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Sources of Information on Lymphoma Associated with Anti-Tumour Necrosis Factor Agents

Comparison of Published Case Reports and Cases Reported to the French Pharmacovigilance System

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Abstract

Background: Anti-tumour necrosis factor (TNF) agents, through their intense immunoregulatory effect, have been suspected to increase the risk of malignant lymphoma. However, the classical epidemiological approaches conducted over about the last 10 years have not totally succeeded in addressing the question of a causal or artifactual association. Therefore, the analysis of a substantial set of case reports, although usually considered as poorly generalizable to the general population, could be particularly informative. Two main sources of case reports in postmarketing settings are available; publications in medical journals and reports to pharmacovigilance systems.

Objective: The aim of the study was to compare the characteristics of case reports from both these sources in order to understand whether they provided the same information for the investigation of the causal link between lymphoma and anti-TNF agents.

Methods: All case reports of malignant lymphoma in patients treated with an anti-TNF agent published in MEDLINE and all reports to the French pharmacovigilance system up to 1 February 2010 were identified. Cases of malignant lymphoma identified in postmarketing surveillance from both sources were compared regarding the following variables: age, sex, anti-TNF agent involved, indication for use, type of lymphoma, prior or concomitant immunosuppressive drugs and time to onset of lymphoma.

Results: A total of 81 published case reports and 61 cases reported to the French pharmacovigilance system were compared. In published reports, patients were

younger (p = 0.03) and more frequently receiving a first anti-TNF treatment (p = 0.03), particularly infliximab (p = 0.03). Conversely, in the pharmacovigilance system reports, a succession of different anti-TNFs (p = 0.03) and adalimumab (p < 0.0001) were more frequently reported. Lymphomas in patients treated with anti-TNF agents for Crohn's disease were more prevalent in published cases than in pharmacovigilance reports (p < 0.0001), and in particular involved hepatosplenic T-cell lymphoma. Conversely, rheumatoid arthritis was the main indication for anti-TNF agents in pharmacovigilance reports (p = 0.01). Time to onset was markedly shorter in published cases (median 12 months) than in pharmacovigilance reports (median 30 months; p = 0.0001).
Conclusions: Characteristics of published cases and those reported to the French pharmacovigilance system differed markedly for all characteristics tested, except sex and the use of prior or concomitant immunosuppressive drugs. Published case reports favoured convincing arguments for drug causation whereas cases reported to the pharmacovigilance system were more disparate but could describe more accurately the reality of lymphoma occurrence in this particular population. These results argue for the use of the pharmacovigilance reports when case reports are used to investigate the causal link between lymphoma and anti-TNF agents at the population level. Data from cases notified to the French pharmacovigilance system did not indicate an increased risk of lymphoma during the early phase of anti-TNF treatment. To confirm this hypothesis, a study combining pharmacovigilance reports from several countries, or, if feasible, a cohort study both with a large sample size and a long duration of follow-up would be required.

Background

Anti-tumour necrosis factor (TNF) agents, through their intense immunoregulatory effect, have been suspected to increase the risk of malignant lymphomas. However, the question of a possible induction of lymphoma by anti-TNFs remains unresolved – some studies have shown an increased incidence of lymphoma in patients treated with anti-TNF agents[1,2] while others have failed to confirm this risk.[3-5] The assessment of this adverse drug reaction (ADR) is made complex by the presence of numerous confounding factors known to increase the risk of lymphoma, such as the treated disease (particularly rheumatoid arthritis), its duration and severity, and exposure of most patients to other immunosuppressive agents (notably, methotrexate and thiopurine). Furthermore, the relevance of conventional epidemiological approaches to assessing the risk of lymphoma induced by the anti-TNF agents may be questionable; indeed, (i) randomized clinical trials have more often a too short duration of follow-up to identify delayed lymphomas after the introduction of the anti-TNF treatment; (ii) cohort studies, if under-sized, are not very efficient for the assessment of rare effects (i.e. lymphoma); and (iii) case-control studies may lack statistical power for the investigation of rare exposures (i.e. anti-TNF agents). In such a situation, the analysis of case reports, although often considered poorly generalizable,[6] becomes particularly helpful because case reports represent a quick and inexpensive means of obtaining a large set of lymphoma cases in patients treated with anti-TNF agents. There are two main sources of case reports available in postmarketing surveillance; publications in medical journals and reports to

pharmacovigilance systems. Both sources could be affected by a selection bias, i.e. publication or reporting bias, making the reports possibly non-representative of the whole population of cases of lymphomas observed during or after treatment with anti-TNFs. In the current study, these two sources were compared to understand whether they provided the same information for the investigation of the causal link between lymphoma and anti-TNF agents.

Methods

Case Identification

All cases of lymphoma during or after treatment with anti-TNF agents reported to the 31 French regional pharmacovigilance centres were identified in the national pharmacovigilance database up to 1 February 2010. In parallel, a systematic review of the literature was conducted in the MEDLINE database up to 1 February 2010. The search was performed with the following combination of keywords: 'lymphoma' [MeSH] AND ('adalimumab' OR 'etanercept' OR 'infliximab' OR 'TNF-blockers' OR 'TNF-inhibitors' OR 'anti-TNF') with the language restricted to English and French.

All case reports of malignant lymphoma identified in a postmarketing context were included if the diagnosis was confirmed by histopathological analysis and the delay between the introduction of the anti-TNF agent and the diagnosis of lymphoma was provided or could be calculated. When several anti-TNF agents had been successively used, the time to lymphoma onset was computed by considering the date of introduction of the first anti-TNF agent.

Data Collection and Analysis

Case reports from both sources were compared regarding the following variables: age and sex of the patients, type of anti-TNF agent, indication for use, type of lymphoma, prior or concomitant immunosuppressive drugs and delay of lymphoma occurrence. The Mann-Whitney test was used to compare continuous variables with a non-normal distribution. Qualitative variables were analyzed using the Chi-squared test or the Fisher's exact test as appropriate. Values of $p < 0.05$ were considered significant. The variables and data were analyzed using STATA® software (version 8.2 for Macintosh, STATA Corporation, College Station, TX, USA).

Results

A total of 148 cases of lymphoma after or during anti-TNF treatment were identified: 84 from publications and 64 from the French pharmacovigilance database. For all cases, the malignant character was confirmed by a histopathological diagnosis. Of the 84 published cases, 55 originated from the US, 7 from France, 6 from Sweden, 3 from Turkey, 2 from Japan, Italy and Greece, and 1 each from the UK, Switzerland, Netherlands, Ireland, Austria, Australia and Canada. Three duplicate cases both published and reported to the French pharmacovigilance system were excluded; they concerned one gastric mucosa-associated lymphoid tissue (MALT) lymphoma occurring in a 50-year-old man 26 months after the initiation of three successive anti-TNF agents (etanercept, efalizumab and infliximab),[7] and two cases of T-cell non-Hodgkin's lymphoma arising 3 months and 7 months after the introduction of infliximab and etanercept in men of 47 and 40 years of age, respectively.[8,9]

The analysis was thus performed on 81 published cases and 61 cases notified to the French pharmacovigilance system.[10-43] The comparison of lymphoma cases reported with anti-TNF treatment in publications and to the pharmacovigilance system is presented in table I.

In published reports, patients were younger ($p = 0.029$) and more frequently treated with a single anti-TNF agent ($p = 0.03$), particularly infliximab ($p = 0.03$). On the other hand, in the pharmacovigilance reports, a succession of different anti-TNF agents ($p = 0.03$) or adalimumab ($p < 0.0001$) was more frequently found. Lymphomas in patients treated with anti-TNF agents for Crohn's disease were more prevalent in published cases than in pharmacovigilance reports ($p < 0.0001$), and in particular concerned hepatosplenic T-cell lymphoma (17 in published reports vs 1 in pharmacovigilance reports) in young patients. Conversely,

Table I. Comparison of the characteristics of subjects developing lymphoma after anti-tumour necrosis factor (TNF) treatment in published cases and pharmacovigilance reports

Parameter	Published cases (n = 81)	Pharmacovigilance reports (n = 61)	p-Value
Median age [y (range)]	53.5 (9–84)	59 (33–84)	0.029
Sex ratio, M/F	1.6	0.9	0.086
Type of anti-TNF [n (%)]			
one anti-TNF agent	75 (92.6)	49 (80.3)	0.030
etanercept	29 (38.7)	18 (36.7)	NS
infliximab	44 (58.6)	19 (38.8)	0.030
adalimumab	2 (2.7)	12 (24.5)	<0.0001
more than 1 anti-TNF agent	6 (7.4)	12 (19.7)	0.030
Indication for use [n (%)][a]			
rheumatoid arthritis	34 (42.0)	40 (65.6)	0.01
Crohn's disease	30 (37.0)	6 (9.8)	<0.0001
akylosing spondylitis	4 (4.9)	5 (8.2)	NS
psoriasis arthritis	3 (3.7)	4 (6.6)	NS
JIA	4 (4.9)	0 (0)	NS
others (UC, Still's disease, etc.)	6 (7.4)	8 (13.1)	
uknown	1 (1.2)	0 (0)	
Type of lymphoma [n (%)]			
B-cell NHL	29 (35.8)	32 (52.5)	0.060
T-cell/natural killer-cell NHL	31 (38.3)	8 (13.1)	0.001
Hodgkin's lymphoma	12 (14.8)	8 (13.1)	NS
NHL	8 (9.9)	12 (19.7)	NS
others (lymphoma, thymoma)	1 (1.2)	1 (1.6)	
Prior or concomitant immunosuppressive drugs [n (%)][b]	66 (81.5)	47 (77.0)	NS
Time to lymphoma onset			
months [median (range)]	12.0 (0.2–96.0)	30.1 (2.5–81.6)	0.0001
≤1 year [n (%)]	45 (55.5)	11 (18.0)	<0.0001

a The sum of percentages is >100% because several items could be chosen.

b Immunosuppressive drugs were abatacept, anakinra, azathioprine, ciclosporin, cyclophosphamide, efalizumab, leflunomide, methotrexate, mercaptopurine, rituximab, thalidomide.

F = female; **JIA** = juvenile idiopathic arthritis; **M** = male; **NHL** = non-Hodgkin's lymphoma; **NS** = not significant; **UC** = ulcerative colitis.

rheumatoid arthritis was the indication more frequently associated with lymphoma in the pharmacovigilance reports (p = 0.01). The time to onset was markedly shorter in published reports than in pharmacovigilance reports (median 12 months vs 30 months; p = 0.0001; figure 1).

Discussion

This study shows that published cases markedly differed from those reported to a pharmacovigilance system for all the variables tested, except for sex and the use of prior or concomitant immunosuppressive drugs. This is an important point to note as published cases, thanks to their validation by a peer-review process, are generally considered as the reference to provide information about a novel ADR. In this study, published cases preferentially focused on subjects treated with a single anti-TNF agent and with a short time to lymphoma occurrence that is more easily accepted as demonstrative of drug causality. This has previously been reported by Haramburu et al.[44] who showed, by comparing 500 spontaneous and

500 published reports, that the criteria of causality assessment were more often positive in published reports. As case reports should be presented as convincing and credible to be accepted for publication,[45] it is unlikely that they represent what is observed in real-life settings, e.g. in the present study, the actual pattern of lymphoma occurrence after anti-TNF treatment. Conversely, pharmacovigilance system reports are known to be heterogeneous with regards to the quality of data and link of causality.[46,47] In the present study, the presence of pharmacovigilance reports not demonstrative of drug responsibility (i.e. 'doubtful' and 'possible' cases with causality criteria poorly in favour of drug causation that are not published because they are not convincing enough) is confirmed by the even distribution of the delay to lymphoma onset after initiation of anti-TNF treatment and by the use of a succession of different types of anti-TNF agents. This broader spectrum of cases from the pharmacovigilance database may reflect the more complex reality of the link between lymphoma and anti-TNF agents. This is illustrated by the higher prevalence in the pharmacovigilance reports of rheumatoid arthritis, also a well established risk factor for lymphoma,[48,49] which makes the assessment of the anti-TNF responsibility more complex. Similarly, the lower proportion in published reports of lymphomas involving adalimumab, the most recently marketed of the three anti-TNF agents, could reflect the long delay between the occurrence of an ADR and publication and/or the tendency of editors not to publish an ADR already described with other medicines of the same therapeutic class.

The results presented here illustrate another interesting point: the effectiveness of publications for attracting reports on a novel or unusual ADR. Thus, the numerous reports of hepatosplenic T-cell lymphomas in patients with Crohn's disease treated with infliximab in the literature confirm that a novel ADR, extremely rare but life-threatening and occurring in young patients, has a good chance of being published. Interestingly, this alert was not detected by the French pharmacovigilance system, likely owing to a lack of power but also because infliximab was approved at a later date in the EU for the treatment of Crohn's disease in children (extension of indication in

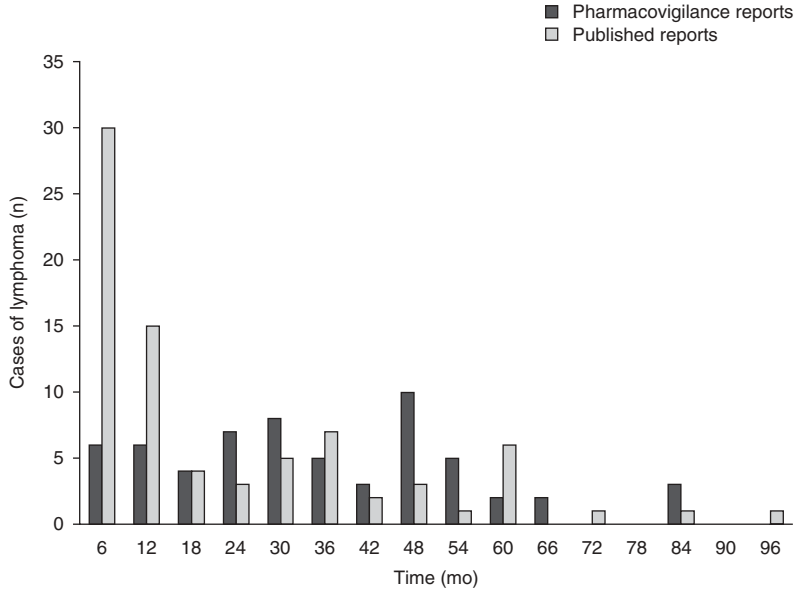

Fig. 1. Delay of lymphoma occurrence after anti-tumour necrosis factor (TNF) introduction in published reports and pharmacovigilance reports. In the published reports, 55.5% of the cases of lymphoma reported were diagnosed during the first year of initial treatment by anti-TNF vs 18.0% in the pharmacovigilance reports ($p < 0.0001$).

the EU on 30 May 2007,[50] first publication in 2005[39]).

The current study, designed to investigate the data sources helpful for studying the relationship between lymphoma and anti-TNF agents, cannot provide a clear-cut answer as to the question of causality; however, it shows that judgement on causality could differ according to the source of information considered. For example, considering published cases, the number (i.e. the risk) of lymphomas appeared to be higher during the first year of anti-TNF treatment and decreased thereafter (figure 1), which could support the hypothesis proposed by some authors that anti-TNF agents have an inducing or revealing effect for the occurrence of lymphoma during the early phase of treatment followed by a reduction of risk caused by control of the inflammatory disease by the anti-TNF agents.[1,48] Interestingly, this hypothesis, which presupposes a causal association between lymphoma and anti-TNFs, was not verified in our sample of pharmacovigilance reports since the number of lymphomas notified appears approximately constant over time.

Cohort studies are among the observational epidemiological approaches most suited to drawing an unbiased picture of lymphoma occurrence over time in patients treated (or having been treated) with anti-TNF therapy, even if, for such a rare and delayed event, they may lack statistical power and data were more or less right-censored in function of the duration of follow-up. Among the 18 572 patients with rheumatoid arthritis exposed for up to 10 years to anti-TNF therapy, Wolfe and Michaud[2] identified 17 lymphomas without any cluster during the early stages of follow-up. Similarly, among the 26 malignant lymphomas identified in a national Swedish cohort of 6604 rheumatoid arthritis patients who started anti-TNF therapy between 1998 and 2006, no trend in risk increase according to the duration of exposure was found.[3] Interestingly, these results are more similar in the present study to the cases reported to the French pharmacovigilance system, and argue for an unrepresentativeness of the published cases in medical journals.

To our knowledge, the present study is the first that has compared case reports from publications and those from a pharmacovigilance system to determine whether they provided the same information to investigate causal inference between a treatment and the occurrence of an event. Most of the previous papers have compared these two data sources with regards to the discovery of a novel ADR,[45,51-53] or for the assessment of the frequency of an ADR.[54,55] Interestingly, Loke et al.[55] showed, in comparing the distribution of the adverse events to amiodarone in three different sources of data (meta-analysis of clinical trials, published spontaneous reports or WHO spontaneous reports), that each data source has its own specific strengths. These results were concordant with those reported in this study, which highlights the performance of published case reports to attract convincing ADRs and the utility of the pharmacovigilance system to collect 'run-of-the-mill' lymphomas after anti-TNF therapy. Indeed, published cases with a chronology or clinical context in favour of drug responsibility were relevant to support a causal link at the individual level; however, taken together, they could produce a biased picture of the way in which the event occurs. On the other hand, pharmacovigilance cases were less convincing *per se* but would provide a better description of the reality of lymphoma occurrence in real-life use and represent less biased material for assessing the causality at the populational level.

The present study has some limitations. First, the two populations compared were not similar: in published reports, the cases of lymphomas occurred in different parts of the world, while the cases issued from the pharmacovigilance database were restricted to France. Consequently, the comparison of the published reports with another pharmacovigilance database could have given different results. Nevertheless, there are no *a priori* arguments to suppose that, except for the value of the reporting rate, the spontaneous reporting process markedly differs from one country to another, i.e. that physicians or pharmacists of different countries declared qualitatively different types of ADRs, unless the pattern of anti-TNF use differed between countries. The three anti-TNF agents investigated in the present study are indicated for the treatment of the same dis-

eases in the US and the EU, even if, as previously highlighted, the indication of infliximab for the treatment of Crohn's disease in children was obtained later in the EU than in the US. However, there were some differences in the pattern of anti-TNF use between the US and EU. In particular, in the EU, infliximab, etanercept and adalimumab were licensed for treatment of active rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis in patients who have had an inadequate response to conventional treatments, with the exception of severe progressive rheumatoid arthritis, while in the US they may be used to reduce the signs of early disease. This may select some subjects with different exposure to immunosuppressive drugs and thus not with the same baseline risk of developing lymphoma. This possible bias is difficult, if not impossible, to control for in the present study. Nevertheless, we compared the previous or concomitant exposure to suppressive drugs, other than the anti-TNF drugs, in the published and pharmacovigilance system cases and did not find any difference. In addition, the French pharmacovigilance database only includes cases that have been previously assessed by at least one senior pharmacologist. This limits the number of spurious reports and makes the French pharmacovigilance cases probably closer to published ones than those contained in pharmacovigilance databases in which all reported cases are recorded, whatever the degree of plausibility for drug causation. Moreover, in restricting the analysis to the cases for which the lymphoma diagnosis was confirmed and for which the duration of exposure to the anti-TNF was known, the number of false positives included in the comparison is probably limited.

Second, some of the lymphoma cases included in the French pharmacovigilance database were identified as part of a regular exchange of information with the national study group Recherche sur les Anti-TNF et les Infections Opportunistes (RATIO), which collects ADRs to anti-TNF agents.[56,57] This could have introduced a kind of selection bias and limits the extrapolation of the present results to another ADR. However, if such a bias was present, it is likely to be of moderate importance since only 16 (26%) of the 61 cases of lymphoma notified to the French pharmacovigilance system were exclusively identified by RATIO. Moreover, suspected ADRs identified during observational studies in postmarketing surveillance are likely to be reported by the investigator to the French pharmacovigilance system as the reporting of any serious adverse event is mandatory in France.[58]

Conclusions

Cases of lymphoma after anti-TNF therapy published in medical journals and reported to the French pharmacovigilance system differed for all characteristics tested, except for sex and the use of prior or concomitant immunosuppressive drugs. Published cases tended to be more convincing for drug causation and reflect anti-TNF agent use worldwide, whereas cases in the French pharmacovigilance system are probably closer to the reality of lymphoma occurrence in clinical practice. These results argue for the use of the pharmacovigilance reports when case reports are used to investigate the causal link between lymphoma and anti-TNF agents at the populational level. Data from cases notified to the French pharmacovigilance system did not indicate an increased risk of lymphoma during the early phase of anti-TNF treatment. To confirm this hypothesis, a study combining other pharmacovigilance reports from several countries or, if feasible, a cohort study both with a large sample size and a long duration of follow-up, would be required.

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