

PREDICTABILITY OF ADVERSE REACTIONS TO BIOPHARMACEUTICALS

PhD thesis

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Budapest
2014

ÖSSZEFOGLALÁS

A farmakovigilancia változik, ma már nemcsak egy tudomány, mely passzívan várja és felismeri a nemkívánatos hatásokat, hanem aktívan előrelátóan keresi és kezeli a kockázatokat. A biotechnológiával készült gyógyszerek farmakovigilanciája a hagyományos kismolekulájú gyógyszerek minden nehézségével foglalkozik, és ezen felül figyelembe veszi azok speciális sajátosságait, köztük az immunogenitást.

A biotechnológiával készült gyógyszerek nemkívánatos gyógyszerhatásairól az amerikai FDA Medwatch Programjában végeztek kutatást, amely a monoklonális antitestekre adott biztonságossági riasztásokra fókuszált. A Medwatch biztonságossági riasztásokhoz a Kaplan-Meier féle időanalízist alkalmaztam, ahol az idő a biztonságossági riasztáshoz az eseményig eltelt időt jelenti, ebben az esetben a „túlélést”.

A kutatás eredményei azt mutatják, hogy a nemkívánatos gyógyszerhatások bizonyos fajta előrejelzése lehetséges a megfigyelt forgalomba hozatal előtti klinikai és nem-klinikai adatok alapján. A már megfigyelt nemkívánatos gyógyszerhatásokon kívül, egy nagyobb százalék előre jelezhető a gyógyszer szerkezete és a gyógyszer célpontja alapján (a gyógyszer hatásmechanizmusa és lehetséges nemkívánatos hatások). Az *in vitro* és *in vivo* prediktív tesztek kiszélesítése és ezek rutin klinikai használata hozzájárulhat a további kiszámíthatósági vizsgálatokhoz.

A Kaplan-Meier analízis eredménye alapján, egy kockázatkezelési terv segíthet a biztonságossági kockázat korai felismerésében. Egy biztonságossági kockázat felismeréséig eltelt idő közegészségügyileg rendkívül fontos. A biztonsági kockázatok korai felismerése csökkenti a nemkívánatos gyógyszerhatások által okozott morbiditást és mortalitást, ezáltal számos előnnyel jár az egészségügynek.

A nemkívánatos gyógyszerhatások előrejelzése különösen fontos magas rizikójú esetekben, ahol a várható előny szintén magas. Egy nemkívánatos gyógyszerhatás újbóli megismétlődése (rechallenge) egy jó példa arra, amikor az előny nem indokolja a kockázatot. A megismétlődés fontos minden gyógyszeres terápiában és terápiás kockázatkezelésben, azonban a biotechnológiával készült gyógyszereknél kialakult immunológiai nemkívánatos gyógyszerhatások esetében az újbóli megismétlődésnek sajátos kockázatjósító funkciói vannak. Minden egyes jelentős nemkívánatos hatásnak, mely potenciálisan a kezelés megszakításához vezet, van egy reakció specifikus kiújulási algoritmus. Ebben az esetben egy olyan mintán alapuló algoritmus alkalmazását javaslom, amelyet minden egyes magas-kockázatú, magas-előnyű esethez igazítani kell.

1 SUMMARY

Pharmacovigilance is changing. It is no longer a passive discipline of awaiting and detecting adverse reactions, but active in predicting and managing risks. Pharmacovigilance of biopharmaceuticals deals with all the complexities of conventional small molecule drugs, and on top of that, takes into account its own specificities. Most notably, this is immunogenicity. For biopharmaceuticals the task is, therefore, multiple-fold more complex.

Medical product database search for adverse drug reactions to biopharmaceuticals was performed on the US FDA Safety Information and Adverse Event Reporting Program (FDA Medwatch). The search focused on safety alerts for monoclonal antibody therapeutics. Kaplan Meier analysis of time to Medwatch safety alert was also applied, in which the time to safety alert was used as time to event i.e. “survival”.

The findings in this work indicate that a certain level of prediction of adverse drug reactions (ADRs) is possible based on observed pre-marketing clinical and non-clinical data. In addition to the actually observed ADRs, a large percentage can be predicted based on drug structure and the drug target (i.e. mechanism of action and potential adverse reaction). Expanding the spectrum of in vitro and in vivo predictive tests and their application in routine clinical use could contribute further to predictability assessment.

As demonstrated by the Kaplan-Meier analysis, risk management planning may lead to earlier detection of safety concerns. Time to detection of an important safety finding is of utmost importance to public health. Earlier detection of safety concerns leads to decreased morbidity and mortality due ADRs and hence a range of benefits to healthcare.

Predicting ADRs is particularly important in high-risk situations in which the expected benefit is also high. Rechallenge following an ADR is such an example in which the benefit may, or may not, justify the risk. Rechallenge is of importance in all pharmacotherapy and therapeutic risk management. However, in immunological ADRs to biotherapeutics, rechallenge has particular risk-predictive features. Each significant adverse reaction potentially leading to treatment discontinuation should have a reaction-specific rechallenge algorithm. A sample generic algorithm is proposed in this thesis which should be adapted to each particular high-risk high-benefit situation.

2 OBJECTIVES

The overall objective of this thesis is to identify and assess the factors determining the safety of biopharmaceuticals, taking into account all available non-clinical and clinical methods for evaluation. Immunogenicity is the most specific safety concern of biopharmaceuticals and therefore the focus of this thesis.

- The specific primary objective is to assess to what extent serious ADRs are predictable and to identify the available methods for reliable evaluation of immunological adverse reactions.
- Analysis of time to detection of ADR is also regarded as an individual objective, since early detection is of major importance for public health.
- Rechallenge of patients who developed an immune-mediated ADR is given special attention as a secondary objective. It is of particular importance for biopharmaceuticals as it may lead to a more severe reaction following subsequent administration.

The starting point is purely scientific evaluation of predictability based on the available literature sources including regulatory databases and scientific publications. However, regulatory aspects of benefit-risk assessment and risk management planning within the pharmaceutical development and product life cycle management are considered.

3 METHODS

Methods applied were twofold: The initial step consisted of regulatory authority medical product database search for US FDA Medwatch safety alert for adverse reactions to therapeutic monoclonal antibodies (mAbs). The second step was Kaplan-Meier analysis of time alert, based on the data collected as part of the initial step.

3.1 Regulatory authority medical product database search

Medwatch safety alerts for mAbs were taken as search trigger. Adverse reactions were cross-checked with the initial product label at the time of approval.

Alerts were assigned to one of the two categories:

- Observed: When increased frequency, severity, or other new properties were reported for essentially similar previously identified suspected adverse reactions.
- Not observed: Reactions not described in the product label. It does not refer to events which may have been suspected based on mechanism of action or chemical structure. This novel definition is based on objective clinical findings. It does not account for pharmacological-toxicological assessment of what may have been hypothesized.

Summary statistics were performed using Microsoft Excel.

3.2 Kaplan-Meier analysis

The Kaplan-Meier estimate is the simplest way of computing the survival over time in spite of difficulties associated with subjects or situations. It involves computing of probabilities of occurrence of event at a certain point of time and multiplying these successive probabilities by any earlier computed probabilities to get the final estimate. The analysis uses time to event, commonly referred to as “survival”. The equivalent to survival in this analysis is the time to Medwatch safety alert.

The analysis has been extended outside of its usual application to an unconventional type of data. Several modifications to the original intent and the usual use were implemented.

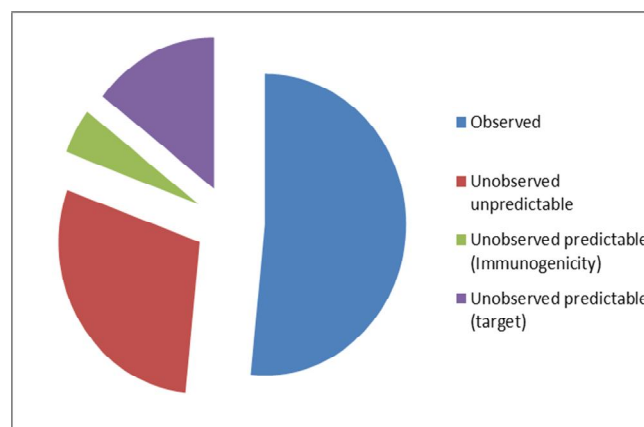
The analysis was performed using MedCalc software: Version 12.4.0 - Last modified: January 2, 2013, © 1993-2013 MedCalc Software bvba, MedCalc Software, Acacialaan 22, B-8400 Ostend, Belgium. <http://www.medcalc.org/>

4 RESULTS

4.1 Predictability of serious adverse reaction alerts for monoclonal antibodies

Until Dec-2009, inclusive, 36 mAb alerts were issued containing 61 terms; 32 were assessed as observed. Many reactions which were not observed could have been predicted: 3 alerts for immunologic reactions and another 9 arguably predictable based on antibody target. Therefore, 18 out of 61 alerts (29.5%) according to this extended classification remain unobserved and unpredictable.

Figure 1: mAb alert predictability



Many unobserved reactions could have been predicted, for example:

- Immunogenicity and anti-drug antibodies (ADAs), but no hypersensitivity reactions, were detected in pre-approval trials for adalimumab, basiliximab and daclizumab.
- Bevacizumab alert dated Ap2007 described cases of tracheoesophageal fistula. Very similar to gastrointestinal perforations described in initial label (Feb-2004) this is apparently a direct extension of bevacizumab's mechanism of action i.e. binding to vascular endothelial growth factor (VEGF).

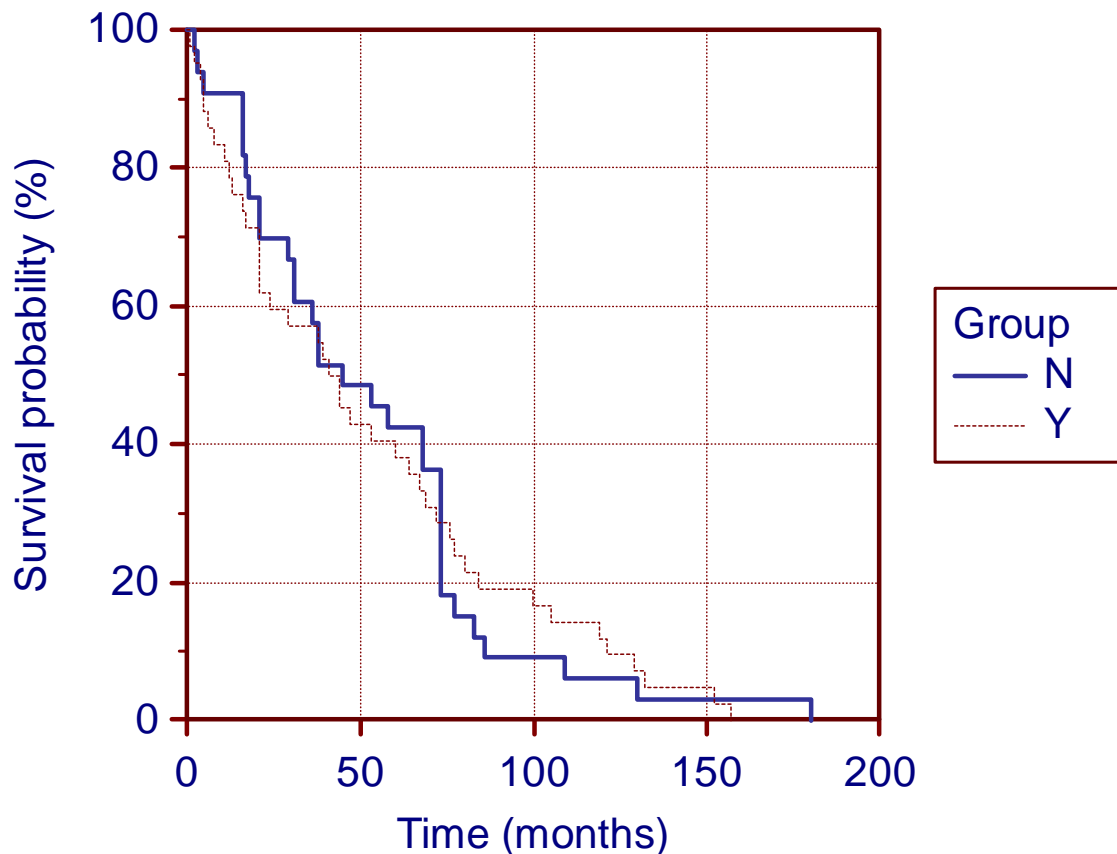
On the other hand, some alerts were issued for reactions classified as observed, such as:

- According to the initial Sep-1998 label: "HERCEPTIN administration can result in the development of ventricular dysfunction and congestive heart failure." This was based on trials using other cardiotoxic drugs (anthracyclines), but post-approval trials strengthened the evidence; so Aug-2005 cardiotoxicity alert was classified observed.
- Immunomodulation by TNF- α inhibitors lead to several alerts for increased rate of infections, in particular opportunistic infections including histoplasmosis and tuberculosis. Since an increased infection rate should dictate vigilance towards all infections, we classified these alerts as observed.

4.2 Kaplan-Meier estimate of time to safety alerts

Time to publication of safety alerts was assessed by means of Kaplan-Meier estimate. The time coverage was extended up to Sep-2013, inclusive. There were 75 alerts: 42 observed vs 33 unobserved. Median time to alert (median survival) is somewhat shorter for observed alerts (labelled Y) with respect to unobserved (labelled N): with 41 and 45 months, respectively. The mean time to survival is almost the same: with 52.55 and 52.52 months, respectively (Chi-square statistic gives a value of 0.001131. The statistical difference using logrank test is non-significant with a $P = 0.9732$. The absence of statistical difference is demonstrated by the graphical representation of the curves which are almost super-imposable (see Figure 2).

Figure 2: Kaplan-Meier survival curve of time to Medwatch safety alert



Legend: Observed alerts (labelled Y); Unobserved alerts (labelled N);

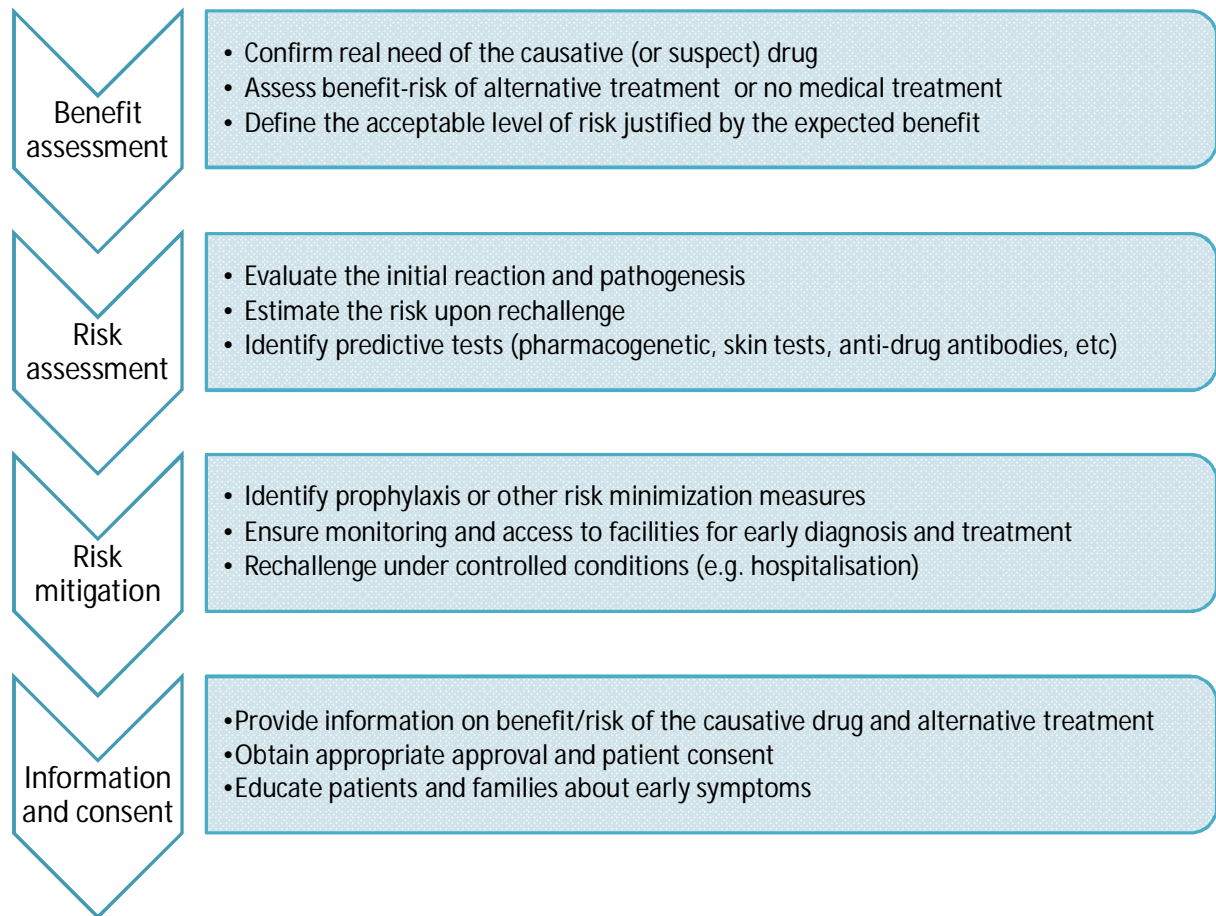
Even if not demonstrable by overall statistics over the entire period covered, the graph shows that there is a slight tendency of earlier reporting of observed alerts. Similarly to median values, the mean (SD) times to alert were also slightly shorter for observed alerts with respect to unobserved: 46.9 (39.6) and 51.2 (32.9) months, respectively.

5 NEW SCIENTIFIC FINDINGS:

- The findings in this work indicate that a certain level of prediction of ADRs is possible based on pre-marketing clinical and non-clinical data. At the same time, there is apparently insufficient effort placed on risk prediction and mitigation during drug development. The effort of drug manufacturers is understandably focussed on demonstration of safety and efficacy overall. Patients at risk of developing ADRs are often excluded from development programs due to risk of liability, but in real-life they equally require treatment.
- As demonstrated by the Kaplan-Meier analysis, risk management planning may lead to earlier detection of safety concerns. Time to detection of an important safety finding is of utmost importance to public health. Earlier detection of safety concerns leads to decreased morbidity, mortality due ADRs and hence a range of benefits to healthcare. At the same time, the application of Kaplan-Meier analysis has been extended to the field of risk management planning; a field in which it has not been traditionally used.
- Predicting ADRs is particularly important in high-risk situations in which the expected benefit is also high. Rechallenge following an ADR is such an example in which the benefit may, or may not, justify the risk. Rechallenge is of importance in all pharmacotherapy and therapeutic risk management. However, in immunological ADRs to biopharmaceuticals, rechallenge has particular risk-predictive features. It is proposed that each significant adverse reaction potentially leading to treatment discontinuation should have a reaction-specific rechallenge algorithm.

Before attempting rechallenge the treating physician must consider the following (Figure 3):

Figure 3: Points to consider in clinical decision making in the setting of intentional rechallenge



6 CONCLUSIONS

As in all pharmacotherapy and medical interventions in general, the expected benefits must outweigh the expected risk. Risk management for biopharmaceuticals is achieved by two principal means. The first step is risk estimation or prediction. This includes the measures taken to reliably assess risk factors of immunogenicity in a particular patient. The second step is risk mitigation, which covers the measures taken to decrease the risk to the minimum.

Pharmacogenomics showed success in estimating the likelihood of adverse reactions to several small molecule drugs. Several immunogenicity assessment tests have been evaluated, but better predictive factors still need to be established for biopharmaceuticals.

Risk of an ADR is particularly high when an ADR (or suspected ADR) has already occurred and the treatment should be resumed. Patients and populations at risk should be identified as part of risk-management planning. For biopharmaceuticals more than for other drugs, rechallenge following ADRs is a major challenge. The set of predictive methods should be particularly elaborate for such situations. A detailed algorithm for assessment of immune response tailored to each individual biopharmaceutical should describe the conditions under which benefit outweighs the risk.

Developmental (pre-registrational) as well as established post-marketing risk management and minimisation action plans should routinely address both predictive methods and mitigation of consequences of biopharmaceutical immunogenicity starting from early development. The assay battery used in pre marketing should form a package with the drug; therefore. This is in accordance with the current requirement in which an RMP is approved along with a drug.

Risk management plans are now provided as open access to the public, including prescribers, pharmacists and patients. However, RMPs are still a document applicable primarily to the industry and regulators, and have not truly entered clinical/pharmacy practice. Early identification of risk on individual patient level is relevant at the individual's, as well as on the global level. Involvement of patients in their own healthcare is growing. They are key stakeholders contributing to safety and, last but not least, pharmacoeconomics of early identification of risks.

7 ACKNOWLEDGEMENTS

I am deeply grateful to two exceptional mentors: Prof. Romána Zelkó and my co-mentor Prof. Sándor Kerpel-Fronius, with whom I have had the privilege of communicating for their invaluable comments and support. I thank them not only for professional but also personal support and motivation to carry on with this demanding task. They invested their knowledge, experience, time, effort and patience in this thesis and I will do my best to demonstrate, over time, that the investment was worthwhile.

Finally, I have a special gratitude to my family, who have given me un-failing support and an appreciation for my work. With the thesis complete, more of my free time will be devoted to them.

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