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Earlier identification of risks: cumulative probability analysis of time to safety alerts for therapeutic monoclonal antibodies

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Key words

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Abstract. Objective: Previous analysis of US FDA Medwatch safety alerts for monoclonal antibody therapeutics demonstrated that premarketing clinical trials can predict more than half of safety concerns. We expanded this analysis to assess whether the predictable alerts are detected sooner than the unpredictable alerts. Methods: Times to alert were compared using Mann-Whitney test, Kolmogorov-Smirnov test, and using curves displaying cumulative frequencies of alerts over time. Results: Until December 31, 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 months between medians of time to alert was observed, the difference was not demonstrated as significant. Cumulative frequency curves show that predictable alerts were detected sooner until month 73 after approval, when ~ 80% of alerts were detected. Immunological reactions (such as infusion reactions, anaphylaxis, and reactions due to antibodies) were identified early; all 12 such alerts were released before the curves of cumulative frequencies cross at month 73. On the other hand, reactions occurring after the curves cross are predominantly late-occurring cancers and opportunistic infections. Conclusions: The results imply that focus on predictable reactions defined as potential risks may play a role in early detection of important safety concerns.

activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem” [1]. Pharmacovigilance today must aim for a more proactive approach to predict adverse effects and avoid them, and only detect and assess them where the predictive model fails or proves to be insufficient. Pharmacovigilance is no longer a passive discipline of awaiting and detecting adverse reactions, but active in predicting and managing risks.

A medicinal product is authorized on the basis that, in the specified indication(s), at the time of authorization, the risk-benefit balance is judged to be positive for the target population. Planning the necessary pharmacovigilance activities to characterize the safety profile is based on specific issues identified from pre- or postauthorization data and from pharmacological principles. In order to ensure risk minimization after marketing approval, risk management plans are developed at the time of application for marketing authorization. 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).

In a previous analysis of the FDA Medwatch safety alerts for therapeutic monoclonal antibodies (mAbs) suspected adverse reactions identified before approval for market the were compared with safety alerts issued later. The analysis showed that preapproval clinical trials can observe more than half of safety concerns reported after the approval [3]. In addition, a large proportion of unobserved reactions during preapproval clinical trials could have been expected based on the mechanism of action and antibody target. Al-

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Introduction

It was not long ago in 2002 that the World Health Organization proposed the definition of pharmacovigilance as: “The science and

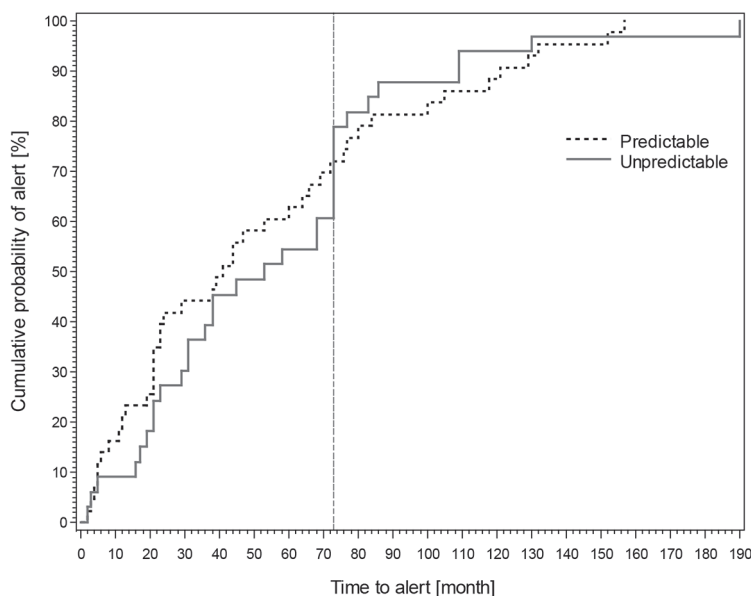


Figure 1. Cumulative probability curve for time to Medwatch safety alert.

though retrospective assessment necessarily implies an element of subjectivity, there appears to be room for improvement in predicting adverse reactions to mAbs by focusing on potential risks.

In this study, we expanded the previous analysis to assess whether the alerts that can be predicted because of increased frequency, severity, or other new properties reported during preapproval clinical trials are detected sooner than the alerts based on adverse drug reaction not reported before. We hypothesized that the predictable alerts were issued sooner.

Methods

All the FDA Medwatch safety alerts (available on FDA website [4]) issued until December 31, 2013 inclusive, were evaluated. Adverse reaction terms were cross-checked with the initial product label from Drugs@FDA database [5]. 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 have been described in the initial product label form. This refers to events that were ob-

served prior to marketing approval, but were new findings strengthened the evidence. It does not refer to events that 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 [3].

Time from approval to predictable vs. unpredictable alerts was compared using Mann-Whitney test (two-sample nonparametric test as normality of data was violated), Kolmogorov-Smirnov test (used for comparison of distribution of two datasets), and using curves displaying cumulative frequencies of alerts over time (similar to Kaplan-Meier curves). 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). Therefore, the alerts detected up to 73 months after registration were analyzed in addition to analysis of the whole dataset. Statistical analysis was performed using SAS® v 9.3 (SAS Institute, Cary, NC, USA).

Results

Until December 31, 2013 inclusive, 76 Medwatch alerts for therapeutic monoclonal antibodies were reported; 43 predictable vs. 33 unpredictable (Table 1).

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 months 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 attempts 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

Table 1. Time to safety alert.

Name	Approval date	Alert date	Alert message	Predictable (Yes/No)	Months to alert
Adcetris (brentuximab vedotin)	Aug-2011	Jan-2012	PML **	N	5
Adcetris (brentuximab vedotin)	Aug-2011	Jan-2012	Pulmonary toxicity (interaction)	Y	5
Arzerra (ofatumumab)	Oct-2009	Sep-2013	Recommendations to decrease risk of hepatitis b reactivation**	Y	47
Avastin (bevacizumab)	Feb-2004	Aug-2004	Arterial thromboembolic events	Y	6
Avastin (bevacizumab)	Feb-2004	Jan-2005	Arterial thromboembolic events	Y	11
Avastin (bevacizumab)	Feb-2004	Sep-2006	Reversible posterior leukoencephalopathy syndrome	N	31
Avastin (bevacizumab)	Feb-2004	Sep-2006	Nasal septum perforation	N	31
Avastin (bevacizumab)	Feb-2004	April-2007	Tracheoesophageal fistula	N	38
Avastin (bevacizumab)	Feb-2004	Jul-2008	Microangiopathic hemolytic anemia in combination with sunitinib malate	N	53
Avastin (bevacizumab)	Feb-2004	Mar-2013	Serious eye infection	N	109
Cimzia (certolizumab pegol)	Apr-2008	Jun-2008	Lymphoma and other cancers in children and young adults**	N	2
Cimzia (certolizumab pegol)	Apr-2008	Sep-2008	Histoplasmosis, coccidioidomycosis, blastomycosis, and other opportunistic infections**	Y	5
Cimzia (certolizumab pegol)	Apr-2008	May-2009	Histoplasmosis and other invasive fungal infections**	Y	13
Cimzia (certolizumab pegol)	Apr-2008	Aug-2009	Lymphoma and other cancers in children and young adults**	N	16
Cimzia (certolizumab pegol)	Apr-2008	Sep-2011	Risk of infection from legionella and listeria**	Y	41
Cimzia (certolizumab pegol)	Apr-2008	Apr-2011	Hepatosplenic T-cell lymphoma**	N	36
Erbix (cetuximab)	Feb-2004	Sep-2005	Observation periods following infusion/infusion reactions*	Y	19
Erbix (cetuximab)	Feb-2004	Sep-2005	Hypomagnesemia	N	19
Herceptin (trastuzumab)	Aug-1998	May-2000	Hypersensitivity reactions*	Y	21
Herceptin (trastuzumab)	Aug-1998	May-2000	Infusion reactions*	Y	21
Herceptin (trastuzumab)	Aug-1998	May-2000	Pulmonary reactions	N	21
Herceptin (trastuzumab)	Aug-1998	Aug-2005	Cardiotoxicity	Y	84
Humira (adalimumab)	Dec-2002	Nov-2004	Infections with the combined use of anakinra	Y	23
Humira (adalimumab)	Dec-2002	Nov-2004	Hypersensitivity reactions, including anaphylaxis*	N	23
Humira (adalimumab)	Dec-2002	Nov-2004	Hematologic events, including pancytopenia and aplastic anemia	Y	23
Humira (adalimumab)	Dec-2002	Jun-2008	Lymphoma and other cancers in children and young adults**	Y	66
Humira (adalimumab)	Dec-2002	Sep-2008	Histoplasmosis, coccidioidomycosis, blastomycosis, and other opportunistic infections**	Y	69
Humira (adalimumab)	Dec-2002	May-2009	Histoplasmosis and other invasive fungal infections**	Y	77
Humira (adalimumab)	Dec-2002	Aug-2009	Lymphoma and other cancers in children and young adults**	Y	80
Humira (adalimumab)	Dec-2002	Sep-2011	Risk of infection from legionella and listeria**	Y	105
Humira (adalimumab)	Dec-2002	Apr-2011	Hepatosplenic T-cell lymphoma **	Y	100
Lucentis (ranibizumab)	Jun-2006	Feb-2007	Higher stroke incidence with higher dose	Y	8
NeuroSpec (Technetium fanolesomab)	Jul-2004	Dec-2005	Cardiopulmonary events (market suspension)	N	17
Raptiva (efalizumab)	Oct-2003	Jul-2005	Immune-mediated hemolytic anemia*	N	21
Raptiva (efalizumab)	Oct-2003	Jul-2005	Thrombocytopenia	Y	21
Raptiva (efalizumab)	Oct-2003	Jul-2005	Infections	Y	21
Raptiva (efalizumab)	Oct-2003	Oct-2008	PML, fungal, and other opportunistic infections**	Y	60
Raptiva (efalizumab)	Oct-2003	Feb-2009	PML (market suspension)**	Y	64
Remicade (infliximab)	Aug-1998	Oct- 1998	Adverse events due to antibodies*	Y	2
Remicade (infliximab)	Aug-1998	Oct-2001	Tuberculosis and other opportunistic infections**	Y	38
Remicade (infliximab)	Aug-1998	Oct-2001	Heart failure	N	38
Remicade (infliximab)	Aug-1998	Aug-2004	Lymphoma and other malignancies**	Y	72
Remicade (infliximab)	Aug-1998	Dec-2004	Hepatic reactions	Y	76
Remicade (infliximab)	Aug-1998	Jun-2008	Lymphoma and other cancers in children and young adults**	Y	118

Table 1. Continuation.

Name	Approval date	Alert date	Alert message	Predictable (Yes/No)	Months to alert
Remicade (infliximab)	Aug-1998	Sep-2008	Histoplasmosis, coccidioidomycosis, blastomycosis, and other opportunistic infections**	Y	121
Remicade (infliximab)	Aug-1998	May-2009	Histoplasmosis and other invasive fungal infections**	Y	129
Remicade (infliximab)	Aug-1998	Aug-2009	Lymphoma and other cancers in children and young adults**	Y	132
Remicade (infliximab)	Aug-1998	Sep-2011	Risk of infection from legionella and listeria**	Y	157
Remicade (infliximab)	Aug-1998	Apr-2011	Hepatosplenic T-cell lymphoma**	Y	152
Rituxan (rituximab)	Nov-1997	Nov- 1998	Infusion reactions*	Y	12
Rituxan (rituximab)	Nov-1997	Oct-2004	Hepatitis B virus reactivation**	N	83
Rituxan (rituximab)	Nov-1997	Dec-2006	PML**	N	109
Rituxan (rituximab)	Nov-1997	Sep-2008	PML leading to death 18 months after the last dose**	N	130
Rituxan (rituximab)	Nov-1997	Sep-2013	Recommendations to decrease risk of hepatitis B reactivation**	N	190
Simponi (golimumab)	Apr-2009	Aug-2009	Lymphoma and other cancers in children and young adults**	Y	4
Simponi (golimumab)	Apr-2009	Sep-2011	Risk of infection from legionella and listeria**	Y	29
Simponi (golimumab)	Apr-2009	Apr-2011	Hepatosplenic T-cell lymphoma**	Y	24
Simulect (basiliximab)	May-1998	Oct-2000	Hypersensitivity reactions, including anaphylaxis*	N	29
Synagis (palivizumab)	Jun-1998	Nov-2002	Anaphylaxis*	Y	53
Tysabri (natalizumab)	Nov-2004	Feb-2005	PML**	N	3
Tysabri (natalizumab)	Nov-2004	Feb-2008	Liver injury	Y	39
Tysabri (natalizumab)	Nov-2004	Aug-2008	PML**	N	45
Tysabri (natalizumab)	Nov-2004	Sep-2009	PML**	N	58
Tysabri (natalizumab)	Nov-2004	Apr-2011	PML**	N	77
Tysabri (natalizumab)	Nov-2004	Jan-2012	PML**	N	86
Xolair (omalizumab)	Jun-2003	Feb-2007	Anaphylaxis*	Y	44
Xolair (omalizumab)	Jun-2003	Jul-2009	Ischemic heart disease	N	73
Xolair (omalizumab)	Jun-2003	Jul-2009	Arrhythmias	N	73
Xolair (omalizumab)	Jun-2003	Jul-2009	Cardiomyopathy and cardiac failure	N	73
Xolair (omalizumab)	Jun-2003	Jul-2009	Pulmonary hypertension	N	73
Xolair (omalizumab)	Jun-2003	Jul-2009	Cerebrovascular disorders	N	73
Xolair (omalizumab)	Jun-2003	Jul-2009	Embolic, thrombotic, and thrombophlebitic events	N	73
Yervoy (ipilimumab)	Mar-2011	Jun-2011	Severe immune-mediated adverse reactions*	Y	3
Zenapax (daclizumab)	Dec-1997	Aug-2003	Increased mortality	N	68
Zenapax (daclizumab)	Dec-1997	Aug-2003	Hypersensitivity reactions*	N	68
Zevalin (ibritumomab tiuxetan)	Feb-2002	Oct-2005	Cutaneous or mucocutaneous reactions	Y	44

*Immunological reaction; **Cancers and opportunistic infections; CD = cluster of differentiation; EGF = epidermal growth factor; HER2 = human epidermal growth factor receptor 2; IgE = immunoglobulin E; PML = progressive multifocal leukoencephalopathy; RSV = respiratory syncytial virus; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor.

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 a more informative look 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 (Figure 1). The majority of alerts (~ 80% of all 76 alerts) were detected by month 73 after approval. Such a finding suggested that we should analyze the alerts issued until 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 ($n = 26$). The p-value of the Kolmogorov-Smirnov test and the Mann-Whitney test were more or less closer to being significant ($p = 0.373$ and $p = 0.086$).

Immunological reactions (such as infusion reactions, anaphylaxis and reactions due to antibodies) were identified early; all 12 such alerts were released before the Kaplan-Meier curves cross at month 73. On the other hand, reactions occurring after the curves on

the graph cross are predominantly cancers and opportunistic infections.

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 analyzed.

Analyzing the type of adverse reactions identified over time, it is noteworthy that all immunological reactions were observed in the initial period, before the curves cross. They generally occur early in the treatment course and may be expected even if not predictable according to the definition used in this analysis. It is also likely that predictable safety concerns have been previously observed because they are more frequent, and, hence, they can be confirmed earlier postapproval. Cancers and opportunistic infections are examples of reactions that may take more time to develop and/or may take more time to be detected. They are generally reported later, but, due to repeated alerts for TNF- α blockers and some other products, the data is somewhat distorted. Even though some are unpredictable according to the definition used in this analysis, these late-occurring reactions may (retrospectively) equally be considered as expected based on drug target. Specific methods for their prediction and detection should equally be considered in product life-cycle risk management.

Risk management plans for further mAbs, and possibly other products, should take into account that predictable alerts can be expected ~ 12 months sooner than the reactions that were not identified during the preapproval clinical trials. Early detection using the methods described here may correlate with event reporting frequency (assuming more frequent events are detected earlier), event specificity (assuming that adverse reactions specific to a drug, and otherwise not encountered are detected earlier), event severity (assuming severe reaction are reported earlier), background reporting rate (assuming common medical conditions do not lead to a suspicion of causal relationship), or other factors. The methods proposed in this study may be applied to other datasets in pharmacovigi-

lance in real-time identification of adverse drug reaction reporting frequencies, leading to earlier detection of drug safety concerns.

It is noteworthy that all mAbs covered by this study are originator products. Recent marketing of biosimilar versions of these complex proteins poses further challenges to safety assessment [6, 7].

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 focus on such predictable reactions defined as potential risks may play a role in early detection of important safety concerns.

Conflict of interest

The authors declare no conflict of interest.

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