

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



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What is FDA Medwatch alert?

MedWatch is the FDA Safety Information and Adverse Event Reporting Program established for the following purposes:

- To collect clinically important safety information after marketing approval. According to the collected information FDA issues safety alerts, i.e. important safety warnings to health care professionals, consumers, drug manufactures.
- The FDA issues an alert
 - for known adverse reaction if this is reported more frequently and/or is more severe,
 - for previously unknown reaction or
 - if new important information related to safety is revealed

Example:

Avastin®(bevacizumab) - used for treatment of several types of cancer which was approved for market on Feb 26, 2004

Avastin (bevacizumab) Aug 2004

Audience: Oncologists and other healthcare providers

FDA and Genentech, Inc. issued an important drug warning to healthcare providers that there is evidence of an increased risk of serious arterial thromboembolic events, including cerebrovascular accident, myocardial infarctions, transient ischemic attacks, and angina related to Avastin. [...]

[UPDATE January 6, 2005]

[August 12, 2004 - Letter - Genentech]

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm166896.htm>

Comparison of time to “Observed” and “Unobserved” FDA alerts

Up to 31-Dec-2013 inclusive, 76 Medwatch alerts for therapeutic mAb were reported; 43 “Observed” vs. 33 “Unobserved”

Name	Approval Date	Alert Date	Alert Message	Observed (Yes/No)	Months to alert
brentuximab vedotin	Aug-2011	Jan-2012	PML **	N	5
brentuximab vedotin	Aug-2011	Jan-2012	Pulmonary toxicity (interaction)	Y	5
ofatumumab	Oct-2009	Sep-2013	Recommendations to Decrease Risk of Hepatitis B Reactivation **	Y	47
bevacizumab	Feb-2004	Aug-2004	Arterial thromboembolic events	Y	6
bevacizumab	Feb-2004	Jan-2005	Arterial thromboembolic events	Y	11
bevacizumab	Feb-2004	Sep-2006	Reversible posterior leukoencephalopathy syndrome	N	31
bevacizumab	Feb-2004	Sep-2006	Nasal septum perforation	N	31
....				...	...

Legend: * Immunological reaction; ** Cancers and opportunistic infections;

“Observed” and “Unobserved” alerts

Therapeutic monoclonal antibodies (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 it is clear that they are causing important adverse drug reactions.

Knowing that premarketing CTs do not detect all adverse drug reactions the MedWatch alerts were classified to “Observed” and “Unobserved”.

Premarketing clinical trials

Drug available on market

Alert to adverse reactions identified before the approval (described in the initial product label form)

=
“Observed” alerts

Alert to adverse reactions NOT identified before the approval (NOT described in the initial product label form)

=
“Unobserved” alerts

According to results of the previous study large proportion of “Unobserved” alerts can be predicted based on mechanism of action or based on extrapolation from “Observed” adverse drug reactions.

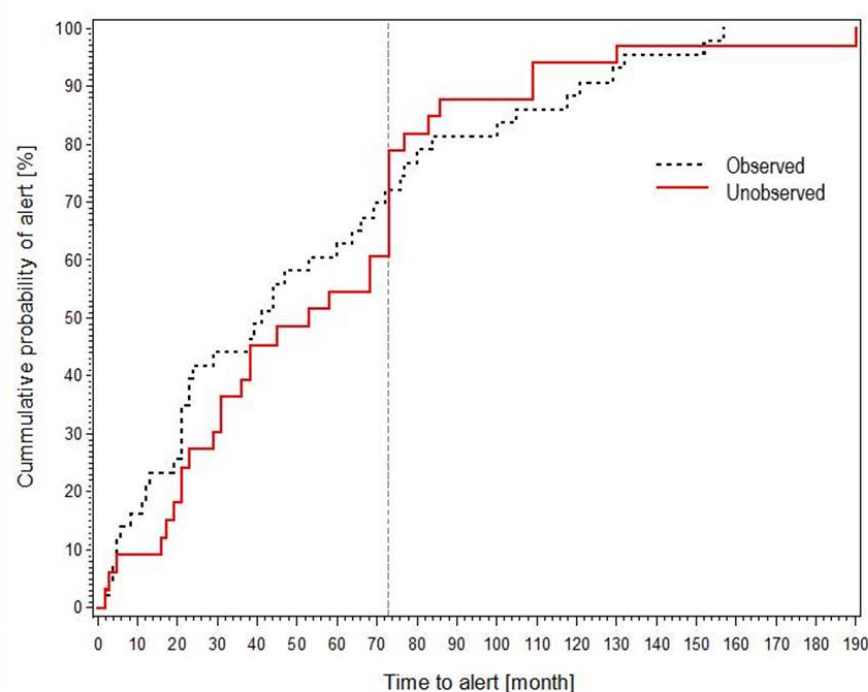
In this study we expanded the previous analysis to assess whether “Observed” alerts are detected sooner after approval than “Unobserved” alerts.

As we believe that large proportion of “Unobserved” alerts can be predicted the comparison of time to “Observed” and “Unobserved” alerts shows us delay of safety warnings which can be potentially avoided.

Conclusions

- The analysis demonstrated a trend towards earlier reporting of observed alerts, but without clear statistical significance.
- Observed difference between time to OBSERVED and time UNOBSERVED alert was about 12 months.
- Such a type of analysis should be considered as supportive tool of Pharmacovigilance and risk management planning.

Cumulative frequencies for “Observed” and “Unobserved” alerts



Overall

Kolmogorov-Smirnov test: p=0.822	Time to alert [months]	“Observed” 43 (57%)	“Unobserved” 33 (43%)
	median (IQR)	41 (19-77)	53 (23-73)
Mann-Whitney test: p=0.524.	mean (SE)	52.07 (6.69)	55.91 (7.06)

Alerts up to 73 months since approval

Kolmogorov-Smirnov test: p=0.373	Time to alert [months]	“Observed” 31 (57%)	“Unobserved” 26 (43%)
	median (IQR)	23 (11-44)	37 (21-68)
Mann-Whitney test: p=0.086.	mean (SE)	29.29 (3.90)	40.77 (4.88)

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