting superiority findings)	Yes
Edoxaban[14,15]	Warfarin	Prevention of stroke or systemic embolism in patients with nonvalvular atrial fibrillation	Hazard ratio of 1.38	The margin was considered wide	No justification was provided in the EMA public assessment report, but the FDA approval package states that the margin was accepted by the FDA	Yes
Antidiabetic 1*	Antidiabetic	Type 2 diabetes mellitus	Mean difference from baseline HbA_{1c} of 0.4%	The margin was considered wide (0.3% was recommended instead)	No (the pharmaceutical company stated in the EMA marketing authorization application they did not change the margin because it was accepted by the FDA)	Yes

(*continued on next page*)

Table II. (*Continued*)

Drug	Comparator	Indication	Margin	Response From the EMA	Justification for Not Following the EMA's Recommendation	Approval by the EMA
Antidiabetic 2*	Antidiabetic	Type 2 diabetes mellitus	Mean difference from baseline HbA_{1c} of 0.4%	The margin was considered wide (0.3% was recommended instead)	No (the pharmaceutical company stated in the EMA marketing authorization application they did not change the margin because it was accepted by the FDA)	Yes

FDA = US Food and Drug Administration; Hb = hemoglobin.
* Data are confidential.

fraction in general depends on the effect size of the active comparator(s), how much effect size of the active comparator that stakeholders are willing to lose to fulfil an unmet medical need, and the feasibility of the trial (with regard to sample size) with the chosen preserved fraction.[1,4–9,17] In most of the other 18 of 30 margins that were defined by other approaches (Table I), the EMA stated that these margins were too wide and recommended stricter margins instead.

Acceptance of the EMA's Recommendations and Its Impact on Drug Approvals

Data on pharmaceutical companies' following of the recommendations of the EMA were available for only 15 of 30 margins (Figure I). Most of these data were found in EMA public assessment reports (n = 7) and the drug-registration documents from the Dutch Medicines Evaluation Board (n = 3). The EMA's recommendations were followed in the cases of 10 of the 15 margins (67%), and were ignored in 5. A company's refusal to adhere to the recommendations was due to the following reasons: the margin had been accepted by the FDA (n = 3), the trial was ongoing by the time of the scientific-advice request (n = 1), and the company was expecting a result of superiority over the active comparator (n = 1) (Table II). The first 3 margins were considered too wide by the EMA, whereas the FDA concluded that they were sufficiently strict for assessing noninferiority. One of them was defined following the statistical approach preferred by the FDA (ie, defining the margin based on the limit of the CI that was the closer to the null effect). This margin, a hazard ratio of 1.38 for the risk for stroke or systemic embolism among patients with nonvalvular atrial fibrillation, was determined with a 50% preserved fraction, which was considered lenient by the EMA. As discussed earlier, the preserved fraction is arbitrarily chosen based on data that experts consider to be clinically relevant. This subjectivity is reflected in the variability of the preserved fractions that were used in the published noninferiority trials (0%–85%).[18–22] Guidance on the proper choice of this fraction, with illustrative examples, might help to decrease the number of follow-up scientific-advice requests/meetings needed for a decision on the margin, and may minimize the likelihood of disagreement between the EMA and the FDA. The

other two cases in which the EMA concluded differently than the FDA concerned a margin that is considered generally accepted for noninferiority analysis of antidiabetics. In response to a request for scientific advice on 2 new antidiabetics, the FDA twice accepted as a noninferiority margin a reduction from baseline in hemoglobin A1c of 0.4%. However, the EMA recommended a 0.3% reduction from baseline in hemoglobin A1c as a margin instead. The FDA has stated that a reduction from baseline in hemoglobin A1c of 0.3% or 0.4% is typically acceptable as a noninferiority margin for antidiabetics given that it is not greater than the estimate from the historical placebo-controlled trials of the active comparator, while the EMA considers 0.3% as generally acceptable.[23,24] Neither guideline shows why these margins are considered acceptable for noninferiority analysis.

The proportions of drugs approved by the EMA for which recommendations were and were not followed were similar—5 of 6 versus 4 of 5, respectively (Figure I)—suggesting that the approval decisions were available for only 11 margins; however, the numbers are insufficient to conclude whether a refusal to follow the EMA's advice could have affected the approval decisions, which can be assessed in a future study with a larger number of margins.

CONCLUSIONS

The present study shows that the main concern of regulatory authorities on proposals of noninferiority margins in scientific-advice letters is about the strictness of the proposed margin and what this would mean for clinical practice. Future studies using more recent data, including data from the FDA, may help in assessing the impact of guideline recommendations about noninferiority margins on drug approval and may assist in reaching consensus among regulators about the choice of a margin.

DISCLOSURES

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

ACKNOWLEDGMENTS

This work was supported by the Saudi Food and Drug Authority, which had no role in the preparation, review, or approval of the manuscript, and had no role in the publication of the article.

T.A., A.D., R.G., C.G.W., A.M.T., H.L., and O.K. wrote the article and designed the research: T.A. performed the research and analyzed the data: All of the authors have declared that the contents of the article are true and approved the final version of the article.

The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of, or reflecting the position of, the EMA or one of its committees, working parties, or any of the national agencies. This work was part of Turki Althunians PhD project. The PhD fees were paid by his employer (the Saudi Food and Drug Authority).

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