

Analysis of Time to FDA Medwatch Safety Alert for Therapeutic Monoclonal Antibodies

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ABSTRACT

Previous analysis of US FDA Medwatch safety alerts for monoclonal antibody therapeutics demonstrated that pre-marketing clinical trials can predict more than half of safety concerns. We expanded this analysis to assess whether predictable safety alerts, i.e. reactions for which there was a hint based on clinical trials, are detected sooner after drug approval than unpredictable safety alerts.

Up to 31-Dec-2013 inclusive, 76 Medwatch alerts for therapeutic monoclonal antibodies were reported; 43 predictable vs. 33 unpredictable. Predictable alerts were reported at a median (IQR) of 41 (19-77) months after approval vs. 53 (23-73) months for the unpredictable alerts. The mean (SE) was 52.07 (6.69) months and 55.91 (7.06) months for the predictable and unpredictable, respectively. Time to alerts for predictable vs. unpredictable reactions were compared using Mann-Whitney test, Kolmogorov-Smirnov test and using curves displaying cumulative frequencies of alerts over time (similar to Kaplan-Meier curves). Although the difference of 12 month between medians of time to alert was observed, the difference was not demonstrated as significant. P-value of Kolmogorov-Smirnov test comparing distribution of time to alerts for predictable and unpredictable reactions was 0.822, p-value of Mann-Whitney test comparing median values of time to alerts was 0.524.

Survival analysis is appropriate for time to event data, however, only data on mAbs for which the alerts have been already detected are available, i.e there was no time to alert to be censored. Therefore, we used curves displaying cumulative frequencies of alerts over time instead of Kaplan-Meier curves used for analysis of censored data. The curves of cumulative frequencies provide more informative view into the data than standard descriptive statistics or tests. The curves show that predictable alerts were detected sooner than unpredictable alerts until month 73 after approval when about 80% of all 76 alerts were detected. Immunological reactions (such as infusion reactions, anaphylaxis and reactions due to antibodies) were identified early; all 12 such alerts were all released before the curves of cumulative frequencies cross at month 73. On the other hand, reactions occurring after the curves on the graph cross are predominantly cancers and opportunistic infections.

The results demonstrate a trend towards earlier reporting of predictable alerts in the early post-approval phases, implying that risk management planning may play a role in early detection of important safety concerns. The evaluation of earlier detection of safety concerns is of major clinical and public health significance. Our analysis shows the value of displaying curves of cumulative frequencies over time using an unconventional type of data.

Key Words: Monoclonal antibody, safety, alert, pharmacovigilance, risk management, FDA, Medwatch, Kaplan-Meier.

INTRODUCTION

A medicinal product is authorised on the basis that in the specified indication(s), at the time of authorisation, the risk-benefit balance is judged to be positive for the target population. Planning of the necessary pharmacovigilance activities to characterise the safety profile is based on specific issues identified from pre- or post-authorisation data and from pharmacological principles. The aim of pharmacovigilance is risk identification and characterisation allowing for risk minimisation or mitigation wherever possible. In order to ensure risk minimisation after marketing approval, risk management plans are developed at the time of application for a marketing authorisation. This approach is taken both by the European authorities in the form of risk management plans (RMP) and the United States Food and Drug Administration (US FDA) in Risk Minimization Action Plans (RiskMAPs).

The aim of this study is to contribute to risk management by showing the time profile of reported safety concerns for monoclonal antibody drugs.

Monoclonal antibodies (mAbs) are innovative therapeutic agents with excellent potential. The mAb can be used in a variety of indications from rheumatoid arthritis and other immune-mediated inflammatory diseases to cancer. The action of those drugs is based on a principle using the affinity of antibodies to specific antigen (cell surface or soluble antigens). The therapeutic mAb were hoped to be free from a wide range of adverse effects because they are binding very specifically their target. According to current studies and clinical practices it is clear that they are causing important adverse drug reactions, many of them have been identified only after their approval for market. Adverse reactions of mAb are under priority review by the FDA.

After marketing approval, FDA collects clinically important safety information and issues safety alerts via MedWatch program (The FDA Safety Information and Adverse Event Reporting Program). MedWatch alerts provide timely new safety information on human drugs, medical devices, vaccines and other biologics, dietary supplements, and cosmetics. The alerts contain actionable information that may impact both treatment and diagnostic choices for healthcare professional and patient. In previous analysis of the FDA Medwatch safety alerts for therapeutic mAbs published in 2011 suspected adverse reactions identified before the approval for market were compared with safety alerts issued later. The analysis showed that pre-approval clinical trials can observe more than half of safety concerns reported after the approval¹. In addition, a large proportion of unobserved reactions during pre-approval clinical trials could have been expected based on the mechanism of action and antibody target. Although retrospective assessment necessarily implies an element of subjectivity, there appears to be room for improvement in predicting adverse reactions to mAbs. Finally, the authors advised that adverse reaction risk management and pharmaceutical care must focus on the observed reactions, but all effort should be made to extrapolate from the observed reactions to predict further safety issues.

In this study we expanded the previous analysis to assess whether the alerts which can be predicted because of increased frequency, severity, or other new properties reported during pre-approval clinical trials are detected sooner than the alerts based on adverse drug reaction not reported before. We hypothesised that the predictable alerts have been issued sooner. Demonstrating such as hypothesis would have important clinical implication in risk management planning.

METHODS

All FDA Medwatch safety alerts (available on FDA website²) issued up to 31-Dec-2013 inclusive was evaluated. Adverse reaction terms were cross-checked with the initial product label from Drugs@FDA database³. Time since approval to alert was compared between predictable and unpredictable alerts.

An alert was considered *predictable* (observed) when increased frequency, severity, or other new properties were reported for previously identified suspected adverse reactions, i.e. the adverse drug reactions that has been described in the initial product label form. This refers to events which were observed prior to marketing approval, but new findings strengthened the evidence. It does not refer to events which may have been suspected based on mechanism of action or chemical structure. *Not predictable* (unobserved) was applied to reactions not described in the initial product label. Detailed procedure on classification of alerts has been previously described.

Time from approval to predictable vs. unpredictable alerts was compared using Mann-Whitney test (two-sample non-parametric test as normality of data was violated), Kolmogorov-Smirnov test (used for comparison of distribution of two dataset) and using curves displaying cumulative frequencies of alerts over time (similar to Kaplan-Meier curves). Statistical analysis was performed using SAS® v 9.3 (SAS Institute, Cary, NC).

RESULTS

Up to 31-Dec-2013 inclusive, 76 Medwatch alerts for therapeutic monoclonal antibodies were reported; 43 predictable vs. 33 unpredictable.

Predictable alerts were reported at a median (IQR) of 41 (19-77) months after approval vs. 53 (23-73) months for the unpredictable alerts. The mean (SE) was 52.07 (6.69) months and 55.91 (7.06) months for the predictable and unpredictable, respectively. Although the difference of 12 month between medians of time to alert was observed the difference was not demonstrated as significant. P-value of Kolmogorov-Smirnov test comparing distribution of time to alerts for predictable and unpredictable reactions was 0.822, p-value of Mann-Whitney test comparing median values of time to alerts was 0.524.

This kind of data tempts to use methods of survival analysis; however, data only about mAbs for which the alerts have been already detected are available, i.e. there was no time to alert to be censored. Therefore, we used curves displaying cumulative frequencies of alerts over time instead of Kaplan-Meier curves used for analysis of censored data. The curves of cumulative frequencies provide more informative view into the data than standard descriptive statistics or tests. The curves show that predictable alerts were detected sooner than unpredictable alerts until month 73 after approval when the curve for predictable and unpredictable alerts crossed (Figure 1). The majority of alerts (about 80% of all 76 alerts) were detected until month 73 after approval. Such a finding suggested to analyse the alerts issued up to 73 months after approval separately: Predictable alerts (n=31) were reported at a median (IQR) of 23 (11-44) months after approval vs. 37 (21-68) months for the unpredictable alerts (n=26). P-value of Kolmogorov-Smirnov test and Mann-Whitney test were more or less closer to be significant (p=0.373 and p=0.086).

DISCUSSION

The analysis demonstrated a trend towards earlier reporting of predictable alerts, but without clear statistical significance. However, this finding should be interpreted taking into account the type of data analysed. Our study provides an innovative option for analysis of safety concerns. Such a type of analysis should be considered as supportive tool of Pharmacovigilance and risk management planning; however for clear statistical evidence more robust data would be needed to be analysed. Our study has several limitations. First limitation is that the analysis is based only on reported alerts excluding reactions which can be assumed (according initial product label) however have not occurred yet. Our analysis does not adjust for frequency of application of the corresponding drugs. Further, the sample size can be an issue. Analysis of higher number of alerts can show more clear evidence and could enable to subgroup analysis according to type of mAb, treatment regimen or type of the adverse reaction. Another way how to improve our results could be to analyse time from the first application instead of time from approval for market.

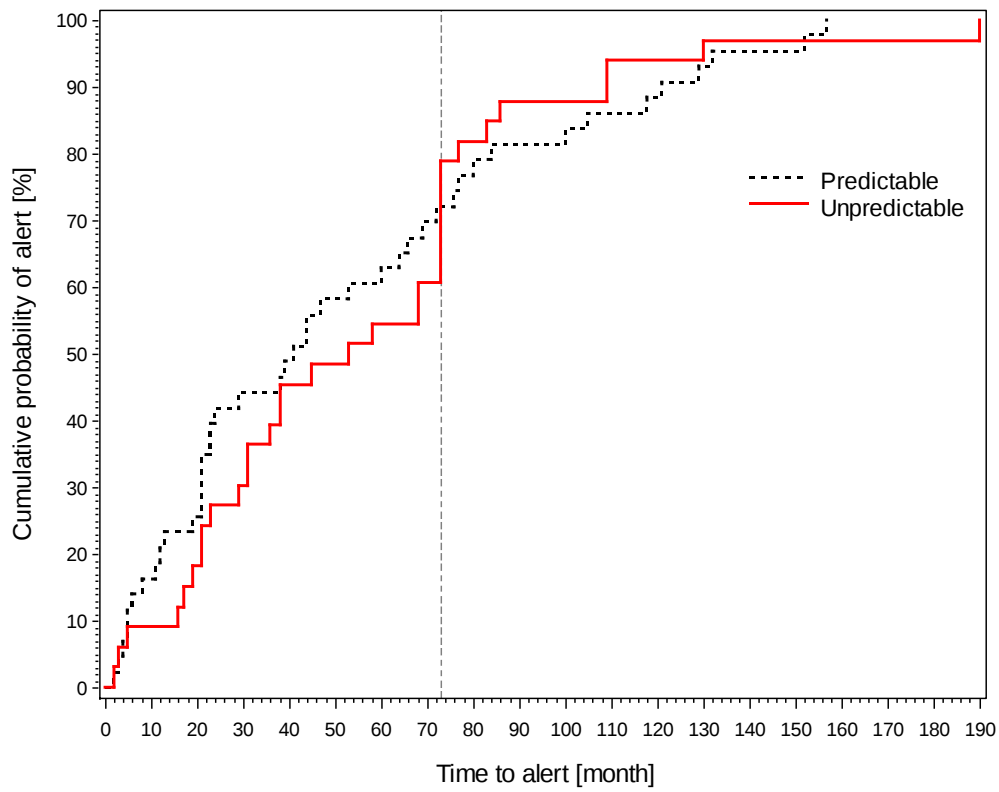
Despite the limitations listed above such a type of analysis enables an illustrative way of presenting the time to safety alerts. Such a type of analysis should be considered as supportive tool of Pharmacovigilance and risk management planning which must aim for more proactive approach to predict adverse effects and avoid them, and only detect and assess them.

CONCLUSION

Analysis of time to detection of an important safety finding is of utmost importance to public health. This analysis does not demonstrate that predictable reactions can be observed any earlier, but indicates certain value in its evaluation. It also suggests that risk management planning may play a role in early detection of important safety concerns. Risk management should use appropriate methods to evaluate safety concerns not only in early post-approval but also to identify methods appropriate for all phases throughout product life-cycle.

Conflicts of interest: The authors declare no conflicts of interest.

Figure 1: Cumulative frequencies for predictable and unpredictable Medwatch safety alert



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