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Modelling the Time to Onset of Adverse Reactions with Parametric Survival Distributions

A Potential Approach to Signal Detection and Evaluation

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Abstract

Background: It has been postulated that the time to onset of adverse drug reactions is connected to the underlying pharmacological (or toxic) mechanism of adverse drug reactions whether the reaction is time dependent or not.
Objective: We have conducted a preliminary study using the parametric modelling of the time to onset of adverse reactions as an approach to signal detection on spontaneous reporting system databases.
Methods: We performed a parametric modelling of the reported time to onset of adverse drug reactions for which the underlying toxic mechanism is characterized. For the purpose of our study, we have used the reported liver injuries associated with bosentan, and the infections associated with the use of the tumour necrosis factor (TNF) inhibitors, adalimumab, etanercept and infliximab, which are used in Crohn's disease and rheumatoid arthritis, reported to EudraVigilance between December 2001 and September 2006.
Results: The main results reflect the fact that the reported time to onset is a surrogate of the true time to onset of the reaction and combines three hazards (occurrence, diagnosis and reporting) that cannot be disentangled. Consequently, the modelling of the time to onset of reactions reported with TNF inhibitors showed differences that could reflect different pharmacological activities, indications, monitoring of the patients or different reporting patterns. These variations could also limit the interpretation of the parametric modelling.
Conclusions: Some consistency that was found between the occurrences of the infections with the TNF inhibitors suggests a causal association. There are statistical issues that are important to keep in mind when interpreting the results (the impact of the data quality on the fit of the distributions and the absence of a test of hypothesis linked to the absence of a relevant

comparator). The study suggests that the modelling of the reported time to onset of adverse reactions could be a useful adjunct to other signal detection methods.

Background

The time to onset of adverse reactions is recognized to be one important criterion used to assess possible causality during medical evaluation of individual case reports, and is part of the characteristics that make a good case report.[1,2] One of the main reasons that has been put forward to promote the reporting of well documented individual cases of adverse drug reactions (including the information on the time to onset) is to help elucidate the mechanism of the underlying toxicity.[1] The hazard of developing an adverse drug reaction is the general function that specifies the instantaneous rate at which an event occurs for individuals who did not experience the reaction until a certain time. In that context, an event is taken in a general sense; in our case this event is an adverse drug reaction. The hazard function represents the evolution of this hazard over time. Therefore, the estimation of this function is one important element of risk characterization.[3] This is particularly true for the long-term time-dependent adverse events.[4] Many pharmacoepidemiological studies assume in their underlying hypotheses, often erroneously and without adequate checking, that the hazard is constant over time. Likewise, the limitations of the assumptions underlying the incidence rate (constant hazard models) have recently been highlighted in the literature.[5]

The estimation of the hazard of occurrence of a reaction is particularly important as it is directly connected to the underlying mechanism of the toxicity. It also allows the identification of particular risk windows in the course of a treatment. A new approach for classifying adverse drug reactions, the dose-time-susceptibility (DoTS) classification, discusses the time-relatedness of adverse drug reactions as one of three key components of this new classification.[6] The DoTS classification is based on sound pharmacological principles and includes the above three components. It argues that, unlike conventional thinking, all adverse reactions may be classified by dose-relatedness as one dimension of the DoTS classification. Furthermore, one of the merits of the DoTS approach is that it links the time dependency to the proposed pharmacological classification. It classified this time-relatedness in time-dependent (subclassified as rapid, first dose, early, intermediate, late and delayed reactions) and time-independent reactions. This time-relatedness assumes that the underlying toxic mechanisms obey the law of mass action describing adverse drug reactions as interactions between chemical entities. If correct, the time-dependency and time-independency classification should be confirmed by some statistical evidence concerning the hazard of developing the adverse reaction. Therefore, this classification makes it clear that whether the occurrence of the reaction proceeds from a hypersusceptibility, a collateral or a toxic adverse drug reaction from the dose-relatedness viewpoint, the time to onset (and its corresponding hazard) is directly related to the underlying mechanism of the toxicity or intercurrent event (altered susceptibility) leading to the toxic effect.

This lack of integration of the rate of occurrence of a specific risk via the use of hazard functions is also highlighted by the development or use of causality assessment methods and data mining algorithms used in pharmacovigilance.

As far as the causality algorithms are concerned, one study published recently suggests that causality assessment algorithms can lead to a wrong diagnosis even in situations where the time to onset is a critical element to assess the causal relationship between the administration of the drug and the occurrence of the reaction (i.e. hypersensitivity reactions).[7] Some causality assessment methods are extremely sensitive to any differences of judgement concerning the time to onset of adverse drug reactions.[8] Therefore, it is

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important to have a consistent and logical approach to the evaluation of the time to onset of reactions. Some very useful attempts have been made to standardize the criteria used to perform the causality assessment of individual cases for different types of adverse reactions, in particular for drug-induced liver disorders. These consensus conferences classified the chronological criteria for the time to onset as suggestive, compatible and incompatible with corresponding time to onset ranges, but again the reasoning behind this classification was not always provided; however, the risk window provided in these recommendations is not clearly justified on scientific grounds.[9]

With respect to the current data mining algorithms, most of the current quantitative methods are built on the principle of disproportionality analysis.[10,11] These methods, with the exception of some logistic regression models that have included some (chemical or pharmacological) characteristics of the drugs of interest, do not consider any case-level time elements in their methods nor do they integrate any information on the underlying mechanism of the toxic effect.[11]

The purpose of our study is to develop a novel mechanistic approach to quantitative signal detection based on the use of temporality techniques, parametric time to onset analysis and, in particular, on the statistical modelling of the reported time to onset of adverse drug reactions on a spontaneous reporting system database. The main objective of our study is to illustrate the potential use of hazard functions in the context of signal detection. This is considered in a broad sense from the actual detection of previously unrecognized drug-event pairs to the evaluation of the association. We illustrate the use of hazard functions in quantitative signal detection by performing a modelling of the reported time to onset recorded in a postmarketing system using parametric survival distributions. This approach hypothesizes that in the presence of a true signal, the hazard of developing an adverse drug reaction, hence the reported time to onset, can be associated with the underlying toxic mechanism. It would potentially use some crucial information from the spontaneous case reports that is neither used in a structured manner in the current data mining algorithms nor in conventional signal detection. The evaluation of the time to onset still requires detailed clinical review of each individual case; however, it is acknowledged that there is no standardized definition of the time to onset for adverse drug reactions in the post-authorization setting. One specific objective of our study is to assess whether the (reported) time to onset of adverse reactions and the corresponding hazard function can indicate an association with the underlying mechanism of the toxicity.

We discuss our approach to the modelling of the reported time to onset (and the link between the shape of the hazard function and the underlying mechanism of the toxicity) using a set of different criteria that are traditionally used to assess possible causality.[12] In particular, it has been argued in the past that some of the Bradford-Hill criteria could be used to assess causality from spontaneous reports and interpret the results of data mining algorithms.[12,13] Temporality, assessed together with other causality criteria such as consistency of the findings (within and across products), specificity of the association, plausibility of the association and coherence in conjunction with the experimental evidence, could be used as a basis to identify true signals in a spontaneous reporting system database and provide a scientific rationale to link the shape of the hazard function to the underlying mechanism of the toxicity. Taking the example of consistency across products, the time to onset of identical reactions induced by products of the same class (sharing identical mechanisms of action and similar toxicity mechanisms) should show similar patterns in terms of hazard function or, similarly, any differences could reflect different toxic mechanisms (providing such mechanisms are plausible). It is possible that reactions in anatomically distant sites may share a common pathophysiology (e.g. angioedema of the head and neck with ACE inhibitors and pancreatitis due to angioedema of the pancreatic duct). The latter are purely hypothetical at this point but highlight exploratory possibilities for evaluating possible signals. On the other hand, with many drugs, liver

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injuries such as hepatitis and acute hepatic failure may represent distinct entities with differing pathophysiologies, rather than just a range of expression of a given pathophysiology; however, the modelling of the time to onset of adverse reactions has never been used as a systematic approach to signal detection and evaluation on spontaneous reporting systems. Provided that the limitations of spontaneous reporting are kept in mind, the parametric modelling of the hazard function could be a rational novel approach to study the reported time course of events for these different reactions. It would also enable comparisons to be made between products when appropriate and to evaluate associations between the observed differences with any possible pharmacological or toxic mechanism whenever possible. We have used non-parametric and parametric time to event analysis methods to model the time to onset of a series of adverse reactions reported to a spontaneous reporting system database and compute the functions associated with the reported hazards of developing some adverse reactions. We have performed our study on two well established adverse drug reactions to test the validity of our approach: the liver injuries associated with bosentan (Tracleer®) and on the infections associated with the administration of tumour necrosis factor (TNF)-α inhibitors. Our study compares the results of the parametric modelling of the time to onset of these adverse drug reactions with the known properties of these products.

Materials and Methods

The study was conducted on a dataset reported to EudraVigilance from December 2001 until September 2006. EudraVigilance is a data processing network and management system for reporting and evaluating suspected adverse reactions during the development and following the marketing authorization of medicinal products in the European Economic Area (EEA). The reports were extracted on the basis of the product names and international non-proprietary names for the suspected drugs. Only reports appropriately documented, for which the treatment start dates and reaction start dates fields contained exact dates (i.e. DD/MM/YYYY), were retained for the study. The potential duplicates were removed from the analysis on the basis of the report identification numbers, patient characteristics and identical product names, as well as identical dates (treatment start date and reaction start date). Medical Dictionary for Regulatory Activities (MedDRA®) version 9.1 was used as medical terminology. The reports transmitted to EudraVigilance are compliant with the International Conference on Harmonisation (ICH) standards and in particular with the ICH E2B(M) standards, which means that the information related to the adverse reaction is recorded in a standardized data model and a date of occurrence of the reaction is attributed to each reaction term as appropriate.

To obtain an acceptable fit of the parametric distribution, only the reaction terms for which at least five reports containing documented fields concerning the time to onset of the reaction have been selected in the study. The drug-event pairs were selected on the basis that the causal relationship between the administration of the product and the occurrence of the reaction is well established and the mechanism of the underlying toxicity is characterized. We first focused on a modelling of the reported time to onset of liver injuries associated with bosentan. The elevations in liver aminotransferases, i.e. AST and ALT, associated with bosentan are dose dependent.[14,15] These increases may be partly due to competitive inhibition of the elimination of bile salts from hepatocytes but other mechanisms, which have not been clearly established, are probably also involved. This is one reason for which the product was the subject of risk management activities in the post-authorization period. Second, we performed a modelling of the reported time to onset of infections associated with TNF inhibitors. The occurrence of infections with TNF inhibitors results directly from the inhibition of the TNFα. In both cases, to reflect the real situation of detection of potential signals on a spontaneous reporting system database (such as EudraVigilance), all the valid cases, whether genuinely due to a true adverse effect of

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the product or resulting from a confounding factor, were retained for the analysis. An assessment of the individual cases to remove those due to alternative aetiologies (e.g. ischaemic hepatopathy for bosentan or underlying infection for the TNF inhibitors) was not performed. It is acknowledged that some of these reported reactions might have been be due to the underlying disease.

A set of hepatic adverse reactions reported during the administration of bosentan has been selected. These MedDRA® reaction terms reflect conditions that can occur during a liver injury (both from the hepatobiliary disorders and investigations system organ class [SOC]). The selected MedDRA® preferred terms (PTs) are ALT increased, AST increased, blood alkaline phosphatase NOS (not otherwise specified) increased, blood bilirubin increased, cholestasis, γ-glutamyltransferase increased, hepatic disorder NOS, hepatic failure, hepatic function abnormal NOS, hepatitis NOS, hepatotoxicity NOS, hyperbilirubinaemia and liver function tests NOS abnormal. Case reports in which bosentan was identified as a suspected drug were selected in the study. Only the spontaneous reports from EudraVigilance were considered and a comparison with other hepatotoxic medicines was not performed.

The second part of the study focused on the infections associated with three medicinal products containing a TNFα inhibitor as the active substance. These products were adalimumab (Humira®), etanercept (Enbrel®) and infliximab (Remicade®). All the valid reports for which any one of these products were considered as suspect and containing a PT reaction term belonging to the primary SOC Infections and infestations have been selected.

The time to onset was computed on the basis of the exact drug start and reaction start dates populated in the reports. The reliability of the reaction start date in a spontaneous reporting system is not known. Simple summary statistics were computed on the reports (number of reports used to perform the parametric modelling of the reported time to onset, mean reported time to onset and median reported time to onset with the 95% confidence interval [CI]). The non-parametric analysis was conducted with a Kaplan-Meier approximation of the survivor function and the CI was computed with Greenwood formula. The comparison of the estimates of the survivor function was performed with the log-rank test. The parametric modelling of the time to onset of adverse reactions was performed with the exponential, Weibull, lognormal and normal distributions. These distributions correspond to different types of hazard functions. The exponential distribution corresponds to a hazard that is constant over time. The Weibull distribution corresponds to a hazard function that is monotone, i.e. constantly increasing or decreasing over time. The third type of distribution has a hazard with a sense of variation that is variable over time (increasing then decreasing). This is the case of the lognormal and normal distributions. These distributions are traditionally used in continuous failure time models.[16] The assessment of the goodness of the fit of the models was performed in two successive steps. First, once fitted, the appropriateness of the fit was assessed visually using a plot of the observed values against the fitted values obtained with the selected parametric distributions. In a second step, when the fit was considered satisfactory, the distribution resulting in the best fit was selected using goodness of fit tests (log likelihood and Anderson-Darling tests). The corresponding hazard functions were computed with the parameters of the fitted distribution (intercept, scale and/or mean of the fitted distribution).

Results

The summary statistics for the time to onset of hepatotoxic events included in the study with the administration of bosentan are shown in table I. The data suggest that the reported liver injuries associated with bosentan start with some abnormalities of the liver function tests (starting with an increase of AST and ALT) followed by a rise in bilirubin. The reported risk of hepatitis is delayed and seems to occur after approximately 1 year of treatment. Hepatic failure seems to occur after 3 months to 1 year of treatment with bosentan.

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Table I. Summary statistics for the time to onset of preferred term (PT) suggesting a liver injury associated with bosentan administration. Lower 95% CI and upper 95% CI represent the lower and upper bounds, respectively, of the CI of the median

MedDRA® PT name	No. of reports[a]	Mean (SE) [d]	Median (d)	Lower 95% CI (d)	Upper 95% CI (d)	Minimum (d)	Maximum (d)
ALT increased	71	129 (33)	71	56	92	2	2246
AST increased	74	69 (9)	37	31	58	1	280
γ-Glutamyltransferase increased	10	53 (20)	43	4	NA	4	191
Blood bilirubin increased	21	129 (34)	57	43	191	4	597
Hyperbilirubinaemia	8	720 (65)	713.5	538	NA	533	919
Liver function tests abnormal NOS	162	141 (19)	57	46	68	1	1442
Hepatic disorder NOS	24	123 (27)	43.5	33	221	7	375
Hepatic function abnormal NOS	46	51 (5)	45.5	34	58	2	125
Hepatitis NOS	13	320 (57)	428	147	NA	7	736
Hepatic failure	7	396 (282)	96	65	NA	57	2220

a The number of reports expresses the number of reports received in EudraVigilance in which the drug start treatment date and the reaction start date are documented (exact dates).

d = day; **MedDRA®** = Medical Dictionary for Regulatory Activities; **NA** = not applicable; **NOS** = not otherwise specified; **SE** = standard error.

The comparison of the Kaplan-Meier estimates of the survivor function for the increased ALT or AST did not show any difference in the time to onset (log-rank test $p = 0.06$). A similar comparison including the PT liver function tests NOS abnormal was, however, significant (log-rank test, $p = 0.03$). The comparison of the Kaplan-Meier estimates of the survivor function for the time to onset of increased AST or increased ALT, hepatic function abnormal, hepatitis NOS and hepatic failure was significant (log-rank test, $p < 0.001$). However, the comparison of the Kaplan-Meier estimates of the time to onset of the AST or ALT increased and hepatic failure did not show any significant differences (log-rank test, $p = 0.08$). These results do not support a difference in time to onset of increased ALT or increased AST and hepatic failure (analysis based on very few reports), but the time to onset of hepatitis (NOS) was found to be significantly different (figure 1). The results of the fitting of the parametric survival distributions to the time to onset of the reactions suggesting a possible liver injury are shown in table II, and the corresponding hazard functions are displayed in figure 1.

The non-parametric study confirmed the recommendations given in the summary of product characteristics (SPC) for Tracleer®, which specifies that the liver enzyme changes typically occur within the first 26 weeks of treatment since approximately 85% of the patients were reported to have developed an increase of ALT or AST within this timeframe.[17]

The plot of the hazard functions shows a risk of increased aminotransferases (AST then ALT), followed by a risk of hepatitis starting approximately 200 days after the initiation of the treatment, peaking at day 600 and decreasing abruptly thereafter. The reported hazard functions show a fairly constant and residual risk of hepatic failure starting shortly after the initiation of the treatment without any indication of time dependency (the liver toxicity might proceed from different mechanisms: one dose-dependent and one time-independent).

The results concerning the reported onset of all types of serious infections associated with the administration of medicinal products containing a TNFα inhibitor as an active substance showed statistically significant reported differences among the three products (table III, log-rank test, $p < 0.001$ and figure 2). The best fit was obtained with a lognormal distribution for the infections associated with etanercept and infliximab, and with a Weibull (with a monotone decreasing hazard) for the infections associated with adalimumab (table IV). The shape of the corresponding hazard functions is shown in figure 2. The Kaplan-Meier analysis of the reported time to onset

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of all infections associated with TNFα inhibitors showed that infections associated with infliximab and etanercept have a reported time to onset that was shorter than that with adalimumab.

The reported time to onset for six types of infections (corresponding to six different MedDRA® preferred reactions terms) could be modelled for all three products included in the study (these infections are cellulitis, herpes zoster, pneumonia NOS, tuberculosis NOS, sepsis and urinary tract infections). The summary statistics for the time to onset of these reactions are shown respectively in table V. Concerning other types of infections, appropriately documented reports could only be used for our modelling for two of the three products included in the study (including fungal infection, erysipelas, hepatitis B, meningitis, bronchitis acute, lower respiratory tract infection, *Pneumocystis carinii* pneumonia, disseminated tuberculosis, septic shock, septic arthritis and pyelonephritis). The comparison of the Kaplan-Meier estimates of the survivor function for the reactions reported for the three products was significant for the occurrence of reported cases of pneumonia NOS (log-rank test, $p = 0.001$) and for the reported cases of herpes zoster infection (MedDRA® term herpes zoster, log-rank test, $p < 0.001$) but not for the other reported reactions. The comparison of the Kaplan-Meier estimates of the survivor function for the adverse reactions that had only been reported for two of the three products were significant for the *Pneumocystis carinii* pneumonia (log-rank test, infliximab vs etanercept, $p = 0.004$) and for the pulmonary tuberculosis (log-rank test, infliximab vs etanercept, $p = 0.02$).

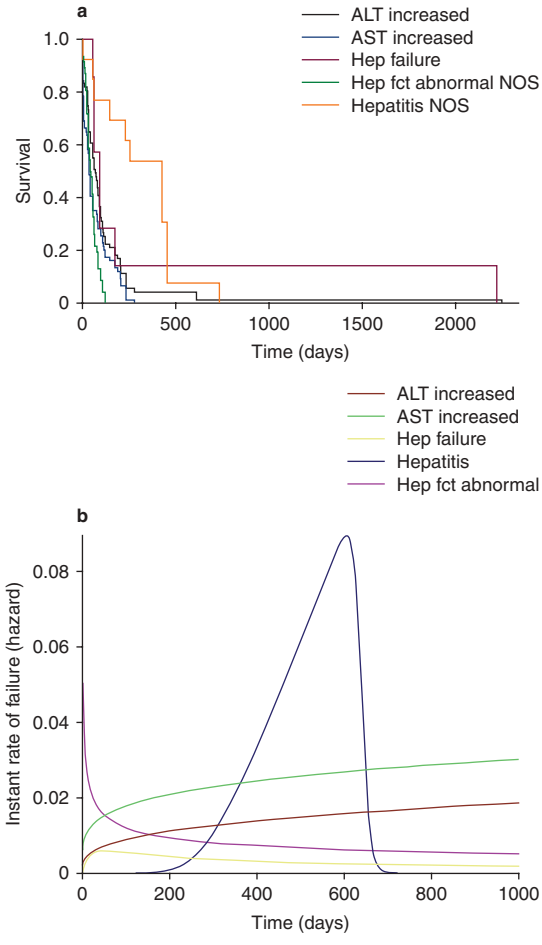

Fig. 1. (**a**) Kaplan-Meier estimate of the time to onset of reactions suggesting a possible liver injury associated with bosentan administration. The 95% CIs are not displayed. (**b**) Plot of the hazard functions corresponding to the fitted parametric distributions of the time to onset of liver injuries possibly associated with bosentan administration. **Hep** = hepatic; **Hep fct** = hepatic function; **NOS** = not otherwise specified.

The corresponding results of the fit of the parametric survival distributions for these reactions are shown in table VI. The respective hazard functions corresponding to the fitted parametric distributions of the time to onset of each type of infection reported for each of the individual products are shown in figure 3 (etanercept and infliximab) and figure 4 (adalimumab).

The hazard of reported onset of an infection when treated with infliximab and etanercept reaches a maximum during the first 50–100 days of treatment, with a higher reported risk of infections associated with infliximab than the other two products (etanercept and adalimumab). The hazard of reported onset of infection with adalimumab administration is best modelled with a Weibull function (with a rapidly monotone decreasing hazard). The hazard of reported onset of infection associated with adalimumab administration may persist over time in comparison with the other TNF inhibitors (figure 2). The hazard functions corresponding to the reported times to

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Table II. Results of the fit of parametric survival distributions for the time to onset of reactions suggesting a possible liver injury

MedDRA® preferred term	Parametric distribution for which the best fit was obtained	Scale parameter	Mean (95% CI) [d]
ALT increased	Weibull	1.32	124 (91, 169)
AST increased	Weibull	1.23	69 (52, 92)
γ-Glutamyltransferase increased	Weibull	1.29	52.5 (23, 118)
Blood bilirubin increased	Weibull	1.25	128 (75, 219)
Hyperbilirubinaemia	Weibull	0.219	723 (608, 861)
Liver function tests NOS abnormal	Lognormal	1.47	160 (116, 223)
Hepatic disorder NOS	Lognormal	1.34	141 (67, 295)
Hepatic function abnormal NOS	Weibull	0.63	51 (42, 61)
Hepatitis NOS	Normal	204	320 (209, 430)
Hepatic failure	Lognormal	1.19	277 (87, 879)

d = day; **MedDRA®** = Medical Dictionary for Regulatory Activities; **NOS** = not otherwise specified.

onset consistently show an early reported risk of herpes zoster, urinary tract infection, pneumonitis and sepsis with the three products. Differences were observed with the reported risk of cellulitis and tuberculosis (both delayed with adalimumab).

We studied the occurrence of pneumonias reported with infliximab (these are reactions for which treatment start dates and reaction onset dates were populated with precise dates; this part of the study, which was aimed at comparing the reported occurrence of different types of pneumonia, could not be performed with the other products). The study of these different types of pneumonias reported with infliximab (pneumonia NOS, *Pneumocystis carinii* pneumonia, pneumonia bacterial NOS, pneumonia haemophilus, pneumonia influenzal, pneumonia klebsiella and pneumonia mycoplasmal) showed that the Kaplan-Meier estimates of the survivor function of the time to onset were significantly different (log-rank test, $p = 0.02$). The summary statistics are shown in table VII. The results of the fit of survival parametric distributions are shown in table VIII. These results suggest that there are reported differences in the time to onset of these pneumonias. In particular, the time to onset of an influenzal, klebsiella or mycoplasmal pneumonia is significantly longer than the occurrence of a *Pneumocystis carinii* pneumonia. No uniform pattern in terms of the hazard of developing one of these pneumonias could be found. The hazard is variable over time (the sense of variation of the hazard function actually changes during the course of treatment) for most of these pneumonias (*Pneumocystis carinii* pneumonia, pneumonia influenzal and pneumonia klebsiella).

A final analysis was performed on the reports of tuberculosis (no distinction was made between primary and reactivation) with the three products. The hazard functions of the reported time to onset showed a very similar pattern for the tuberculosis associated with the administration of infliximab and etanercept (these reported times

Table III. Summary statistics for the time to onset of infections (all reactions) associated with the administration of medicinal products containing a tumour necrosis factor-α inhibitor as active substance. Lower 95% CI and upper 95% CI represent the lower and upper bounds, respectively, of the CI of the median

Product	No. of reports[a]	Mean (SE) [d]	Median (d)	Lower 95% CI (d)	Upper 95% CI (d)	Minimum (d)	Maximum (d)
Etanercept (Enbrel®)	1045	296 (14)	117	108	125	1	2706
Infliximab (Remicade®)	508	168 (12)	72	64	83	1	1841
Adalimumab (Humira®)	121	320 (25)	286	190	360	12	1734

a The number of reports expresses the number of reports received in EudraVigilance in which the drug start treatment date and the reaction start date are documented (exact dates).

d = day; **SE** = standard error.

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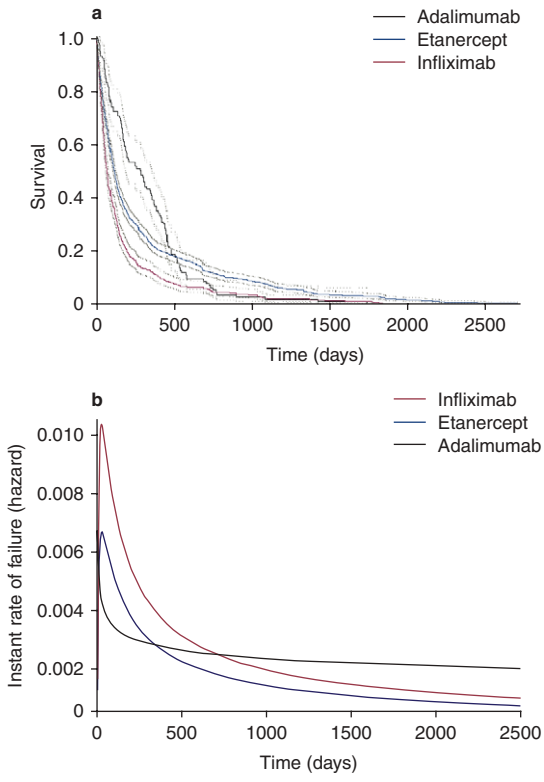

Fig. 2. (**a**) Kaplan-Meier estimate of the time to onset of infections associated with the administration of a medicinal product containing a tumour necrosis factor (TNF)-α inhibitor. The dotted lines show the 95% CIs computed with the Greenwood formula. (**b**) Corresponding plot of the hazard functions corresponding to the fitted parametric distributions of the time to onset of infections possibly associated with the administration of medicinal products containing a TNFα inhibitor as an active substance.

to onset were best modelled with a lognormal distribution with very similar scale parameters). The corresponding hazard functions showed a reported risk of tuberculosis shortly after the initiation of the treatment, with a peak occurring approximately 100 days after the initiation of the treatment (the risk is reportedly higher for infliximab than etanercept). The hazard functions showed a delayed reported risk with adalimumab increasing gradually and peaking approximately 600 days after the start of the treatment. Different types of tuberculosis could be studied for etanercept and infliximab (tuberculosis NOS, disseminated tuberculosis and pulmonary tuberculosis, including the cases of tuberculosis pleurisy). The modelling of the hazard function for the cases of tuberculosis reported with infliximab showed very similar patterns of occurrence of these tuberculosis infections (best modelled with a lognormal distribution), with a peak occurring within the first 100 days after the initiation of treatment (figure 4). In the case of etanercept, the reported occurrence of pulmonary tuberculosis was best modelled by a Weibull distribution with a monotone decreasing hazard, whereas the cases of tuberculosis NOS were best modelled with a lognormal distribution (hazard variable over time) [tables IX and X].

Discussion

Time to Onset: A Concept Involving Several Mechanisms that Cannot be Disentangled

The overall probability of having an adverse drug reaction reported in a spontaneous reporting system is a combination of the following probabilities: a probability of occurrence of the reaction, a probability of diagnosis of the reaction conditional on the fact that it had occurred and, finally, a probability of reporting conditional on the fact that a diagnosis of adverse drug reaction was made (or at least a suspected causal association came to the mind of the reporter). Each of these probabilities of occurrence in time

Table IV. Results of the fit of parametric survival distribution to the time to onset of infections (all reactions) reported with all three medicinal products containing a tumour necrosis factor-α inhibitor (reports for which the drug start and the reaction start both contain exact dates)

MedDRA® preferred term	Parametric distribution for which the best fit was obtained	Scale parameter	Mean (95% CI) [d]
Etanercept (Enbrel®)	Lognormal	1.37	315 (281, 353)
Infliximab (Remicade®)	Lognormal	1.24	168 (145, 194)
Adalimumab (Humira®)	Weibull	0.83	320 (276, 371)

d = days; **MedDRA®** = Medical Dictionary for Regulatory Activities.

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Table V. Summary statistics for the time to onset of five infections associated with the administration of a medicinal product containing a tumour necrosis factor-α inhibitor (infliximab, etanercept and adalimumab) and reported for all products. Lower 95% CI and upper 95% CI represent the lower and upper bounds, respectively, of the CI of the median

Product/MedDRA® preferred term	No. of reports[a]	Mean (SE) [d]	Median (d)	Lower 95% CI (d)	Upper 95% CI (d)	Minimum (d)	Maximum (d)
Cellulitis							
Infliximab	17	283 (74)	92	52	591	1	981
Etanercept	62	356 (52)	210	124	356	23	1918
Adalimumab	6	437 (80)	480	325	NA	86	710
Herpes zoster							
Infliximab	49	129 (21)	72	51	121	4	534
Etanercept	67	330 (52)	163	138	247	7	2448
Adalimumab	7	263 (68)	86	52	NA	71	710
Pneumonia NOS							
Infliximab	125	159 (23)	80	66	98	1	1841
Etanercept	333	228 (23)	86	75	96	2	2496
Adalimumab	35	379 (63)	287	174	456	12	1734
Sepsis NOS							
Infliximab	41	209 (50)	62	47	153	5	1372
Etanercept	52	349 (72)	115	90	155	10	1972
Adalimumab	16	231 (52)	154	62	480	15	1734
Tuberculosis NOS							
Infliximab	13	228 (78)	73	60	NA	28	1054
Etanercept	26	283 (75)	143	78	334	19	1398
Adalimumab	16	323 (43)	358	191	449	62	692
Urinary tract infection							
Infliximab	6	327 (265)	46	30	NA	1	1776
Etanercept	47	232 (49)	111	66	151	13	630
Adalimumab	13	347 (67)	315	143	NA	28	775

a The number of reports expresses the number of reports received in EudraVigilance in which the drug start treatment date and the reaction start date are documented (exact dates).

d = days; **MedDRA®** = Medical Dictionary for Regulatory Activities; **NA** = not applicable; **NOS** = not otherwise specified; **SE** = standard error.

must be understood as being probability of failure (or an event occurring) conditional on survival until time (t) [equation 1].

$$P(t \leq T \leq t + x \mid T \geq t) \quad \text{(Eq. 1)}$$

In this equation, T defines the time of occurrence of the event between time t and t + x conditional on survival (conditional on the fact that the event did not occur) until time t. The hazard is computed by taking the limit of this probability when x tends to zero.

Therefore, the overall probability (P) of reporting can be expressed as [equation 2]:

$$P(\text{occurrence}) \bullet P(\text{diagnosis} \mid \text{occurrence}) \bullet P(\text{reporting} \mid \text{diagnosis}) \quad \text{(Eq. 2)}$$

The resulting hazards (h) are obtained by computing the instantaneous rates.[16] This implies that equation 2 leads to [equation 3]:

$$h(\text{occurrence}) \bullet h(\text{diagnosis} \mid \text{occurrence}) \bullet h(\text{reporting} \mid \text{diagnosis}) \quad \text{(Eq. 3)}$$

The overall hazard of occurrence of an adverse drug reaction is a combination of the three mechanisms; therefore, for the same reaction, differences in the reported hazard can only be explained by:

1. Differences in the hazard of occurrence that are the result of different pharmacological (pharmacodynamic, pharmacokinetic) and toxicological properties of the medicinal product or different monitoring practices of the patients that

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will prevent or delay the occurrence or minimize the consequences of the reaction.
2. Differences in the hazard of diagnosis that are the result of an awareness of the reporting physician of the existence of a possible link between the administration of the product and the occurrence of the reaction. Other stochastic components may also cause some variability (e.g. reaction starting without any clinical manifestations).
3. Different mechanisms or pattern of reporting of the reactions.

Modelling of the Reported Time to Onset of the Liver Injuries Associated with Bosentan

Results from the non-parametric analysis showed the practical difficulties of understanding and interpreting the course of events over time when considering this graphical display. Similarly, the summary tabulation provides some information that can be misleading. The mean and median times of occurrence of liver failure suggest a delayed risk after the initiation of the treatment. The plot of the estimated hazard functions shows an increased hazard for the reported elevation of AST in comparison with the reported elevation of ALT. This pattern is suggestive of a mitochondrial toxicity (AST is extensively present in hepatocyte mitochondria). The effect of bosentan on mitochondria is unknown.[17] No time consistency in very similar reactions (blood bilirubin increased and hyperbilirubinaemia) was observed. The increase of liver enzymes was best modelled with a Weibull distribution with a monotone increasing hazard function that might be suggestive of a direct

Table VI. Results of the fit of parametric survival distribution to the time to onset of infections reported with all three medicinal products containing a tumour necrosis factor-α inhibitor (reports for which the drug start date and the reaction start are both populated with exact dates)

MedDRA® preferred term	Parametric distribution for which the best fit was obtained	Scale parameter	Mean (95% CI) [d]
Cellulitis			
Infliximab	Weibull	1.52	297 (140, 630)
Etanercept	Lognormal	1.22	387 (259, 579)
Adalimumab	Normal	195	437 (281, 593)
Herpes zoster			
Infliximab	Lognormal	1.19	142 (92, 219)
Etanercept	Lognormal	1.33	376 (242, 583)
Adalimumab	Weibull	0.67	264 (160, 437)
Pneumonia NOS			
Infliximab	Lognormal	1.25	162 (121, 217)
Etanercept	Lognormal	1.33	217 (178, 264)
Adalimumab	Weibull	0.96	379 (276, 521)
Sepsis NOS			
Infliximab	Lognormal	1.37	211 (118, 379)
Etanercept	Lognormal	1.33	342 (208, 561)
Adalimumab	Lognormal	1.12	257 (128, 515)
Tuberculosis NOS			
Infliximab	Lognormal	1.08	218 (105, 456)
Etanercept	Lognormal	1.08	267 (158, 452)
Adalimumab	Normal	171	323 (239, 406)
Urinary tract infection			
Infliximab	Lognormal	2.17	466 (19, 11246)
Etanercept	Lognormal	1.19	228 (146, 354)
Adalimumab	Weibull	0.72	346 (233, 514)

d = days; **MedDRA®** = Medical Dictionary for Regulatory Activities; **NOS** = not otherwise specified.

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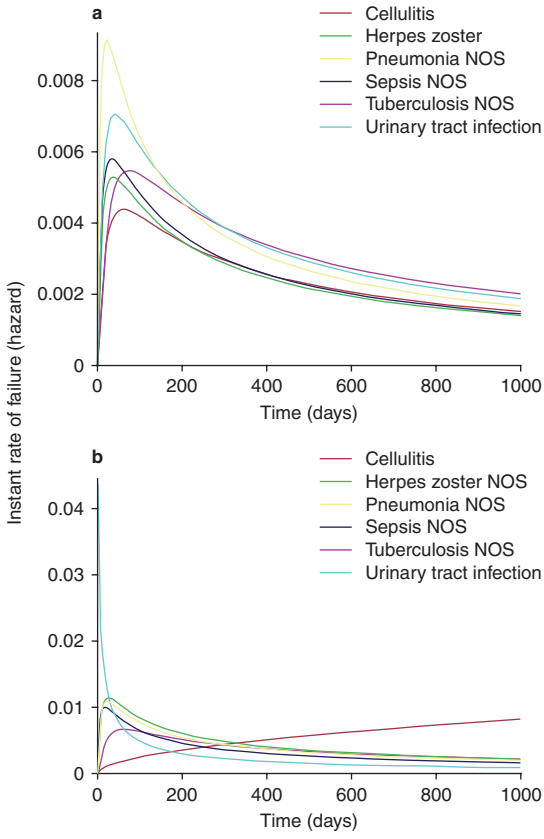

Fig. 3. (**a**) Plot of the hazard functions corresponding to the fitted parametric distributions of the time to onset of infections possibly associated with the administration of etanercept. (**b**) Plot of the hazard functions corresponding to the fitted parametric distributions of the time to onset of infections possibly associated with the administration of infliximab. **NOS** = not otherwise specified.

cumulative dose-dependent toxic mechanism (as it was hypothesized in the clinical studies because of the delayed time to onset of the liver injuries).[17] The other serious liver adverse reactions were best modelled with a function where the sense of variation of the hazard function varies over time (lognormal or normal distribution). The plot of the hazard functions of the fitted distributions provides an overview of the evolution of the hazard of developing a liver adverse reaction that is consistent with the pattern of the toxicity (figure 1). The reported hazard of hepatitis seems to increase approximately 200 days after the initiation of the treatment to reach a maximum after 600 days. This reported risk decreases abruptly thereafter. We interpret these results as indicative of the fact that the occurrence of adverse reactions and their reporting is possibly influenced by the existing risk minimization activities surrounding the authorization of bosentan.[18] In contrast to the summary statistics included in the summary tabulations, the reported hazard of a hepatic failure is low, fairly constant over time and without indications of specific time dependency (this profile is reflected in the EU SPC for bosentan).[17] In our case, it is difficult to know without additional assessment whether the cases of liver injuries or whether these few cases of reported onset of liver failures were actually induced by bosentan or resulted from the underlying or concomitant disease or other concomitant medication even though most of the cases of liver failure reported with bosentan have been considered to be related to the administration of the product.[18] Alternatively, it might suggest that bosentan may cause a range of liver toxicities involving more than one mechanism. As with many drugs, hepatitis and acute hepatic failure may be the outcome of distinct entities with differing pathophysiologies, rather than just a range of expression of a given unique pathophysiology; however, the modelling of the hazard function confirms the features of the liver toxicity of bosentan. This pattern is characteristic of a dose dependent, dose related and predictable hepatotoxicity.[18,19]

Modelling of the Reported Time to Onset of the Infections Associated with Tumour Necrosis Factor (TNF)-α Inhibitors

The risk of serious infections associated with the use of TNFα inhibitors is an adverse effect linked to the pharmacodynamic properties of the products and is also well characterized.[20,21] The estimated odds ratio of serious infection in patients with rheumatoid arthritis receiving either of two TNFα inhibitors (infliximab or adalimumab) compared with placebo for all doses was equal to 2.0 (95% CI 1.3, 3.1).[22] The safety profile of the three products with respect to the occurrence of infections, as described in the product information, is very similar and comparable to the findings of our study.[20,23-25] The sites of serious

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infections reported in the cases transmitted to EudraVigilance are similar to sites described in previous studies (serious skin and soft tissue, urinary tract and lower respiratory tract infections).[26]

Both Kaplan-Meier and reported hazard of occurrence of infections associated with TNFα inhibitors showed that infections associated with infliximab and etanercept have a reported time to onset that is shorter than with adalimumab. Since differences in reported hazards between products can only be explained by a different hazard of occurrence or reporting, it has been postulated that differences in pharmacokinetic properties and mechanisms of action might explain the differences in the risk of developing infections amongst the three TNFα inhibitors.[27] The mean terminal half-life of adalimumab given subcutaneously is longer than the terminal half-life of the other two products (adalimumab is equal approximately to 2 weeks, the half-life of infliximab is equal to 8–9.5 days and the half-life of etanercept is approximately equal to 70 hours). In addition, infliximab is given intravenously whereas etanercept and adalimumab are given subcutaneously (maximum concentration equal to 48 hours and 5 days, respectively), which results in lower peak concentrations for these two products. Finally, from a pharmacodynamic point of view, etanercept differs from infliximab and adalimumab in that it also binds lymphotoxin-α (TNFβ).[28] Lymphotoxin-α mediates a large variety of inflammatory and antiviral responses; however, these pharmacodynamic differences between etanercept and infliximab do not seem to translate into any meaningful differences of reported hazard of occurrence of infections. Likewise, some differences in the time to reported onset of very similar reactions (bacterial pneumonias associated with infliximab) have been observed for the same medicinal product and are most likely the result of different reporting patterns.

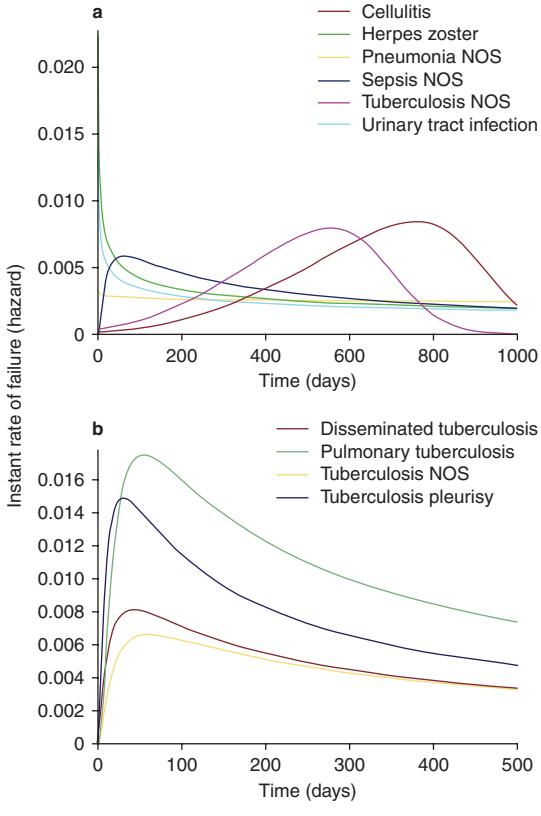

Fig. 4. (**a**) Plot of the hazard functions corresponding to the fitted parametric distributions of the time to onset of infections possibly associated with the administration of adalimumab. (**b**) Hazard functions of the reported time to onset of all cases of tuberculosis associated with infliximab administration. **NOS** = not otherwise specified.

Modelling of the Reported Time to Onset of Tuberculosis Associated with TNFα Inhibitors

The TNF plays a central role in the control of granulomatous infections. The risk of tuberculosis in patients with rheumatoid arthritis as well as the increased risk of tuberculosis associated with the use of TNFα inhibitors in this population have been established.[29] This risk has particularly been suggested in the spontaneous reporting systems, including reports with atypical presentations, and extrapulmonary and disseminated tuberculosis, in some instances with a fatal outcome.[20,30-32] The occurrence of tuberculosis was previously reported to occur in the early phase of treatment, but some cases have been reported after as long as 2 years from initiation of treatment.[33,34] Significant differences in the reported hazard of developing a tuberculosis have been found across products.[20,35] Such differences were not found in clinical studies and this suggests that these differences may be due to different reporting mechanisms affecting the products in

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Table VII. Summary statistics of the time to onset of pneumonias associated with infliximab administration. Lower 95% CI and upper 95% CI represent the lower and upper bounds, respectively, of the CI of the median

MedDRA® preferred term	No. of reports[a]	Mean (SE) [d]	Median (d)	Lower 95% CI	Upper 95% CI	Minimum (d)	Maximum (d)
Pneumonia NOS	125	159 (23)	80	66	98	1	1841
Pneumocystis carinii pneumonia	51	71 (7)	60	46	81	11	202
Pneumonia haemophilus	7	75 (17)	60	38	NA	12	148
Pneumonia influenzal	7	178 (35)	193	79	NA	25	289
Pneumonia klebsiella	6	154 (32)	171	83	NA	28	243
Pneumonia mycoplasmal	5	143 (33)	179	69	NA	42	220

a The number of reports expresses the number of reports received in EudraVigilance in which the drug start treatment date and the reaction start date are documented (exact dates).

d = days; **MedDRA®** = Medical Dictionary for Regulatory Activities; **NA** = not applicable; **NOS** = not otherwise specified; **SE** = standard error.

different ways.[29] The hazard of reported onset of tuberculosis with infliximab in our study was found to be higher than that of etanercept. Previous studies (conducted on the US FDA Adverse Event Reporting System) have shown that granulomatous infections were reported to occur earlier with infliximab than with etanercept;[35] however, in our study a striking difference was found between the reported onset of tuberculosis with adalimumab, which was significantly delayed compared with the other two products. Again, referring to the combination of hazards given in equation 3, the differences can only be explained by different pharmacological properties or different reporting mechanisms. From a pharmacological viewpoint, several explanations have been put forward to explain such differences. Some include differences in the pharmacological profile between the products and the ability of infliximab to inhibit interferon-γ indirectly.[28,29,36-40] The different pharmacological properties are reflected by the different indications in which these products have been authorized[41]. Some pharmacokinetic differences between these products might also explain the reported differences;[28] however, if these observed differences were only due to the different pharmacokinetic properties between the products, it is difficult to understand why they did not influence the occurrence of the non-granulomatous infections in a similar way. From the reporting viewpoint, the differences might also be explained by the introduction of screening procedures when the occurrence of tuberculosis was discovered and publicized, and might have induced a shift of the risk to later stages of the treatment for adalimumab (by a better screening and identification of the patients with tuberculosis or at risk of developing a tuberculosis at the earlier stages of treatment) and by different reporting patterns. Adalimumab was authorized after this risk was known for two other products.[42] In addition, risk minimization activities such as use of antituberculous prophylactic treatment could have impacted on the clinical manifestation of tuberculosis-related events in

Table VIII. Result of the fit of survival parametric distribution for the time to onset of pneumonias associated with infliximab administration

MedDRA® preferred term	Parametric distribution for which the best fit was obtained	Scale parameter	Mean (95% CI) [d]
Pneumonia NOS	Lognormal	1.25	162 (121, 217)
Pneumocystis carinii pneumonia	Lognormal	0.729	73 (58, 91)
Pneumonia haemophilus	Weibull	0.61	75 (47, 119)
Pneumonia influenzal	Normal	93.9	178 (109, 248)
Pneumonia klebsiella	Normal	78.4	154 (91, 217)
Pneumonia mycoplasmal	Weibull	0.485	143 (92, 223)

d = days; **MedDRA®** = Medical Dictionary for Regulatory Activities; **NOS** = not otherwise stated.

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Table IX. Summary statistics of the time to onset of the cases of tuberculosis associated with infliximab or etanercept administration. Lower 95% CI and upper 95% CI represent the lower and upper bounds, respectively, of the CI of the median

MedDRA® preferred term	No. of reports[a]	Mean (SE) [d]	Median (d)	Lower 95% CI	Upper 95% CI	Minimum (d)	Maximum (d)
Infliximab							
Disseminated tuberculosis	16	197 (70)	101	56	216	15	1072
Pulmonary tuberculosis	21	77 (14)	57	35	134	9	258
Tuberculosis NOS	13	228 (78)	73	60	NA	28	1054
Tuberculosis pleurisy	7	86 (25.5)	49	25	NA	9	182
Etanercept							
Pulmonary tuberculosis	17	153 (32)	108	90	234	11	525
Tuberculosis NOS	26	283 (75)	143	78	334	19	1398

a The number of reports expresses the number of reports received in EudraVigilance in which the drug start treatment date and the reaction start date are documented (exact dates).

d = days; **MedDRA®** = Medical Dictionary for Regulatory Activities; **NA** = not applicable; **NOS** = not otherwise specified; **SE** = standard error.

more recent times. Our interpretation is supported by a postmarketing analysis that demonstrated that the implementation of intensified screening in clinical trials resulted in a decrease in the rate of tuberculosis;[34] however, the time to onset of the tuberculosis was not discussed.

Associating a Reported Hazard with the Underlying Mechanism of the Adverse Drug Reaction

We can conclude from our study that the association of a hazard function to a toxic mechanism is probably complicated by other intercurrent mechanisms (in particular, the discovery, diagnosis and reporting of the reaction). The findings from the modelling of the time to onset of liver injuries associated with bosentan differ slightly from the consensus conferences on the drug-induced liver injuries, but we studied only the liver injuries associated with one medicinal product subject to risk minimization activities. The modelling of the liver injuries associated with bosentan confirmed partly the findings from clinical trials and the recommendations given in the summary of product characteristics for this product. A direct toxic mechanism of liver injuries from bosentan leading to increased aminotransferases might be associated with a monotone increasing risk. Further work involving other drugs with or without risk minimization is recommended to clarify this association. The reported onset of conditions likely to be related to immunosuppression induced by the pharmacodynamic effect of the TNFα inhibitors was linked to a variable hazard (increasing then decreasing after 6 months to 1 year of treatment depending on the products). The reported differences observed between the TNFα inhibitors were found in previous studies and several explanations on the underlying mechanisms

Table X. Result of the fit of survival parametric distribution for the time to onset of pneumonias associated with infliximab administration

MedDRA® preferred term	Parametric distribution for which the best fit was obtained	Scale parameter	Mean (95% CI) [d]
Infliximab			
Disseminated tuberculosis	Lognormal	1.13	188 (93, 382)
Pulmonary tuberculosis	Lognormal	0.812	78 (52, 116)
Tuberculosis NOS	Lognormal	1.08	218 (105, 456)
Tuberculosis pleurisy	Lognormal	1.04	95 (36, 248)
Etanercept			
Pulmonary tuberculosis	Weibull	0.829	154 (103, 228)
Tuberculosis NOS	Lognormal	1.08	267 (158, 452)

d = days; **MedDRA®** = Medical Dictionary for Regulatory Activities; **NOS** = not otherwise specified.

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were provided; however, it is probably too premature to conclude on any direct relation between the reported hazard and the underlying pharmacological mechanisms. Our study shows the potential value of the parametric modelling of the reported time to onset as a tool for signal detection and evaluation. Survival analysis has been used in the past for analytical purposes but not routinely for pharmacovigilance signal detection.[43]

Statistical Limitations and Potential Use of the Hazard Functions Modelling Approach

In planning and conducting the study we considered the value of a formal test of hypothesis like other data mining algorithms; however, we considered this not to be feasible. The building of a test of hypothesis involves the availability of an appropriate comparator. This has proved difficult as we could not identify a suitable comparator (e.g. one that would lead to identical toxicity with similar pathophysiological mechanisms but known to be due to the underlying disease). In the absence of a suitable comparator, our approach relies mostly on the checking of causality criteria, including temporality, to accept or refute a possible signal (the consistency of the findings, specificity of the association, temporality, plausibility of the association, coherence with the conjunction of the pharmacological evidence); however, the validity of this approach is not demonstrated on the basis of our two true positives. The limitations of the use of these criteria on a spontaneous reporting system must be kept in mind. Furthermore, at least in theory, the censoring and competing nature of the events should also be taken into consideration. Unfortunately, since there is a major imbalance (over-representation of censored information) between events and competing risks, the inclusion of censored/competing risk information in our current model would have resulted in major biases in the estimation of the (sub)-hazard function(s). Second, the spontaneous reporting system does not collect information on competing risks relating to efficacy outcomes. Since the data from spontaneous reporting are not drawn from a random sample of the studied population, the inferential value of all the data mining algorithms used on spontaneous reporting systems is limited.

The main foreseeable limitations of this new approach to signal detection is the minimum number of reports required to obtain an acceptable fit of the distributions as well as the quality of the data collected. This technique requires a minimum of reports to obtain an acceptable fit as well as documented dates for start of the treatment and occurrence of the reaction. This was particularly illustrated by the infections associated with TNF inhibitors where we could only find an appropriate number of reports for two of the three products included in the study for a series of infections known to be a complication of anti-TNF therapy. Data quality will certainly be a limiting factor of this method, as it would be for any method based on spontaneous reporting. In particular, the identification and removal of duplicate reports is an important quality issue that interferes with the robustness of all the data mining algorithms and also with our method (even when the reports are well documented and a careful removal is undertaken). Our method also requires well documented cases, in particular on the drug and reaction(s) start dates. The method, like the disproportionality analysis, might also suffer from reporting biases, but in future may also be tested on other datasets, such as automated healthcare databases. Finally, some ill-defined adverse event terms (in the bosentan example, liver function tests, hepatic disorder and hepatic function abnormal) are difficult to interpret. Therefore, a method based on this approach is expected to have a low sensitivity in comparison with the existing data mining algorithms based on disproportionality analyses where only a minimum of information is necessary to run the algorithm.[44] However, since it is connected to the underlying toxic mechanism of the adverse drug reaction, other parameters that have a direct impact on the occurrence of some toxicities (such as the presence of risks factors or the dose administered in the case of dose-dependent effects) can be integrated in the model to further improve the detection of true signals. Therefore, we can infer that this method will probably be complementary to other quantitative methods that do

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not currently integrate any information on the time to onset of reactions. It could make a contribution in the framework of signal identification or risk evaluation to help discriminate the true signals from the signals of disproportionate reporting due to a confounding factor.

Conclusions

Our study is preliminary but it shows that the modelling of the time to onset of adverse reactions could be a useful tool to further characterize those reactions reported during the post-authorization phase that were not identified during clinical development of the product. The actual time to onset is a reported time to diagnosis, which is considered to be a surrogate to the real time to onset. Its interpretation is further complicated by the reporting mechanisms. Additional studies should also take into consideration the hazard of reporting adverse reactions in general and this could be done, for example, by studying observational data related to the underlying confounding disease. Modelling of the time to onset could be a useful tool to define objective criteria concerning the occurrence of adverse drug reactions and the possible underlying mechanisms. Further studies should be performed to investigate the relationship between the hazard function and the underlying mechanism of the toxicity, in particular cumulative dose-effect studies. As time-related information may be captured well in large observational healthcare databases, we would recommend that our method should also be tested in such datasets.

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