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Today's Challenges in Pharmacovigilance

What can we Learn from Epoetins?

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Abstract

Highly publicized safety issues of medicinal products in recent years and the accompanying political pressure have forced both the US FDA and the European Medicines Agency (EMA) to implement stronger regulations concerning pharmacovigilance. These legislative changes demand more proactive risk management strategies of both pharmaceutical companies and regulators to characterize and minimize known and potential safety concerns. Concurrently, comprehensive surveillance systems are implemented, intended to identify and confirm adverse drug reactions, including the creation of large pharmacovigilance databases and the cooperation with epidemiological centres. Although the ambitions are high, not much is known about how effective all these measures are, or will be. In this review we analyse how the pharmacovigilance community has acted upon two adverse events associated with the use of erythropoiesis-stimulating agents: the sudden increase in pure red cell aplasia and the possible risk of tumour progression associated with these products. These incidents provide important insight for improving pharmacovigilance, but also pose new challenges for regulatory decision making.

The occurrence of high-profile safety issues in the recent past, such as the market withdrawal of cerivastatin (Lipobay®) in 2001 and of rofecoxib (Vioxx®) in 2004 has led to an increased and renewed focus on the safety of medicines.[1,2] Although proposals for preparing pharmacovigilance systems for future needs has been ongoing for some time,[3] it seemed that these cases brought the theme of drug safety to the attention of a wider audience. This and other safety issues, such as with rosiglitazone (Avandia®),[4] led to debate on the role of pharmacovigilance systems and regulatory agencies.[5,6] What followed was an extensive assessment of the workings of pharmacovigilance systems and discussions on the legislative possibilities of regulatory agencies.[7-9]

Both in the US and the EU, regulatory requirements have been developed to recognize and address both known and unknown safety concerns for newly approved drugs (figure 1). In the US, companies are now occasionally required to submit a risk evaluation and mitigation strategy (REMS), and in Europe, risk management plans (RMP) for new products need to be submitted to the regulatory authorities and implemented. Such requirements are aimed at recognizing (possible) safety concerns that have been inadequately addressed in the clinical development phase and to devise strategies for the minimization of known risks. In both cases, specific actions may be necessary to address identified and potential safety concerns and important missing information.[13,17]

Simultaneously, there is an ongoing effort to strengthen pharmacovigilance tools (figure 1).[9] In Europe this resulted in the agreement of the European risk management strategy including the implementation of the European Network of Centers for Pharmacoepidemiology and Pharmaco-

Legislative developments:
Both in the US and the EU, regulators now require the provision of detailed risk management strategies as part of an application for marketing authorization. With the adoption of directive 2004/27/EC in the EU, it is now mandatory to submit a risk management plan (RMP) for all new active substances, biosimilars and generics of substances for which a risk has been identified for the reference product.[10] Furthermore, an RMP can be requested by regulatory authorities, e.g. following changes in the marketing authorization or in response to newly identified safety issues. An RMP consists of an overview of the current safety situation of a product, a pharmacovigilance plan and, if necessary, a detailed description of proposed risk minimization activities.[11]
Similarly, changes introduced in US legislation by the 2007 US FDA Amendment Act have given the FDA the possibility of requiring the submission of a detailed plan to ensure the safe use of a product. These risk evaluation and mitigation strategies (REMS) contain an analysis of possible risks and measures to manage known or expected safety issues.[12] Unlike the European RMPs, REMS are requested by the FDA on a case-by-case basis. Changes in legislation have ensured that both the EU and the FDA have the means to enforce these commitments through re-authorization procedures, monetary penalties or even product withdrawals.[13] In Europe, amendments to existing legislation have been adopted that are aimed at further improving pharmacovigilance practices.[14]
Tools and methods:
A second development is the introduction of systems that will enable proactive monitoring of drug safety. In the US in 2008, the first steps have been made to create a new system that will allow the proactive monitoring of products. This Sentinel system will be a public-private partnership that should result in an electronic system that is able to query a multitude of data sources in order to monitor the safety of medicines.[15] The aim is to build this system, as much as possible, on existing data sources, including electronic medical records systems, administrative claims databases and registries. The aim is to design a system that is able to both detect new signals and confirm emerging safety issues. The systems will depend on close collaboration with various experts from both public and private institutions. In Europe, the first steps have been made in developing the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP).[16] Like the Sentinel system, ENCePP is formed by a network of existing pharmacoepidemiological centres and databases. It is a key part of the European risk management strategy and one of the key goals is to enable a proactive approach to monitor drug safety. Besides improving the safety of medicines, both systems aim to provide a platform for pharmacoepidemiological research.

Fig. 1. Developments in pharmacovigilance.

vigilance (ENCePP) project. In the US, the FDA launched the Sentinel Initiative as part of its Critical Path Initiative. Although differences exist, both programmes are strongly focused on increasing technical capabilities of safety signal detection through the development of new data collecting systems, linking of existing databases and collaboration between pharmacoepidemiological centres. It is expected that this will allow faster and quantitative assessment of safety signals, both those signals recognized at marketing authorization as those emerging during the product's life cycle.[15,18]

What can we expect from these developments and how will they add to the solving of current impediments of pharmacovigilance? The possible effects of these developments on the performance of regulatory systems have been the subject of discussion.[9,18] We aim to build upon these discussions and provide examples around erythropoiesis-stimulating agents (ESAs) in order provide insights into the opportunities and challenges of these legislative and methodological developments.

1. Safety Issues Associated with Epoetin

Erythropoietin is hormone glycoprotein that promotes proliferation of red cell precursors, thus increasing the amount of circulating erythrocytes. Over the past years, ESAs have been the subject of extensive regulatory scrutiny. Renewed concerns on the safety of ESAs were triggered by a recent publication indicating an increased risk of stroke in pre-dialysis renal patients receiving darbepoetin versus patients receiving placebo.[19] The results of this study emphasize the importance of continuous evaluation of the benefit-risk balance of products throughout their lifecycle. The first ESA, epoetin-α, was authorized in 1988 in Europe (Eprex®) and 1989 in the US (Epogen®) for the treatment of anaemia in patients with chronic renal failure.[20] In 1993, the approval was extended in the US to include the treatment of anaemia in patients with non-myeloid cancer receiving chemotherapy; the EU followed in 1994.[21,22] ESAs have subsequently demonstrated favourable benefit-risk balance in yielding autologous blood from patients in predonation programmes, reducing exposure to allogenic blood transfusions in patients undergoing major elective orthopaedic surgery. In the US only, ESAs are authorized for reducing anaemia in zidovudine-treated HIV-infected patients. The most common serious adverse reactions to epoetins are connected with its mechanism of action. These include cardiovascular events, hypertension and thrombotic events, which may be explained by the increased haematocrit resulting from ESA treatment.[23-25] Two adverse events associated with the use of ESAs have had a profound impact on their use, i.e. pure red cell aplasia (PRCA) and risks of increased tumour progression. We will provide a short overview of the history of these cases; for more extensive reviews of these cases the reader is referred to McKoy et al.[26] for the PRCA case and Glaspy[25] for the tumour progression case.

1.1 Pure Red Cell Aplasia

PRCA is a rare haematological disorder characterized by severe anaemia, very low levels of reticulocytes and a (virtual) absence of erythroid precursors in the bone marrow. The pathology of PRCA varies; in patients receiving the epoetin-α Eprex® it was found to be the result of the formation of antibodies against recombinant erythropoietin cross-reacting with endogenous erythropoietin.[27] Only one confirmed case of PRCA due to anti-erythropoietin antibodies had been described in 1996.[28] Until 1998, the incidence of antibody-mediated PRCA was very low, with only three described cases of antiepoetin antibody formation.[29-31] In 1998, this changed when the number of reported PRCA cases associated with ESAs increased. Urgent safety restrictions were initiated to warn of the possibility of PRCA in patients receiving ESAs by the end of 2001 in several countries outside the US. Global awareness of this adverse event was sparked in early 2002, through the publication of a case series of renal patients who developed PRCA while receiving subcutaneous ESAs.[27] In the period that followed, over 200 cases were identified and the apparent increase in immunogenic properties was mainly ascribed to a change in the formulation of pre-filled syringes of epoetin-α marketed outside

the US (Eprex®) where human serum albumin was replaced as a stabilizer by polysorbate 80 and glycine.[32] To counter this increase in PRCA, regulatory authorities in Europe contraindicated the subcutaneous administration of Eprex®. Simultaneously, the marketing authorization holder of Eprex®, Johnson & Johnson, issued warnings to healthcare providers in Europe, Canada and Australia.

It is widely accepted that the formulation change led to alterations in the product. This change was implemented in response to a request by the Committee for Human Medicinal Products (CHMP) to prevent a (theoretical) risk of transmission of Creutzfeldt-Jakob disease through human serum. However, the question of how this could lead to PRCA was the subject of intense debate. The hypothesis brought forward by the manufacturer of Eprex® suggested that the new formulation 'leached' organic molecules from the stoppers of the pre-filled syringes. This was addressed by replacing uncoated stoppers with Teflon coated stoppers. Another hypothesis suggested that the new formulation could lead to a higher concentration of aggregates, which could be worsened by exposure to changes in temperature. Changes were implemented, both in the production process and in the distribution chain, to ensure that the proper temperature was maintained, the 'cold chain management'.[33] Following the regulatory measures restricting the use of Eprex® and the changes implemented by its manufacturer, the number of reported cases of PRCA in patients receiving ESAs steadily dropped. This supported the idea that PRCA was an adverse reaction mainly associated with Eprex®. In May 2006, the subcutaneous use of Eprex® was reintroduced, but only for patients who had no intravenous access. Two large, prospective, observational studies to assess the incidence of PRCA in patients receiving any ESA (EPO-IMU-401 and EPO-IMU-402) were initiated by the marketing authorization holder in 2003. The studies enrolled 9791 patients and found 15 patients who showed an unexplained loss of response, but none developed PRCA. One patient was borderline positive for anti-erythropoietin antibodies without it leading to clinical symptoms.[34] This study has stopped enrolment based on a greatly reduced rate of spontaneous reported cases of PRCA. A registry (the 'Prospective Immunogenicity Surveillance' [PRIMS] registry) that will assess the immunogenicity profile of all currently available ESAs for a period of 3 years is ongoing. No results from this study are currently available.

1.2 Increased Risk of Tumour Progression

More recently, the use of all ESAs for the treatment of chemotherapy-induced anaemia has been restricted both in the US and the EU. These restrictions followed (interim) results of post-approval clinical trials that indicated increased mortality and tumour progression in patients receiving ESAs compared with patients receiving placebo. Concerns that erythropoietin may stimulate tumour progression were already expressed when epoetin-α received market authorization for chemotherapy-induced anaemia in 1993. These concerns emerged because of the finding that erythropoietin could stimulate endothelial cell proliferation *in vitro*, a process that is thought to be linked to angiogenesis and tumour growth.[35] This resulted in a postmarketing commitment to the FDA upon approval to conduct a study on the possible stimulatory effects of epoetin-α on solid tumour growth, study N93-004. This study, initiated in 1993, was to be prematurely terminated in 2002 having enrolled only 224 of 400 patients and failing to demonstrate differences in tumour progression or overall survival.[36]

The following year, in 2003, the first study was published that demonstrated a significantly increased mortality of patients with head and neck cancer treated with epoetin-β to a target haemoglobin (Hb) level of ≥15 g/dL in men (or ≥14 g/dL in women) versus patients receiving placebo.[37] This high target value was chosen because previous studies suggested that anaemia reduced the efficacy of chemotherapy.[38] This study was the first well designed, randomized controlled trial that demonstrated a significantly increased locoregional tumour progression in patients receiving an ESA versus placebo. Finally, a third clinical trial maintaining Hb levels of ≥13 g/dL in patients

with breast cancer showed an increase in mortality in patients receiving ESAs.[39] These clinical findings led to warnings in the prescribing information in 2004 (US) and Summary of Product Characteristics in 2005 (EU) of all ESAs. However, controversy remains on what the effects of ESAs were in approved target Hb levels (>10 and ≤12 g/dL). Clinical data are still awaited to answer this question. Interim results of two further clinical studies demonstrated a decreased survival rate in patients receiving ESAs.[40,41] Following these results, as of 2008, regulatory authorities in the US and EU issued warnings not to prescribe ESAs for the correction of anaemia in cancer patients undergoing curative treatment, preferring blood transfusion over ESA treatment in these patients.[42,43] Although regulatory measures have been taken to limit the use of ESAs for chemotherapy-associated anaemia, there is still uncertainty about what may cause this increased mortality. While consensus exists that treating patients to achieve high Hb levels increases the risk for thromboembolic events and death, the possible stimulatory effects of ESAs on tumour progression remain uncertain.[44] Applying the legislative changes introduced by the FDA Amendment Act of 2007, the FDA imposed REMS for epoetins in the US in April 2009. The REMS include the creation of a medication guide explaining the risks of epoetins when used in an oncology setting and a training programme (Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs [APPRISE]) that each prescriber of epoetins needs to complete. Physicians who are not enrolled in APPRISE may be suspended from access to ESAs. The programme covers the risks associated with epoetins and should ensure that every healthcare provider discusses these risks of ESAs with their patients before initiating treatment. The regulatory actions that were initiated in both cases in Europe and the US are depicted in figure 2.

2. What were the Challenges of these Cases?

Both cases deal with serious safety issues and reflect the difficulties in dealing with early pharmacovigilance data. Furthermore, they demonstrate the gap between data that are needed to fully weigh the relevance of adverse events and the data that are available. During development of the first ESAs, the formation of anti-epoetin antibodies was suspected. However, no cases of antidrug antibody formation were reported during the clinical development of epoetin-α or in the first years after the product entered the market. Suspicions on the possible stimulatory effects of erythropoietin on tumour progression also already existed at the time of approval for the treatment of chemotherapy-induced anaemia in 1993. However, it was not until 2004 that the first regulatory warnings were issued. The high background incidence of tumour progression in the target population hampered the detection of additional risk in individual patients receiving ESAs. This made it nearly impossible to confirm a relation between the use of ESAs and the adverse events without performing adequately powered clinical studies. When the results of these studies became available, the information provided related to patients who were treated in order to achieve high Hb levels (>13 g/dL). This led to controversy on how these results were to be interpreted for patients treated with approved doses. Three other studies, of which two were performed using 'on label' dosing regimens did not demonstrate an apparent reduction in overall survival.[36,45,46] Furthermore, anaemia was found to be associated with lower survival rates in various cancers, which may lead to survival results that were confounded by indication.[47] The controversy was further complicated by the fact that the first study results related to head and neck cancer and late-stage breast cancer, whereas no data were available for other cancers. As more data emerged from other studies[48] it became clear that these negative effects occurred for multiple cancers. While several studies confirmed the overall negative effects on overall survival and warranted regulatory measures, only a limited number of studies included endpoints that included measures of tumour response and/or local regional progression.[48,49] The role of erythropoietin in tumour progression is still being debated.

In the case of PRCA, the diagnosis was adequately made by haematologists and, once the

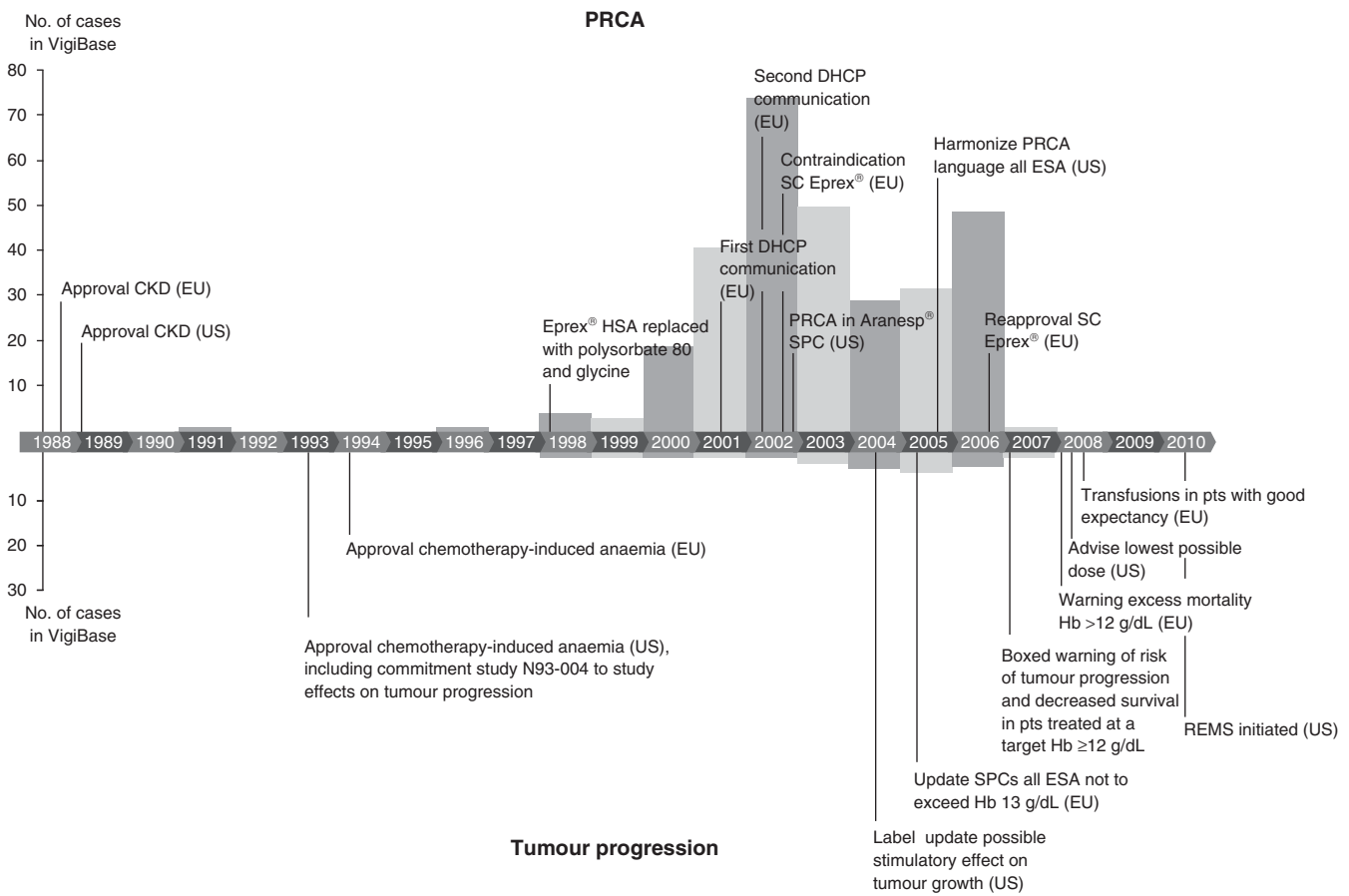

Fig. 2. Timeline of regulatory events based on US and EU label updates. Regulatory events are based on documents issued by the US FDA, European Medicines Agency (EMA) and company websites. VigiBase is the adverse event database maintained by the WHO. It contains adverse events reported in 94 countries and holds over 4 million case reports. We performed a search in VigiBase using WHO Adverse Reactions Terminology (WHO-ART) to identify all reports of pure red cell aplasia (PRCA) [protruding upward] and tumour progression (protruding downward) in patients receiving any erythropoiesis-stimulating agent (ESA) that was added to VigiBase up to 31 December 2008. The search yielded 344 reports of PRCA and 23 cases of tumour progression. The graph includes only those cases for which a date of onset was reported or, if this was not available, the date when the treatment was stopped. For PRCA, only patients with a diagnosis of PRCA, regardless of the presence of anti-erythropoietin antibodies, were included. It does not include patients with anti-erythropoietin antibodies without a diagnosis of PRCA (n = 304). The tumour progression group includes all cases of 'neoplasm aggravated' (n = 7) and 'condition aggravated' (n = 16) when the indication was malignant disease (n = 10). It does not include cases of new neoplasms or cases of aggravation of anaemia due to haematological malignancies. Some preferred terms for specific neoplasms may include aggravation of malignancy; however, we did not include these terms. **CKD** = chronic kidney disease; **DHCP** = direct healthcare professional communication; **Hb** = haemoglobin; **HSA** = human serum albumin; **pts** = patients; **REMS** = risk evaluation and mitigation strategies; **SC** = subcutaneous; **SPC** = summary of product characteristics.

relation with anti-erythropoietin antibodies was demonstrated, the relation of this diagnosis to ESA treatment could be confirmed by the presence of these antibodies. As more cases of PRCA were reported, information from spontaneous reports was sufficient evidence to initiate regulatory actions. Altogether, this resulted in a considerably shorter time to regulatory action in the case of PRCA. Since this adverse event was mainly associated with a single product and alternative products were available, regulatory actions limiting the use of epoetin-α were relatively fast. Restricting the entire class of ESAs had further implications. Although the practice of providing allogenic blood transfusions has improved since epoetins have become available, and they provide an alternative, their use is also associated with complexities such as transfusion reactions, immunomodulation and possibly even tumour progression, in addition to practical issues such as the increased pressure on blood supplies.[50]

ESAs were initially approved for reducing the need for allogenic blood transfusions. Epoetin-α received marketing approval based on a limited number of patients. At that time, the risk of transmission of infectious disease, including HIV, through blood transfusions was of great concern.[51] In the 1980s and 1990s, various measures, including pre-donation screening programmes, had greatly reduced the number of transfusion-transmitted infectious diseases.[52] Such changes in the practice of collecting and testing of blood supplies greatly improved the safety of transfusions, thus decreasing the need for reducing their use. In addition to reducing transfusion requirements, the first ESA trials in renal patients also reported increased energy and generally improved quality of life (QOL).[20] The first trials that demonstrated an improved QOL following ESA treatment were performed in renal patients who had baseline Hb levels of <7 g/dL. Subsequent studies have not convincingly demonstrated a further improvement in QOL in patients treated to achieve Hb levels >11 g/dL. The benefits of ESA therapy were widely accepted in nephrology. Early clinical guidelines recommended an Hb target of between 10.5 and 11.5 g/dL.[53] However, this universal acceptance of the benefits of ESAs had a downside. It prevented the execution of well designed studies to establish the optimal dosage of ESA on the grounds that it was deemed unethical to withhold patients from treating their anaemia.[54] This changed with the publication of the CHOIR (Correction of Hemoglobin in the Outcomes in Renal Insufficiency) trial in 2006, where no benefit of treating patients with high doses of ESA was found.[55] In 2009, the results of the TREAT (Trial to Reduce Cardiovascular Events With Aranesp Therapy), were published. This trial studied the possible protective effect of darbepoietin on cardiovascular disease.[19] Besides finding an increased incidence of stroke in patients receiving darbepoetin, the results also showed a negligible improvement in QOL in patients treated to achieve high Hb (>12 g/dL) versus patients in the comparator group. The beneficial effects on QOL of ESA treatment for chemotherapy-induced anaemia were more controversial. Early clinical practice guidelines on the use of ESAs in oncology questioned the positive effects of ESA on QOL because of a lack of well defined studies using accepted outcomes.[56] In 2007, doubts about the positive effect of ESA treatment on QOL in oncology patients persisted.[57] When, in 2003, results emerged demonstrating a reduced overall survival for patients receiving ESA, this shifted the ultimate treatment goal to overall survival.

The described cases illustrate some important challenges for the practice of pharmacovigilance. First, finding new associations between a product and an adverse event and, second, confirming a relationship between a product and a suspected adverse event in a relevant patient population. Pharmacovigilance also has a sentinel function to monitor changes in the benefit-risk profile of pharmaceuticals. These functions are discussed in more detail below.

3. Benefits and Pitfalls of a Proactive Approach

Pharmacovigilance has been described as 'a search for the unexpected'.[58] One could argue that with increasing knowledge of medical sciences and improved preclinical methods, pharmacovigilance may be becoming less about finding *new*

associations and more about confirming, characterizing and quantifying expected and/or suspected associations in real patient populations. Adverse drug reactions are often characterized as 'related to a product's pharmacology' (type A reactions) or unexpected, rare reactions (type B reactions).[59] According to this classification, the effects of epoetins on tumour progression could be regarded as a type A reaction, and PRCA as a type B reaction. However, this depends on how 'unexpected' is defined. Often suspicions of adverse reactions already exist at the time of marketing authorization. The possible stimulatory effect of epoetins on tumour progression was already suspected at the time of market authorization. Similarly, antibody formation was expected to occur for epoetins. The fact that erythropoiesis-inhibiting serum IgG could lead to PRCA was already known in the 1970s, and the first clinical studies on epoetins specifically looked for anti-erythropoietin antibodies but failed to detect them.[60,61] In that sense, these events are not unexpected but rather inadequately characterized. Which tools are to be employed to optimally characterize adverse events? The two cases demonstrate that different adverse events require different strategies to assess them. In table I we have summarized the characteristics of PRCA and tumour progression, along with various tools that were applied in assessing them.

3.1 What were the Methods Applied in Confirming Pure Red Cell Aplasia and Tumour Progression?

The causal relationship between Eprex® and PRCA could be verified through antibody testing. For these rare events, spontaneous reporting remains a principal method in identifying drug event relationships. On the other hand, the tumour progression case demonstrated that, in the absence of confirmatory methods and a high background incidence of the suspected adverse event in the treated population, it is nearly impossible for individual physicians to connect a pharmaceutical to an adverse event. This accords with only 23 cases of aggravated malignant neoplasms that were identified in the WHO-Uppsala Monitoring Centre (UMC) database, VigiBase (figure 2). Furthermore, spontaneous reporting systems have difficulties in differentiating between the occurrence of new malignancies and the progression of existing malignancies. In these cases, epidemiological or clinical studies need to be applied to demonstrate an association between a drug and an adverse event.

The creation of pharmacovigilance networks such as Sentinel and ENCePP will enable regulators to proactively screen for adverse reactions. The large size of these databases allows for the collection of great volumes of exposure data. This

Table I. Characteristics of two adverse events associated with erythropoiesis-stimulating agents and methods employed for characterization

Adverse event details	PRCA	Tumour progression
Characteristics		
Incidence in patient population	Very rare	Common
RR	High (RR >10)	Low (RR <1.5)
Relation with pharmacology	No	Yes
Methods		
Basic science findings, animal studies	+	+
Spontaneous reports	++	–
Retrospective observational studies	–	–
Prospective observational studies	+/–[a]	+/–[b]
Clinical trials	–	+
Meta-analyses	–	++

a Lack of power.

b Suboptimal study design.

PRCA = pure red cell aplasia; **RR** = relative risk; + indicates available results, ++ indicates available with clear results, +/– indicates available with uncertain results, – indicates not available/unclear results.

will enable the rapid assessment of possible safety signals; however, retrospective observational studies have limitations, two of which are illustrated by our cases. First, problems may occur in identifying very rare events in routinely collected data. An attempt to identify unreported PRCA cases using the US Medicare database failed to find additional cases and highlighted the inaccuracy of claims database coding in this particular case.[62] Second, slight increases in risks of events that are common may be hard to discern using observational data. We identified two small observational studies that demonstrated an increase in metastatic-free survival in patients receiving ESAs.[63,64] As we described, conflicting results emerged from various randomized controlled trials, which indicated a decrease in overall survival.

The recently adopted legislation will necessitate the creation of RMPs. Observational studies are increasingly applied in pharmacovigilance and they are seen as a useful supplementary approach alongside randomized controlled studies.[65] Prospective observational studies, such as those performed upon the reapproval of subcutaneous Eprex®, were not the optimal response to PRCA. The prime objective of these studies was to monitor the incidence of PRCA. It was designed to include 20 000 patients. When this study was initiated, much uncertainty remained on the actual incidence of PRCA. However, after having enrolled about half of the patients, the study was discontinued. No additional PRCA cases were detected. Although this observational study confirmed the low incidence of PRCA, in retrospect and given the increased awareness of PRCA, it was not the most efficient means of identifying new cases.

In certain cases, clinical studies may be the sole appropriate method to assess causality. No cases of PRCA have ever occurred during any clinical trial. The low incidence of PRCA, combined with an average time to onset of 9 months or more, made clinical trials not very suitable for the characterization of this event. Because tumour progression occurs frequently in patients receiving ESAs, clinical trials were the most suitable tool. However, trials are costly and take time to accumulate the necessary data – 8 years in the case of tumour progression. Also, the data were not consistent between different trials. Only after time, when more and more data became available, the balance shifted toward initiation of regulatory actions.

4. Sentinel Function

Besides finding *new* associations between unwanted events and drug exposures, pharmacovigilance has a sentinel function, aimed at the timely flagging of relevant changes in frequency of adverse reactions that are known to be associated with a drug.[66] The Sentinel and ENCePP systems will create opportunities to monitor these events and may be instrumental in detecting rare events such as PRCA, provided they are adequately registered. However, it is unlikely that they will be able to reliably detect small changes in relative risk in patient groups with a high background incidence such as tumour progression. Increasing the size of databases may also increase the number of signals that may warrant further investigation, thereby creating new regulatory challenges.[18] With the advent of biopharmaceuticals and their increasing use in clinical practice, spontaneous reporting may have a renewed importance in monitoring the frequencies of events that are related to the immunogenicity of biopharmaceuticals. Eprex® had been on the market for 10 years before PRCA emerged as an adverse event. The PRCA case demonstrates that adaptations to the manufacturing process may have unforeseen effects on the immunogenicity of a product. While this will often not have clinically relevant effects, in rare cases it may lead to significant changes in the benefit-risk balance of a biopharmaceutical. Spontaneous reports are often the first indication of an increase in frequency in a drug-event relationship and the first step of this sentinel function. These effects can occur anywhere in the lifecycle of a product and may not be adequately characterized by post-approval safety studies. Therefore, there is a need for methods to continuously measure a product's benefit-risk balance. It has not been decided if the Sentinel system will be used for routine prospective monitoring for unknown events, or whether it will be

used to monitor predefined suspected drug-event pairs.[67] Therefore a role for spontaneous reports will remain essential for the monitoring of safety of products.

5. Discussion

The question that remains is 'will the response to these cases be different in the future'? The introduction of risk management planning and the creation of elaborate systems to facilitate proactive screening has handed regulators new tools to identify and respond to safety issues, but what can we learn from ESAs to optimally use these legislative and methodological developments?

Several matters might have been prevented if these systems had been in place. A key concern that ESAs could promote tumour progression already existed at the approval of epoetin-α for chemotherapy-induced anaemia in 1993. However, it took nearly 10 years before the first data became available that provided evidence related to this issue. The new legislation could have enforced the timely collection of the data. Proactive risk management could have ensured that well designed, on-label studies were performed, which may have prevented a lot of controversy over how to interpret the data. On the other hand, the PRCA case shows that great care must be taken to balance the need of providing high quality data to answer safety concerns and the resources required to provide these data. Proactive risk management will aid the identification and management of expected adverse events. However, it is not an answer to changing safety profiles of marketed biopharmaceuticals due to manufacturing changes in later phases of their lifecycle. The PRCA example shows that well meaning risk mitigation strategies can have very serious unintended consequences. Possible unintended effects of these measures should be evaluated and post-marketing surveillance may have a role in monitoring the possible consequences of risk mitigation measures. Biopharmaceuticals are increasingly used and the possibility of immunogenicity-associated adverse events, such as PRCA, thus remains. Despite efforts to design strategies to cope with the risks of unwanted immunogenicity of biopharmaceuticals, subtle changes in the product causing immunogenicity may not be identified before a drug is administered to large groups of patients.[68] The PRCA case demonstrates also that these changes may not be identified without the insights of observant physicians and/or researchers. Harnessing this resource through collecting reports will therefore remain essential for such adverse events. Even though the level of evidence of case reports may often be regarded as poor, spontaneous reports contribute to the majority of safety withdrawals.[69] However, when no doubts exist on the causal relationship between an adverse event and a drug, spontaneous reports may be the sole source for regulatory action. This was also the case for the monoclonal antibody efalizumab (Raptiva®), which was suspended in 2009 after three confirmed spontaneously reported cases of progressive multifocal leukoencephalopathy (PML).[70] Immunogenicity-related adverse events provide a high level of certainty about expected causality. Recently, a framework has been proposed to assess definitive evidence of causality based on spontaneous reports.[71] This framework has been proposed as an augmentation to existing methods to establish causality based on criteria as those outlined by Sir Bradford Hill in 1965.[72] Immunogenicity-related adverse events, such as PRCA, fit well within this framework of 'definitive causality'. Increasing the awareness of reporters for adverse events related to unwanted immunogenicity may be a key pharmacovigilance strategy to monitor these adverse events.

The measures taken to limit the use of epoetins cannot be understood without taking into account the changes in the perceived benefits of ESAs over time. ESAs were granted marketing approval based on relatively small trials that demonstrated a reduced need for blood transfusions.[20] Improved practices in the collection and testing of blood supplies greatly improved the safety of transfusions and thus reduced the need for preventing transfusions. Furthermore, claims that ESAs improved QOL in oncology patients were questionable.[57] When data emerged that pointed to a reduced overall survival due to ESA treatment, the benefit-risk balance had changed on

both the benefit and the risk side. Following restrictions of ESAs in the oncology field, results emerged from trials in the nephrology field that raised questions on the benefits of high Hb-targeted ESA treatment in renal patients. This has led to an overall critical attitude towards ESA treatment that may extend beyond the data that emerged from clinical trials.

It is surprising that these questions still need(ed) answering 20 years after receiving marketing approval. One can wonder why the increase in PRCA has never led to such regulatory scrutiny. Undoubtedly, the nature of PRCA was very different, its incidence was very low and the number of new cases had already decreased as a result of various regulatory actions. Regardless of these differences, at the time of PRCA, the therapeutic value of ESAs was virtually never questioned. In the period when the first results demonstrating a reduced overall survival emerged, criticism arose on the use of ESAs. The expenditure on ESAs had increased dramatically. By 2004, the mean administered ESA dose per patient had increased 4-fold compared with administration immediately after the approval of epoetin-α. Furthermore, half of the patients in the US were treated in order to achieve off-label Hb targets.[73] This led to fierce debate on the role of industry and its influence on clinical practice, which received widespread attention in various media. Altogether, the level of prevailing concerns surrounding anaemia treatment has played a critical role in the way these safety issues were handled. Following the FDA decision to adapt the label of ESAs, the US centres for Medicare and Medicaid services restricted the reimbursement criteria for ESAs. This resulted in even more stringent treatment criteria than those adopted by the FDA or existing clinical guidelines.[74]

Developments in pharmacovigilance tend to lead to 'technocratic' solutions for identifying and confirming possible adverse events. However, many other factors, that may be much less tangible, play a role in the weighing of safety issues. Therefore, careful consideration should also be given to the possibility of employing these legal and technical developments to address unanswered questions that are beyond adverse drug reactions. These should include studying patterns of use and evaluating the benefit-risk balance of medicinal products, particularly when less tangible aspects ('noise') tend to become more powerful in driving regulatory decision making than data and evidence.

The development of new methodologies and large databases containing longitudinal data on large numbers of patients, as is envisaged for the Sentinel system, will allow fast characterization of safety signals. The number of patients who will be included in these programmes may lead to considerable faster assessment of adverse events that are recognized or suspected at approval. This will have great advantages, especially for relatively rare serious events. However, as described for PRCA, extremely rare unexpected events may be difficult to identify in databases. Improving the quality of databases through linking data sources ('record linkage') may increase the likelihood of identifying such rare events. The feasibility of this has been demonstrated by the Research on Adverse Drug events And Reports (RADAR) project, which provides a platform to 'enrich' safety signals through combining information from multiple data sources.[75] While PRCA may seem an exceptional case, other extremely rare adverse events that have been reported for other biopharmaceuticals, such as reported cases of PML with rituximab or hepatosplenic T-cell lymphoma with tumour necrosis factor-α inhibitors, may not be described in sufficient detail or may not be adequately coded in large databases.[76,77] The recent approval of the glucagon-like peptide-1 (GLP-1) antagonist liraglutide left concerns of an increased risk of extremely rare medullary thyroid cancer.[78] Such cases may prove very challenging to identify. Traditionally, pharmacovigilance has focused on the identification of such serious, often rare, events. These can be described as 'classical' type B adverse events with a low incidence and a clear increase in relative risk in a patient population. The creation of tools such as Sentinel and ENCePP may greatly improve the detection and characterization of such events, provided they can be adequately identified. However, unlike PRCA, many of the recent regulatory shake-ups, including the much debated

Vioxx® case, occurred for events that were known or expected at the time of regulatory approval. Just as described for the possible stimulatory role of ESAs of tumour growth, the possible negative effects of hormonal replacement therapy were debated since it was first prescribed.[79] Also, in this case it took many years before the first data from clinical trials emerged, which provided answers to these concerns. Other recent examples include the possible excess cancer risk associated with insulin glargine and the withdrawal of rimonabant® due to depressive symptoms.[80,81] A shift in the emphasis of pharmacovigilance efforts has occurred, from not only detecting new rare events, but also to managing known and/or expected adverse events, as well as improving evidence of benefit and effectiveness. Often it is challenging to confirm or disprove such a suspicion without performing well designed clinical trials. Initiatives such as Sentinel and ENCePP will add a new tier of evidence, with careful consideration of risk management planning being essential to optimal application of all methods available when responding to these safety concerns.

The ESA cases described show that great care must be taken to use new methodologies optimally. They will add another tool to the toolbox for the identification and characterization of adverse drug reactions. To meet the challenges of pharmacovigilance in the future it has been proposed to carefully integrate safety data from multiple sources rather than striving to acquire evidence high up in the 'evidence-hierarchy'.[82] The cases that have been described here support this notion. To optimally respond to safety issues we need to take into account all the strengths and limitations of various pharmacovigilance tools. There is a need to evaluate how various methods are applied in detecting and responding to safety issues. To improve regulatory learning, there is a need to move to systematic learning from these safety issues. Through evaluating the performance of pharmacovigilance systems in dealing with the whole spectrum of adverse events we need to draw lessons from the past to construct the optimal way to identify and respond to unwanted drug effects in the future.

6. Conclusions

Proactive risk planning and improved pharmacovigilance tools and methods will add new opportunities for regulators, for sure, but the job is not done yet. We show here that challenges will remain in dealing with two very diverse safety issues associated with ESAs that teach valuable lessons for applying these newly acquired possibilities. Very rare or seemingly unlikely events, such as including those related to immunogenicity, may remain dependent on reports from observant individuals. Other known or expected events will require careful risk management planning and strict follow-up. To optimally use the increased possibilities provided by these developments, a systematic evaluation of how they are applied in practice is needed. Only then can we fuel regulatory learning to optimally respond to future safety issues.

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