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TNF-α Inhibitors and Leukaemia: International Pharmacovigilance Reports

Since the first report in 2003 of the development of leukaemia in a patient using etanercept,[1] three more observations regarding leukaemia in suspected connection with a tumour necrosis factor-α inhibitor (TNFI) have appeared in the literature: one of etanercept[2] and two concerning infliximab (together with reactivation of tuberculosis in one).[3,4] Because of the serious nature of leukaemia, we think it is important to provide information on relevant international spontaneous report data, which indicate that there is a need for further evaluation. The more so since current product information makes an indecisive reference to a possible link with lymphoma and other malignant diseases.[5]

We examined world-wide safety data collected in the international pharmacovigilance programme of the WHO for the presence of additional reports of leukaemia in association with TNFIs. In this programme, maintained by the Uppsala Monitoring Centre (UMC), case reports regarding patients with suspected adverse drug reactions from national pharmacovigilance centres in 80 countries around the world are stored in a central database, Vigibase.[6]

A search of the UMC's Vigibase revealed that by November 2006 there had been 74 cases of leukaemia reported in suspected connection with infliximab, 39 with etanercept and 12 with adalimumab (table I); six additional likely duplicate reports where excluded. The total number of patients involved was 121, as four patients had been exposed to more than one TNFI. Eight of the reports originated from clinical studies. The reports came from 14 different countries, with a majority (78%) from the USA. The types of leukaemia in these reports are shown in table I.

In 103 of the 121 reports (78% infliximab, 95% etanercept and 92% adalimumab), only TNFIs had been recorded as suspected drugs. Fifty-four patients had simultaneously been using methotrexate or other immunotoxic drugs, and six patients were using sulfasalazine concomitantly. Of the patients, 61 were female and 48 male (gender was not recorded in 12 reports).

Age, as recorded in 82 of the reports, ranged from 3 to 80 years, with a median age of 60 years. Exposure time until the diagnosis of leukaemia ranged from a few months to several years. Acute as well as chronic leukaemia had occurred and myeloid and lymphocytic leukaemias were reported in roughly similar numbers. There was no characteristic pattern in regards to exposure time, patient age or type of leukaemia.

The most common reasons for TNFI use were rheumatoid arthritis and Crohn's disease. In three of the cases, the indication for use of infliximab had been a myelodysplastic syndrome (clinical study reports) and in one myeloid leukaemia, while in one etanercept case the indication was chronic lymphocytic leukaemia. Four other reports were different in that recurrence of a previous leukaemia had occurred. In one of these reports, the patient had been exposed to infliximab as well as etanercept.

Case reports received at the UMC are heterogeneous and vary in regards to source, documentation quality and relationship likelihood; data elements may be missing and secondary review is often difficult. This analysis focuses solely on international pharmacovigilance data; no estimate of incidence rate is possible. The variation in the total numbers of reports for the three TNFIs (table I) is, in the absence of plausible explanations of systematic differential reporting, likely to reflect differences in exposure to each of these medicines. Since the natural course of leukaemia is irreversible and progressive, outcome, dechallenge and rechallenge information are unlikely to be helpful in assessing relationship likelihood. Individual case safety reports reflect the concerns of the reporting health professional or patient. They are based on individual diagnoses and chance associations between the drug and the suspected adverse reaction cannot be excluded.

Table I. Leukaemia in suspected connection with tumour necrosis factor-α inhibitors (TNFIs)[a]

Type of leukaemia	Infliximab (16 794)[b]		Etanercept (26 284[b])		Adalimumab (13 287[b])	
	total no. of reports	no. where TNFI only suspect drug	total no. of reports	no. where TNFI only suspect drug	total no. of reports	no. where TNFI only suspect drug
Leukaemia (NOS)	14	13	9	9	2	2
Leukaemia lymphocytic	5	3	5	5		
Leukaemia myeloid	8	6	3	3		
Leukaemia acute	10	9	1	1	1	1
Leukaemia myeloid acute	12	7	8	8	4	3
Leukaemia lymphocytic acute			1	1	1	1
Leukaemia megakaryocytic acute	2	2				
Leukaemia chronic	1	1				
Leukaemia lymphocytic chronic	12	10	6	5	2	2
Leukaemia myeloid chronic	4	3	1	1		
T-cell leukaemia	1	1	1	1		
Hairy cell leukaemia	1	1	3	3	2	2
Leukaemia recurrent	4	2	1			
Total no. of any leukaemia	**74**	**58**	**39**	**37**	**12**	**11**

a More than one TNFI can be reported as a suspected drug for a case. Four patients had been exposed to more than one TNFI.

b Total number of reports of all suspected adverse reactions for the drug.

NOS = not otherwise stated.

It is of note that infliximab[7] and etanercept[8] are also being used experimentally in the management of lymphoproliferative disorders. There are indications that disorders such as rheumatoid arthritis are themselves a risk factor for haematological malignancies and that this connection is stronger in patients with higher disease activity;[9-11] such patients are more likely to be prescribed TNFIs. Higher disease activity may also require more aggressive drugs (e.g. azathioprine and methotrexate) and regimens, which also may have a risk for leukaemia. Therefore, the international pharmacovigilance data may be confounded to an unknown extent.

In a Swedish population-based cohort study by Askling et al.[11] and in a meta-analysis of clinical trials on infliximab and adalimumab (not including etanercept) by Bongartz et al.[12] where malignancies after TNFI exposure were investigated, only two and one leukaemia cases in each study, respectively, were noted.

Spontaneous reports provide an indication of possible adverse reactions; however, denominator data are lacking and under-reporting[13] should also be considered. Further pharmacoepidemiological studies are needed to determine whether or not TNFIs are associated with an increased risk of leukaemia and other haematological malignancies and, if so, to provide an estimate of the attributable risk.

Ronald H.B. Meyboom,[1,2] *Kristina Star*,[1] *Jenny Bate*,[1] *Ruth Savage*[3] and *I. Ralph Edwards*[1]

1 WHO Collaborating Centre for International Drug Monitoring - the Uppsala Monitoring Centre, Uppsala, Sweden

2 Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht University, Utrecht, The Netherlands

3 Department of Preventive and Social Medicine, New Zealand Pharmacovigilance Centre, University of Otago, Dunedin, New Zealand

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