SAMSUNG BIOEPIS

Swiss Summary of Risk Management Plan (RMP)

for

Benepali™ (Etanercept)

Samsung Bioepis CH GmbH

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Benepali™ is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Benepali™ in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Samsung Bioepis CH GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Benepali™.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR BENEPALI

This is a summary of the risk management plan (RMP) for Benepali. The RMP details important risks of Benepali, how these risks can be minimised, and how more information will be obtained about Benepali's risks and uncertainties (missing information).

Benepali's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Benepali should be used.

This summary of the RMP for Benepali should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Benepali's RMP.

I. The medicine and what it is used for

Benepali is authorised for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis, non-radiographic axial spondyloarthritis, juvenile idiopathic arthritis (including polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis, adolescent psoriatic arthritis, adolescent enthesitis- related arthritis) and paediatric plaque psoriasis> (see SmPC for the full indication). It contains etanercept as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Benepali’s benefits can be found in Benepali’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/benepali

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Benepali, together with measures to minimise such risks and the proposed studies for learning more about Benepali's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure t hat the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Benepali, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Benepali are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Benepali. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Malignancy (including lymphoma and leukaemia) Serious and opportunistic infections (including TB, Legionella, Listeria, parasitic infection) Demyelinating disorders Aplastic anaemia and pancytopenia CHF in adult subjects
Important potential risks	Encephalitis/leukoencephalomyelitis Progressive multifocal leukoencephalopathy Impaired growth and development in juvenile subjects Acute ischemic CV events in adult subjects
Missing information	Not applicable

II.B Summary of important risks

II.B.1 Important identified risks

Malignancy (including lymphoma and leukaemia)	
Evidence for linking the risk to the medicine	Study SB4-G31-RA; proposed Summary of Product Characteristics (SmPC) for Benepali, section 4.4 'Special warnings and precautions for use'; referenced scientific publications.
Risk factors and risk groups	The overall risk of malignancy including cutaneous and non-cutaneous cancers has been reported to be higher in patients with RA compared with healthy subjects. In addition, the proposed SmPC for Benepali states that there is an increased background risk for lymphoma and leukaemia in RA patients with long-standing, highly active, inflammatory disease. Studies have shown that patients with RA have an approximately 2-fold increased risk of lymphoma and leukaemia, a 20% to 50% increased risk of respiratory tract cancer, and a 70% increased risk of non-melanoma skin cancers, but a decreased risk for breast and colorectal cancer.[1,2] The increase in lymphoma risk is limited to those RA patients who have long-standing and very severe disease.[3]
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Registry participation See section II.C of this summary for an overview of the post-authorisation development plan.

Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, parasitic infection)	
Evidence for linking the risk to the medicine	Study SB4-G31-RA; referenced scientific publications.
Risk factors and risk groups	The patients who are on concomitant immunosuppressive therapy, in addition to their underlying disease, can be predisposed to infection.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.3, 4.4, and 4.8 Additional risk minimisation measures Patient card
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> Registry participation See section II.C of this summary for an overview of the post-authorisation development plan.

Demyelinating disorders	
Evidence for linking the risk to the medicine	Study SB4-G31-RA; proposed SmPC for Benepali, Section 4.4 'Special warnings and precautions for use'; referenced scientific publications.
Risk factors and risk groups	Patients with pre-existing or recent-onset central demyelinating disorders.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4 and 4.8 Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities Registry participation See section II.C of this summary for an overview of the post-authorisation development plan.

Aplastic anaemia and pancytopenia	
Evidence for linking the risk to the medicine	Study SB4-G31-RA; proposed SmPC for Benepali, Section 4.4 'Special warnings and precautions for use'; referenced scientific publications.
Risk factors and risk groups	Although no high risk group has been identified, caution should be exercised in subjects being treated with etanercept who have a previous history of significant haematological abnormalities.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4 and 4.8 Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities Registry participation See section II.C of this summary for an overview of the post-authorisation development plan.

CHF in adult subjects	
Evidence for linking the risk to the medicine	Study SB4-G31-RA; proposed SmPC for Benepali, Section 4.4 'Special warnings and precautions for use'; referenced scientific publications.
Risk factors and risk groups	Patients with a previous history of CHF. Patients with diagnosed ischaemic heart disease.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4 and 4.8 Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities Registry participation See section II.C of this summary for an overview of the post-authorisation development plan.

II.B.2 Important potential risks

Encephalitis/leukoencephalomyelitis	
Evidence for linking the risk to the medicine	Study SB4-G31-RA.
Risk factors and risk groups	Patients with pre-existing or recent onset of encephalitis/leukoencephalomyelitis.
Risk minimisation measures	Routine risk minimisation measures None Additional risk minimisation measures None
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> Registry participation See section II.C of this summary for an overview of the post-authorisation development plan.

Progressive multifocal leukoencephalopathy	
Evidence for linking the risk to the medicine	Study SB4-G31-RA; referenced scientific publications.
Risk factors and risk groups	Patients on concomitant immunosuppressive therapy that, along with their underlying disease, could predispose them to PML.
Risk minimisation measures	Routine risk minimisation measures None Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities Registry participation See section II.C of this summary for an overview of the post-authorisation development plan.

Impaired growth and development in juvenile subjects	
Evidence for linking the risk to the medicine	Referenced scientific publications
Risk factors and risk groups	There are currently no known risk groups or risk factors in patients following the administration of etanercept for events in growth and development.
Risk minimisation measures	Routine risk minimisation measures None Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities None

Acute ischemic CV events in adult subjects	
Evidence for linking the risk to the medicine	Study SB4-G31-RA; referenced scientific publications.
Risk factors and risk groups	Currently, there are no known risk groups or risk factors for the development of acute ischemic cardiovascular events with etanercept treatment.
Risk minimisation measures	Routine risk minimisation measures None Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities Registry participation See section II.C of this summary for an overview of the post-authorisation development plan.

II.B.3 Missing information

Not applicable

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Benepali.

II.C.2 Other studies in post-authorisation development plan

BSRBR-RA

Purpose of the study: An established nationwide register for patients with rheumatological disorders treated with biologic agents. The register is designed as a national prospective study whose primary purpose is to assess long-term toxicity from the use of these agents in routine practice.

RABBIT

Purpose of the study: A prospective, observational cohort study whose objectives are to evaluate the long-term effectiveness, safety, and costs associated with tumour necrosis factor-inhibitor therapies in the treatment of RA and to compare this to a cohort of RA patients who are treated with non-biologic DMARDs.

ARTIS

Purpose of the study: A national prospective, observational, uncontrolled cohort study whose objectives are to evaluate the risk of selected AEs in RA, juvenile idiopathic arthritis, and other rheumatic disease patients treated with etanercept.

BADBIR

Purpose of the study: A nationwide registry which seeks to assess the long-term safety of biologic treatments for psoriasis. Recommended by NICE that all patients in the UK receiving new therapies for psoriasis be registered in BADBIR.

References

1 Askling J, Fored CM, Brandt L, et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. *Ann Rheum Dis*. 2005;64:1421–6.

2 Imperato AK, Bingham COI, Abramson SB. Overview of benefit/risk of biological agents. *Clin Exp Rheumatol*. 2004;22(5 Suppl 35):S108-14.

3 Vidal F, Fontova R, Richart C. Severe neutropenia and thrombocytopenia associated with infliximab. *Ann Intern Med.* 2003;139(3):E238-9.

EXTENDED REPORT

Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists

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Background: Patients with rheumatoid arthritis (RA) are at increased risk of malignant lymphomas, and maybe also of leukaemia and multiple myeloma. The effect of tumour necrosis factor (TNF) antagonists on lymphoma risk and characteristics is unclear.
Objective: To assess expected rates and relative risks of haematopoietic malignancies, especially those associated with TNF antagonists, in large population based cohorts of patients with RA.
Methods: A population based cohort study was performed of patients with RA (one prevalent cohort (n = 53 067), one incident cohort (n = 3703), and one TNF antagonist treated cohort 1999 through 2003 (n = 4160)), who were linked with the Swedish Cancer Register. Additionally, the lymphoma specimens for the 12 lymphomas occurring in patients with RA exposed to TNF antagonists in Sweden 1999 through 2004 were reviewed.
Results: Study of almost 500 observed haematopoietic malignancies showed that prevalent and incident patients with RA were at increased risk of lymphoma (SIR = 1.9 and 2.0, respectively) and leukaemia (SIR = 2.1 and 2.2, respectively) but not of myeloma. Patients with RA treated with TNF antagonists had a tripled lymphoma risk (SIR = 2.9) compared with the general population. After adjustment for sex, age, and disease duration, the lymphoma risk after exposure to TNF antagonists was no higher than in the other RA cohorts. Lymphomas associated with TNF antagonists had characteristics similar to those of other RA lymphomas.
Conclusion: Overall, patients with RA are at equally increased risks for lymphomas and leukaemias. Patients with RA treated with TNF antagonists did not have higher lymphoma risks than other patients with RA. Prolonged observation is needed to determine the long term effects of TNF antagonists on lymphoma risk.

Patients with rheumatoid arthritis (RA) are at increased risk of malignant lymphomas,[1–5] but the risk determinants and lymphoma characteristics have only begun to be unravelled.[6–10] For other haematopoietic malignancies in RA, several studies have indicated some degree of increased occurrence of leukaemia,[2 3 11–17] but the reported risks have varied across strata without a consistent pattern, in part because of insufficient statistical power and diagnostic resolution. It is important to verify increased leukaemia risks , however, as they might reflect yet unestablished side effects of antirheumatic agents.[17 18]

With tumour necrosis factor (TNF) antagonists, conspicuously high, and rapid[19] occurrences of malignant lymphomas have been observed.[19–21] Although several case reports, case series,[19 22] and crude incidences in series of patients treated with TNF antagonists have been presented,[23 24] few studies outside a trial setting[21] have examined the occurrence of malignant lymphomas after TNF antagonist treatment in relation to that among patients with RA not treated with biological agents, or provided characteristics of consecutive lymphomas associated with TNF antagonists in a defined population. Likewise, much of the available data on lymphoma risk in RA reflect cohorts both identified and followed up decades ago,[2 3 13 25] and may not apply to contemporary patients. Wolfe and Michaud provide contemporary data based on 29 lymphomas.[9] They observed a 40% increased lymphoma risk in patients with RA not treated with TNF antagonists, and a tripled (in comparison with the general population) lymphoma risk in patients receiving treatment with TNF antagonists.[9]

Evidently, before we can evaluate the risk of haematopoietic malignancies in RA, or the level and characteristics of any increased lymphoma risk associated with TNF antagonists, we need contemporary and comparable data on the expected occurrence of haematopoietic malignancies in RA, data on the incidence and risk of lymphomas in patients with RA associated with TNF antagonists, and information on the characteristics of such patients and their lymphomas.

To provide such data on the expected occurrence and risk of haematopoietic malignancies in RA, we followed up one prevalent (n = 53 067) and one incident (n = 3703) cohort of Swedish patients with RA for cancer occurrence during 1990 through 2003 using high quality nationwide health and census registers. To provide data on the risk for malignant lymphomas in patients treated with TNF antagonists, we followed up a cohort of 4160 patients with RA treated with TNF antagonists to determine cancer occurrence in 1999 through 2003 using the same follow up registers (to provide comparability), and compared their lymphoma risk with that

Abbreviations: EBV, Epstein-Barr virus; DAS, Disease Activity Score; ICD, International Classification of Diseases; NRN, national registration number; RA, rheumatoid arthritis; SIR, standardised incidence ratio; TNF, tumour necrosis factor

of the general population, and with that of other patients with RA. Finally, to describe characteristics of lymphomas occurring in anti-TNF treated patients, we present data on all reported lymphomas among patients with RA treated with TNF antagonists in Sweden through 2004.

SUBJECTS AND METHODS

Setting

Swedish health care is public and population based. Hospital referrals are based on geographical determinants rather than financial capacity or health insurance. Nationwide and population based health and census registers in combination with unique personal identifiers allow record linkage of register data recorded prospectively since the 1960s, with very few losses to follow up and minimum risk of recall bias.

The Inpatient Register cohort of prevalent RA

The Swedish Inpatient Register contains individual based information on inpatient care county wide since 1964 and nation wide since 1987.[26] For every hospital discharge, information on diagnoses and surgical procedures is recorded according to the International Classification of Diseases (ICD) versions 7–10. We identified all subjects above 16 years of age ever discharged with a diagnosis of RA (primary or contributory diagnosis) between 1 January 1990 and 31 December 2003. The ICD codes used were 714A-C, 714W (ICD 9), and M05–6 (ICD 10). We excluded subjects who were also discharged with systemic lupus erythematosus, ankylosing spondylitis, or psoriatic arthritis. For each patient, computerised information on date of entry (first hospital discharge with RA 1964–2003), discharge department, age, sex, and national registration number (NRN, unique to each resident and recorded in all health and census registers) was recorded (table 1). No information on treatment was available.

Table 1 Characteristics of the three Swedish cohorts of patients with RA

	Rheumatoid arthritis cohorts*		
	Inpatient Register	Early Arthritis	TNF antagonist
Overall	53067	3703	4160
Men	15185	1114	1048
Women	37882	2589	3112
Age at start of follow up (years)			
16–44	4666	782	950
45–74	29900	2421	2986
75+	18501	500	224
Calendar period of entry into cohort			
1964–1979	6932	0	0
1980–1989	11867	0	0
1990–1998	20898	1176	11
1999–2001	7667	1478	2398
2002–2003	5703	1049	1751
Person-years	297102	13292	9715
DAS28	–	mean 3.5, median 3.5	mean 5.5, median 5.6
HAQ	–	mean 0.6, median 0.7	mean 1.4, median 1.4

*In the Early Arthritis cohort, values refer to status at 6 months after diagnosis of RA. In the TNF antagonist cohort, values refer to status at the start of anti-TNF treatment.
DAS28, 28 joint count Disease Activity Score; HAQ, Health Assessment Questionnaire.

The Early Arthritis cohort of incident RA

In Sweden, RA is normally diagnosed and followed up by rheumatologists. Centres reporting to the Early Arthritis Register contain a typical mix of small outpatient clinics and larger population based centres. The Early Arthritis Register contains information on subjects with incident (<1 year from onset) RA diagnosed at participating centres since the mid-1990s, with a geographically varying but increasing coverage (40–100% in different regions, overall around 70%) of the estimated number of patients with incident RA.[27] From this register, we collected information on entry (date of diagnosis of RA), date of birth, sex, and the NRN for 3703 incident cases of RA during 1995 through 2003 (table 1).

The TNF antagonist RA cohort

Within the context of a continuing Swedish structured post-marketing surveillance programme (ARTIS) we assembled a cohort of 4160 patients with RA treated with etanercept, infliximab, or adalimumab between 1999 and 2003 (table 1). Details and patient identification methods have been described elsewhere.[28] In brief, patients were identified through the Swedish Medical Products Agency in collaboration with the Swedish Society for Rheumatology, and through regional surveillance programmes of patients treated with TNF antagonists. We made assessments against sales statistics, and estimated that our anti-TNF cohort covered around 80% (higher for etanercept than for infliximab) of all anti-TNF treated patients with RA in Sweden. For each person we collected information on date of birth, sex, NRN, type of TNF inhibitor, Disease Activity Score (DAS)/Health Assessment Questionnaire at the start of treatment, and entry (date of treatment start) and date of discontinuation (table 1).

Register linkages

Through linkage (of all subjects, using the NRN as linkage key) to the Swedish Cancer Register 1964–2003, we collected information on all registered haematopoietic malignancies (ICD 7 = 200–209), including the date of diagnosis. Reporting to this registry is mandatory for clinicians and pathologists, resulting in a completeness of around 99%.[29] Through linkage to the Cause of Death Register 1964–2003 and to the Register of Population and Population Changes 1969–2003, we collected information on marital status, and vital status, including date of death and date of emigration until 31 December 2003.

Statistics

In the analyses of relative risk of haematopoietic malignancies, we used SIRs (the ratio of the observed and expected numbers of cancers) as measures of relative risk. Expected numbers were calculated by multiplying sex-, age-, and calendar period-specific person-years of follow up with corresponding rates from the entire Swedish population. Ninety five per cent confidence intervals were calculated assuming a Poisson distribution of the observed cases. In the analyses of SIRs in each cohort, we defined start of follow up as the latest of 1 January 1990 or date of entry into each cohort, and end of follow up as the earliest of date of death, date of emigration, or 31 December 2003. Because some subjects might have entered into the Inpatient Register RA cohort because of an incipient haematological malignancy, we present results both including and excluding the first year after entry into this cohort. We used Poisson regression to model the relative risk of lymphoma in the patients treated with TNF antagonists relative to that in the two other RA cohorts. Because more than 80% of the total follow up time in the TNF antagonist cohort represented time while receiving treatment, we present relative risks based on the total time of

Table 2 Relative risk of haematopoietic malignancies including 95% confidence intervals (CI) in three Swedish cohorts of patients with RA

	Inpatient Register RA		Early Arthritis cohort		TNF antagonist cohort	
Type	No	SIR (95% CI)	No	SIR (95% CI)	No	SIR (95% CI)
All haematopoietic malignancies	481	1.7 (1.5 to 1.8)	15	1.6 (0.9 to 2.6)	11	2.1 (1.1 to 3.8)
Malignant lymphoma including CLL	319	1.9 (1.7 to 2.1)	11	2.0 (1.0 to 3.5)	9	2.9 (1.3 to 5.5)
Plasma cell neoplasms	45	0.8 (0.6 to 1.1)	0	0.0 (0.0 to 2.2)	0	0.0 (0.0 to 4.2)
Leukaemia excluding CLL	107	2.1 (1.7 to 2.5)	4	2.2 (0.6 to 5.7)	2	2.0 (0.2 to 7.3)
Acute lymphatic leukaemia	2	0.9 (0.1 to 3.2)	0	0.0 (0.0 to 40.8)	0	0.0 (0.0 to 61.1)
Acute myeloid leukaemia	68	2.4 (1.9 to 3.0)	4	4.3 (1.2 to 10.9)	0	0.0 (0.0 to 7.4)
Chronic myeloid leukaemia	13	2.4 (1.3 to 4.1)	0	0.0 (0.0 to 17.7)	0	0.0 (0.0 to 27.0)
Other or undefined leukaemia	23	1.5 (1.0 to 2.3)	0	0.0 (0.0 to 6.8)	2	6.8 (0.8 to 24.7)
Polycytaemia vera	10	0.9 (0.4 to 1.6)	0	0.0 (0.0 to 10.1)	0	0.0 (0.0 to 18.5)

Follow up from 1990 (or entry into cohort, if later) until 31 December 2003. Relative risk estimated comparing each cohort with the general Swedish population, adjusting for age, sex, and calendar period.
CLL, chronic lymphocytic leukaemia.

follow up. Sixty nine per cent of the TNF antagonist cohort had been admitted to hospital for their RA, and 27% of the Early Arthritis cohort had been admitted to hospital for their RA before 31 December 2003. The study was approved by the ethics committee at the Karolinska Institute.

Review of TNF antagonist associated malignant lymphomas 1999–2004

This case series consisted of all lymphomas identified in the register linkage 1999 through 2003, and all malignant lymphomas reported thereafter (that is, during 2004) as part of rheumatologists' reporting of adverse events within the framework of the ARTIS surveillance programme. To confirm the lymphoma diagnoses, paraffin embedded lymphoma tissues were retrieved from pathology departments, reviewed, and reclassified according to the WHO classification, as previously described.[8] Epstein-Barr virus (EBV) in the lymphomas was searched for using EBER in situ hybridisation.[8]

RESULTS

Relative risk of haematopoietic malignancies in the prevalent RA cohort 1990–2003

Based on 481 observed haematopoietic malignancies occurring in the Inpatient Register RA cohort during 297 102 person-years of follow up 1990–2003, the overall relative risk of haematopoietic malignancies was 1.7 (95% CI 1.5 to 1.8; table 2). 319 of these were malignant lymphomas (SIR = 1.9, 95% CI 1.7 to 2.1), 107 were leukaemias (SIR = 2.1, 95% CI 1.7 to 2.5), and 45 were multiple myelomas (SIR = 0.8, 95% CI 0.6 to 1.1). Sex- and age-specific incidences of haematopoietic malignancies in this cohort are tabulated in the Appendix.

Apart from the first year after entry, the increased relative risks of malignant lymphoma or leukaemia did not vary with time of follow up (table 3), although a tendency towards increasing relative risks with time was noted for chronic myeloid leukaemia (table 3A). Excluding the first year of follow up from the analyses resulted in an overall SIR of malignant lymphoma = 1.6 (95% CI 1.4 to 1.9).

Relative risk of haematopoietic malignancies in the incident RA cohort 1995–2003

In the Early Arthritis cohort, the overall relative risks of haematopoietic malignancy (SIR = 1.6, 95% CI 0.9 to 2.6, n = 15), of malignant lymphomas (SIR = 2.0, 95% CI 1.0 to 3.5, n = 11), and of leukaemia (SIR = 2.2, 95% CI 0.6 to 5.7, n = 4, all myeloid) were of similar magnitude to those of the Inpatient Register RA cohort (table 2). The relative risk of lymphoma did not display any convincing trend (p = 0.5) with increasing duration of RA (table 3B).

Relative risk of haematopoietic malignancies after TNF antagonists 1999–2003

In the register based follow up 1999–2003, we identified 11 haematopoietic malignancies (SIR = 2.1, 95% CI 1.1 to 3.8). Nine of these were lymphomas (SIR = 2.9, 95% CI 1.3 to 5.6) and two were leukaemias (SIR = 2.0, 95% CI 0.2 to 7.3). The relative risk (RR) for lymphoma did not display any trend with time of follow up (table 3B). When compared with the lymphoma incidence in the prevalent and incident RA cohorts, the adjusted relative risk of lymphoma in the TNF antagonist cohort was 1.1 (95% CI 0.6 to 2.1) (table 4). When

Table 3A Relative risk including 95% confidence intervals (CIs) and observed number of cancers of selected haematopoietic sites by time of follow up in the Swedish Inpatient Register RA cohort 1990–2003. Relative risks comparing the cohort with the Swedish general population, adjusting for age, sex, and calendar period

	No observed, relative risk (95% CI) by time with RA*					
Site (ICD code)	No	1–4 years	No	5–9 years	No	10+ years
All haematopoietic malignancies	129	1.5 (1.2 to 1.8)	98	1.5 (1.2 to 1.8)	154	1.5 (1.3 to 1.7)
Malignant lymphoma including CLL	80	1.6 (1.2 to 1.9)	68	1.7 (1.3 to 2.2)	102	1.7 (1.4 to 2.0)
Plasma cell neoplasms	14	0.9 (0.5 to 1.5)	7	0.6 (0.2 to 1.2)	13	0.7 (0.4 to 1.1)
Leukaemia excluding CLL	30	1.9 (1.3 to 2.7)	21	1.7 (1.1 to 2.7)	38	2.0 (1.4 to 2.8)
Acute lymphatic leukaemia	1	1.5 (0.0 to 8.2)	0	0.0 (0.0 to 7.1)	0	0.0 (0.0 to 4.5)
Acute myeloid leukaemia	19	2.2 (1.3 to 3.5)	12	1.8 (0.9 to 3.2)	22	2.1 (1.3 to 3.2)
Chronic myeloid leukaemia	2	1.2 (0.1 to 4.4)	4	3.2 (0.9 to 8.1)	7	3.6 (1.5 to 7.5)
Other or undefined leukaemia	8	1.7 (0.7 to 3.4)	5	1.4 (0.5 to 3.3)	8	1.4 (0.6 to 2.8)
Polycytaemia vera	5	1.5 (0.5 to 3.5)	2	0.8 (0.1 to 2.8)	1	0.2 (0.0 to 1.3)

*Counting from date of first discharge listing RA.
CLL, chronic lymphocytic leukaemia.

Table 3B Relative risk of malignant lymphoma in the Early Arthritis cohort and in the TNF antagonist treated cohort by time since entry into each cohort

	No observed, relative risk (95% CI) by years since entry					
	No	<1 year	No	1–2 years	No	3+ years
Early Arthritis cohort	2	1.5 (0.2 to 5.2)	4	1.8 (0.5 to 4.6)	5	2.4 (0.8 to 5.7)
TNF antagonist cohort	4	3.7 (1.0 to 9.4)	3	2.0 (0.4 to 5.8)	2	4.2 (0.5 to 15.3)

the first year of follow up in the Inpatient Register RA cohort was excluded, the corresponding relative risk for the TNF antagonist cohort was 1.3 (95% CI 0.6 to 2.5), and when the follow up of the Inpatient Register RA cohort was restricted to the period 1999–2003, the relative risks remained unchanged (data not shown).

Characteristics of TNF antagonist associated lymphomas 1999–2004

In addition to the nine lymphomas observed in our register based follow up 1999 through 2003, an additional three were reported in the ARTIS programme during 2004. No other lymphomas than those identified in the register linkage had been reported by the rheumatologists during the period 1999 through 2003. The review revealed a distribution of lymphoma subtypes similar to that seen among patients with RA not treated with TNF antagonists,[8] and a low number (n = 1) of EBV positive lymphomas (table 5).

DISCUSSION

In this study we present updated information on the expected occurrence of haematopoietic malignancies in patients with RA. With a striking consistency between the cohorts under study, the results indicate that patients with RA are at increased risk not only of malignant lymphomas but also equally of (myeloid) leukaemia. When using these ''expected'' RA rates as reference we found that patients with RA treated with TNF antagonists were not at any additional increased lymphoma risk compared with patients with RA not treated with TNF antagonists. The case review of TNF antagonist associated lymphomas showed an unremarkable distribution of lymphoma subtypes or EBV positive lymphomas compared with other patients with RA and lymphoma.[8]

The overall level of increase in lymphoma risk associated with RA in our study is in line with previous estimates.[1 2 9 13] For leukaemia, previous studies have indicated—rather than confirmed—the possibility of increased risks. Because of the low background incidence, reported estimates for leukaemia have been less precise than those for lymphomas, often grouped together in one heterogeneous category including all leukaemia types, for example,[3 13] and have been inconsistent across the sexes, follow up categories, etc. In our study, increased relative risks were seen in all strata of follow up and for men and women. Although we can confirm an increased risk of leukaemia in RA, the extent to which the increased leukaemia risk is caused by the RA itself, its treatment, or both, remains unknown, although the increased risk also in the contemporary and incident RA cohort suggests that historic—or ''end stage''—drug regimens in RA like chlorambucil do not in themselves fully explain this increase in risk.

Validation of the RA diagnoses in the Inpatient Register showed that they were diagnostically correct (information available in the medical files versus American College of Rheumatology criteria for RA[30]), close to 90%, with the remainder being made up by other rheumatic diseases or conditions.[7] Based on reported population prevalences of RA, we estimate that around 50% of all prevalent cases of RA in Sweden 2003 are covered by the current analyses, which might therefore serve as updated reference rates in current and future safety evaluation of antirheumatic treatments. Despite the presumed qualitative differences between the prevalent Inpatient Register RA cohort and the Early Arthritis

Table 4 Relative risk (RR) including 95% confidence intervals (CI) of malignant lymphoma in one prevalent cohort, one incident cohort, and one TNF antagonist treated cohort, respectively, of Swedish patients with RA

Covariate	Person-years	Lymphomas (n)	Relative risk (95% CI)
RA cohort			
Inpatient register cohort	297102	319	1.0 (reference)
Cohort with early arthritis	13292	11	0.8 (0.4 to 1.4)
TNF antagonist cohort	9715	9	1.1 (0.6 to 2.1)
Sex			
Male	82596	138	2.0 (1.6 to 2.4)
Female	237513	201	1.0 (reference)
Age at entry (years)			
16–44	27702	9	1.0 (reference)
45–74	190631	197	3.1 (1.6 to 6.1)
75+	101776	133	4.1 (2.1 to 8.0)
Time with RA (years)*			
Missing	437	0	–
0–4	137053	159	0.9 (0.6 to 1.1)
5–9	73708	73	0.8 (0.7 to 1.1)
10+	108911	107	1.0 (reference)

RRs estimated using Poisson regression, adjusted for all parameters in table.
*Counting from date of first discharge with RA (Inpatient Register RA cohort) or specified date of onset of RA (Early Arthritis Register and TNF antagonist cohort).

Table 5 Malignant lymphomas diagnosed between 1 January 1999 and 31 December 2004 among Swedish patients with RA treated with TNF antagonists

Sex	Year of birth	Year of lymphoma	Lymphoma subtype	EBV
F	1918	1999	Unspecified low grade NHL	Neg
F	1940	2000	Diffuse large B cell lymphoma	Neg
F	1926	2000	Follicular lymphoma grade 1	Neg
M	1923	2000	Hodgkin, lymphocyte depletion	Pos
F	1943	2001	Follicular lymphoma grade 3 Diffuse large B cell lymphoma	Neg
F	1954	2002	MALT lymphoma	Neg
M	1943	2002	Diffuse large B cell lymphoma	NA
F	1948	2002	Chronic lymphocytic leukaemia	NA
M	1928	2003	Unspecified NHL	NA
F	1947	2004*	Unspecified high grade NHL	Neg
F	1921	2004*	Unspecified	Neg
F	1952	2004*	Hodgkin, lymphocyte depletion	Neg

*Not included in register based assessment of relative risk.
M, male; F, female; NA, not assessed.

incident RA cohort (for example, method of identification, calendar period of entry, duration of RA, and hospitalisation), the relative risks of haematopoietic malignancies were strikingly similar. Although there was an overlap between the cohorts, there was no overlap of haematopoietic malignancies between the Early Arthritis cohort and the TNF antagonist cohort, and the overlap between the TNF antagonist cohort and the Inpatient Register RA cohort did not measurably affect the relative risks observed (data not shown).

Because of the mandatory (for clinicians as well as pathologists) reporting of malignancies to the Swedish Cancer Register, its coverage is near complete.[29] Previous validations of, for example, 386 lymphomas in Swedish patients with RA 1965–95 showed that 98% of the registered lymphoma diagnoses were indeed correct, although the register information on lymphoma subtype was limited.[7] Our register based design thus provided sensitive and valid outcome information, which was ascertained independently of exposure and uniformly in all cohorts. To determine the validity of the lymphoma diagnoses also in this study, and to increase diagnostic resolution further, we retrieved and reanalysed lymphoma specimens from patients in the TNF antagonist RA cohort. In all cases, the lymphoma diagnosis was substantiated by our review.

Data on the relative lymphoma risk associated with TNF antagonists in routine care (that is, beyond the selected patients' phase III trials which suggest an overall fourfold lymphoma risk[21]) is scarce, and case series presented by, for example, regulatory agencies are difficult to evaluate because of lack of information on the number of treated patients corresponding with the reported numerator of lymphomas.[19] In the hitherto largest attempt to assess relative risks outside the trial setting, Wolfe and Michaud followed up patients reported by some 900 rheumatologists to the National Data Bank for Rheumatic Diseases for self reported (but subsequently validated) lymphoma occurrence, and observed 14 lymphomas occurring in TNF antagonist treated patients, and 15 lymphomas in TNF naïve patients.[9] As in our study, TNF antagonists were associated with a tripled lymphoma risk in comparison with the general population.[9] In light of the moderate number of observed lymphomas in their study and ours, and the differences in study design, follow up, and outcome ascertainment, the results are remarkably consistent.

In a previous investigation by one of the regional Swedish initiatives to monitor TNF antagonists (SSATG)—which is included in our current report—five lymphomas in patients exposed to TNF antagonists were observed and compared with two lymphomas that occurred in a prevalent comparator RA cohort, which resulted in a relative risk for TNF antagonists compared with other patients with RA of 5.0 (95% CI 0.9 to 27).[31] In the pilot Swedish national linkage, the data of which are also included in the current linkage and overlapped with the data reported from the regional initiative, five TNF lymphomas were seen, which corresponded with a doubled relative lymphoma risk (relative risk = 2.2, 95% CI 0.9 to 5.5) compared with other patients with RA.[32]

Random variation and increased statistical precision are reasonable explanations for the seemingly divergent results between the two previous and our current Swedish assessment (relative risk compared with other patients with RA = 1.1, 95% CI 0.6 to 2.1, n = 9). Other tentative explanations include the introduction of TNF antagonists into a prevalent setting of severely ill patients with RA at high risk of lymphoma, but that this degree of selection has attenuated somewhat. Importantly, the apparent difference between the Swedish assessments is unlikely to depend upon differences in the intensity of rheumatologists' reporting of lymphomas as side effects, because all three investigations were based on data reported as part of the mandatory cancer reporting to the Cancer Registry, and no corresponding difference was observed for solid cancers.[31 33 34]

Recent data from our group[6 7] and others[10] suggest that the overall almost doubled lymphoma risk in RA has a striking association with the burden of inflammatory activity (but not with antirheumatic treatment). The marginal or lack of increase in lymphoma risk associated with TNF antagonists in our study must therefore be viewed in the context of anti-TNF treatment of patients with high disease activity, as indicated by the median DAS28 of 5.6 at the start of anti-TNF treatment, and the more than 10-fold gradient in lymphoma risk between low and high overall burden of inflammatory disease activity among patients with RA.[7]

In the reviewed and reclassified lymphoma series, the distribution of lymphoma subtypes was largely similar to that reported by us in a larger series of lymphomas in Swedish patients with RA not treated with biological agents,[8] and with that reported by others.[35] Notably, we found little to suggest an increased proportion of EBV positive lymphomas, which indirectly argues against immune suppression (such as in the immediate post-transplant setting[36]) as a critical risk factor. Early reports to MedWatch highlighted the possibility of an immediate increase in lymphoma risk after the start of anti-TNF treatment.[19 21] In the study by Wolfe and Michaud no pattern of immediate risk was detected, although infliximab

Table 6 The observed sex- and age-specific incidence rates (per 100 000, 95% confidence interval within parentheses) of haematopoietic malignancies in the Inpatient Register RA cohort 1990–2003

	Malignant lymphomas*		Multiple Myeloma		Leukaemia**	
Attained age	Men	Women	Men	Women	Men	Women
16–19	0 (0 to 5389)	0 (0 to 2422)	0 (0 to 5389)	0 (0 to 2422)	0 (0 to 5389)	0 (0 to 2422)
20–39	59 (6 to 213)	18 (2 to 66)	0 (0 to 137)	0 (0 to 43)	0 (0 to 137)	18 (2 to 66)
40–59	120 (74 to 183)	60 (41 to 86)	11 (1 to 41)	6 (1 to 17)	29 (9 to 66)	16 (7 to 31)
60–79	240 (164 to 251)	93 (76 to 112)	16 (6 to 33)	16 (10 to 26)	61 (40 to 89)	37 (27 to 50)
80+	143 (82 to 232)	116 (86 to 153)	27 (5 to 78)	26 (13 to 47)	53 (20 to 116)	38 (22 to 62)

*Including chronic lymphocytic leukaemia.

treated patients had a seemingly shorter latency between the start of treatment and lymphoma diagnosis.[9] In our study we found little to suggest an immediate but transient risk increase. Interestingly, however, all four lymphomas that occurred within the first year after starting TNF antagonist treatment occurred in patients with RA who started the treatment in the first half of our study period (1999–2000, data not shown).

In conclusion, patients with RA are at increased risk not only of lymphoma but also of leukaemia. TNF antagonist treatment of RA is associated with, at the most, a marginally augmented lymphoma risk, which still must be judged in the light of a higher disease activity among patients who are offered TNF antagonist treatment. Characteristics of these lymphomas are similar to those seen in patients with longstanding active RA not treated with biological agents. Of necessity, long term lymphoma risk of TNF antagonists, and temporal trends in this risk, remain unknown and warrant prolonged systematic monitoring of large populations treated with TNF antagonists.

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APPENDIX

Table 6 shows the observed sex- and age-specific incidence rates of haematopoietic malignancies in the Inpatient Register RA cohort 1990–2003.

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Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists

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Overview of benefit/risk of biological agents

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ABSTRACT

Targeted tumor necrosis factor-α antagonists, first approved by the FDA in 1998, have had a significant impact on the treatment of patients with rheumatoid arthritis. In general, the benefit/risk ratio for these agents and the IL-1 receptor antagonist, anakinra, has been quite favorable. However, infrequent adverse events can be serious and require continued pharmacovigilance. Infections, particularly tuberculosis and less commonly fungal infections, are among the most serious adverse events, especially given delays in diagnosis due to subtle or atypical presentations. Questions have also arisen regarding whether anti-TNF-α agents increase the risk of lymphoma, a complicated issue confounded by the multiple risk factors for lymphoma in patients with rheumatoid arthritis and low observed incidence rates of lymphoma, requiring prolonged monitoring. Additional rare reported complications include systemic lupus erythematosus-like syndromes, congestive heart failure and demyelinating syndromes (including cases resembling progressive multifocal leukoencephalopathy). Ongoing post-marketing surveillance of these and other serious adverse events is necessary to determine the true incidence rates, and whether a reassessment of the overall risk-benefit of tumor necrosis factor-α antagonists will be required.

Introduction

Three tumor necrosis factor (TNF)-α antagonists that neutralize TNF-α are available for clinical use: *etanercept*, a protein composed of two p75 TNF-α receptors fused to the Fc portion of IgG1, is approved for rheumatoid arthritis (RA), psoriatic arthritis, psoriasis, ankylosing spondylitis, and juvenile chronic arthritis; *infliximab*, a chimeric IgG1α monoclonal antibody binding TNF-α, is approved in the U.S. for RA and Crohn's disease; and *adalimumab*, a fully humanized IgG1α monoclonal antibody, is approved for RA. Worldwide prescription data through December 2002, reported at the FDA advisory meeting March 2003, indicate that patient exposure for infliximab is estimated at 400,000, etanercept at 150,000 (1), and 2,468 in clinical trials for adalimumab (2).

These biologic agents have had a marked impact in the treatment of RA, demonstrating efficacy in reducing disease activity in patients who have incomplete responses to conventional disease-modifying antirheumatic drug (DMARD) treatment and in retarding radiographic progression (1). Controlled phase III trials during clinical development for TNF-α antagonists did not show an increase in overall serious adverse events above active comparator controls. However, clinical trials do not include sufficient numbers of patients or sufficient time to detect unusual adverse events. Since the conclusion of the clinical trials, post-marketing reports (MedWatch program: www.fda.gov/medwatch) of tuberculosis, opportunistic infection and lymphoma, have led to FDA-mandated label changes (1).

This article focuses on serious adverse events reported since the time of the introduction of these biological agents and reviews the best available evidence by which to judge the overall safety of TNF-α blockade. More detailed discussions concerning infection – particularly tuberculosis (3), demyelination (4), lymphoma (5), congestive heart failure (6) and drug induced lupus (6) – are provided elsewhere in this supplement.

Infections

Serious infections are well-known to occur in untreated RA patients and in patients treated with both traditional DMARDs and TNF-α antagonists (2, 11-11). At the March 2003 Arthritis Advisory Committee meeting, 2782 cases of infections for etanercept and 1100 for infliximab were reported through August 2000 (13). Although there may

be a bias toward increased spontaneous reporting of adverse events shortly after the introduction of novel agents, the evidence does support an increased risk conferred by TNF-α antagonists for the development of certain infections (13). Three recent review articles have addressed the spectrum of infections noted during TNF-α antagonist therapy (2, 8, 9), and a new review included in this supplement (3). The most common infections reported are illustrated in Table I and are discussed below.

Mycobacterium tuberculosis

The infection that appears to be most increased relative to usual occurrence rates in post-marketing data has been Mycobacterium tuberculosis (TB). Through December 2002 in the United States, TB was reported to have developed in 39 patients treated with etanercept, with at least one fatal outcome, and in 335 patients who took infliximab, with at least 12 deaths (1, 11, 14, 16). During adalimumab clinical trials, 13 cases of TB were observed in 2,468 patients, most of which developed before implementation of TB surveillance (2). The baseline TB incidence rate in patients with RA in the United States has been estimated at 6.2 per 100,000 per year (15), although the rate in patients with RA may be higher. Wallis *et al.* recently analyzed the FDA Adverse Event Reporting System database and calculated an estimated 144 TB cases per 100,000 infliximab-treated patients and 35 TB cases per 100,000 etanercept-treated patients based on cases reported from 1998 through the third quarter of 2002 (11)

The majority of TNF-α antagonist associated TB cases are believed to be the result of reactivation of latent disease. Nearly 50% of the TB cases associated with TNF-α antagonists were extrapulmonary and/or disseminated disease. The diagnosis may therefore be delayed due to atypical presentation, with many patients requiring an invasive procedure for diagnosis. It should be noted, however, that even in the absence of TNF-blockers, there may be an increased risk of TB in rheumatoid arthritis patients. For example, a recent study from Spain of 788 biologically naïve RA patients had a 4-fold increased risk of developing TB compared with the general population (134 per 100,000 versus 23 per 100,000 per year, respectively (18).)

Because many TB infections following TNF-α antagonist treatment appear to be cases of reactivation, routine tuberculin skin testing before initiating treatment has been recommended (2, 7, 15, 19, 21). However, in an FDA-sponsored study surveying various practices in the United States, rates of tuberculin skin testing before administration were only 31% for infliximab and 10% for etanercept as of June 2002 (22). Evidence from a review of infliximab clinical trials for spondyloarthropathy as well as from a surveillance study suggests that meticulous screening with chest roentgenograms and a two-step Mantoux skin test along with prophylaxis for latent TB has been effective in reducing reactivation of TB (23, 24). There are no published data, however, that confirm the effectiveness of isoniazid prophylaxis in patients with a positive tuberculin skin test before treatment with TNF-α antagonists. Indeed in 2 patients treated with infliximab, 6 months of isoniazid did not prevent the reactivation of pansensitive TB (25, 26). Physicians must be alert to false-negative tuberculin skin testing as described in RA patients, as well as atypical presentations of TB.

Fungal and other opportunistic infections

Through June 2002, opportunistic infections were reported in 337 patients treated with either infliximab or etanercept for various indications, leading to at least 21 deaths. Reported organisms have included other mycobacteria, fungi such as *Histoplasma capsulatum*, and *Coccidioides immitis, Pneumocystis jirovecii* (carinii), yeasts such as *Cryptococcus neoformans* and Candida species, molds such as Aspergillus, bacteria such as Listeria monocytogenes and Nocardia, the protozoan parasite Toxoplasma, *Brachiola algerae* and cytomegalovirus (1, 7, 11, 12, 27, 28,). Awareness of risk factors, endemic areas, atypical presentations, specialized diagnostic tests, and antimicrobials for these infections are important in minimizing morbidity and mortality (Table I). Patients should be educated to avoid live vaccinations (29), and unpasteurized dairy products as a potential source of Listeria (30). Physicians should be vigilant for unusual presentations of infections before initiating biologics. In one reported case, a patient treated with TNF-patients antagonists developed disseminated sporotrichosis that initially masqueraded as synovitis of an autoimmune etiology (31).

With regard to the underlying mechanisms, one recent study demonstrated a decreased Th1 immune response *in vitro* against *H. capsulatum* by host defense cells treated with infliximab (32). In TNF-deficient mice, impaired granuloma formation is seen, with increased susceptibility to TB and increased dissemination (33,34). Because TNF-α also plays a central role in granuloma formation, the production of cytokines and adhesion molecules, the release of enzymes, and the migration and maturation of inflammatory cells, the neutralization of TNF-α may contribute to an increased susceptibility to infections (9, 35). There is no experimental evidence that the three available TNF-α antagonists differ in this regard, and therefore susceptibility to infection should be viewed as a class effect.

Bacterial infections

Although attention has been drawn to opportunistic infections, common bacteria have also led to serious infections and fatalities in patients treated with TNF-α antagonists. One study compared serious bacterial infections in patients treated with TNF-α antagonists to patients treated with conventional DMARDs, identified 2 years before biologics, calculating an incidence of 0.181 per year for TNF-α inhibitors and 0.008 per year for traditional DMARDs (36). On reviewing each case, C-reactive protein appeared to be a more sensitive marker of infections than temperature, the erythrocyte sedimentation rate, or the white blood cell count, and rose before evidence of infection in several cases.

Although sepsis has been seen with all available TNF-α antagonists to date,

Table I. FDA reported cases of opportunistic infections associated with TNF-α antagonists.

Opportunistic infections	Presentation in reported cases	Transmission	Modes of diagnosis
Mycobacterium tuberculosis (n=374)	Pulmonary Extrapulmonary (over 40% of cases) Disseminated, lymph nodes, tonsils, pleura, peritoneal, meninges, enteric, paravertebral, bone, genital, bladder	Reactivation or Inhalation of tubercle bacilli	◆ TST ◆ Chest radiograph ◆ Culture specimens ◆ Tissue biopsy (extrapulmonary)
Histoplasma capsulatum (n=42)	Constitutional symptoms, Pneumonia: nodular, interstitial, BOOP (*note: CXR can mimic TB) Pancytopenia, hepatosplenomegaly	Inhalation of contaminated soil with bat and bird guano in endemic areas such as the Ohio and Mississippi River valleys	◆ Urine/serum antigen OR ◆ Culture* ≥ 3 specimens improves yield ◆ Histochemistry of tissue or fluids with Gomori methenamine or Grocott silver stains
Candida species (n=90)	Sepsis, esophagitis	Comensal organism	◆ +Hyphae on superficial scraping ◆ Culture of biopsy or body fluid
Listeria monocytogenes (n=38)	Meningoencephalitis, sepsis, cholecystitis, brain abscess, septic joint	Ingestion of delicatessen ready-to-eat meats, soft cheeses, turkey frankfurters, gravad or cold-smoked trout, pate, raw vegetables, raw milk, fish, & poultry	◆ Gram stain ~variable ◆ Culture a site typically sterile ◆ Microbial biochemical assays ◆ MRI to detect brain involvement
Aspergillus fumigatus (n=39)	Invasive Pulmonary aspergillosis	Inhalation of Aspergillus spores	◆ Culture of sputum, BAL or biopsy ◆ Detection of hyphae in sputum ◆ Chest radiograph ◆ IgG titer detects colonization
Cryptococcus species (n=19)	Disseminated, Pulmonary, Pancyotpenia	Primary inhaled fungi Potential source-pigeon droppings or Reactivation	◆ Serum cryptococcal Ag detection ◆ Culture ie blood, urine, prostate secretion, skin, sputum ◆ Tissue methenamine silver, periodic acid-Schiff, mucicarmine stain (High opening pressure on lumbar puncture, CSF cryptococcal Ag)
Nocardia species (n=11)	Note: Details of presentation not described	Soil-borne, traumatic inoculation of skin, has been isolated from secretions in patients with COPD	◆ Biopsy with special staining (Brown-Brenn, modified Fite), & ◆ Culture
Salmonella species (n=11)	Septicemia	Contaminated food or water	◆ Rose spots ◆ Cultures of stool, urine, bone marrow, and gastric or intestinal secretions.
Toxoplasma species (n=5)	Central Nervous System	Oral route, Cat feces Reactivation of latent infection or exogenous sources such as blood or transplanted organs	◆ Toxoplasma IgM, IgG, IgA titers ◆ Isolation of the parasite from blood or other body fluids after sub-inoculation of the sample into the peritoneal cavity of mice.
Brucella species (n=2)	Note: Details of presentation not described	Potential sources: Ingestion of untreated milk or milk products; raw meat (i.e., blood) and bone marrow.	◆ Combination of potential exposure, consistent clinical features and significantly raised levels of Brucella agglutinin

Brucella species (n=2)	Note: Details of presentation not described	Potential sources: Ingestion of untreated milk or milk products; raw meat (i.e., blood) and bone marrow. Inhalation, skin abrasion, autoinoculation, and conjunctival splashing during contact with animals, especially by children and by slaughterhouse, farm, and laboratory workers.	◆ Combination of potential exposure, consistent clinical features and significantly raised levels of Brucella agglutinin ◆ Identity confirmed by phage typing, DNA characterization, or metabolic profiling ◆ Antibodies: high titer IgG indicates active disease, high titer IgM indicates recent exposure
Bartonella species (n=1)	Note: Details of presentation not described	Potential source: Young cats infested with fleas, person-to-person transmission,	◆ Biopsy tissue: clumps of tiny bacilli revealed by Warthin-Starry silver stain

COPD: chronic obstructive pulmonary disease; TST: tuberculosis skin testing; CXR: chest radiograph, CSF: cerebral spinal fluid, Ag: antigen.
Note: Other Mycobacterium species infections have been reported but details of the case are not available.
*Notify microbiology lab; culture requires selective, enriched media or prolonged culture observation
Incidence rates of infections listed above ranged from 1 to 335 cases per 100,000. Median time to onset of infection: 40 days for infliximab, and 236 days for etanercept.

only two cases of septic arthritis have been reported (37, 38). The first was in a 12-year-old girl with group A-hemolytic streptococci, multifocal septic arthritis, and osteomyelitis, whose left toe abscess recurred despite surgical drainage, appropriate antibiotics, and discontinuation of etanercept. The second was a case of bilateral septic hip arthritis with *Staphylococcus aureus* in a 27-year-old woman who had an 11-year history of RA, after treatment with 4 months of etanercept. Currently, no clinical studies have been conducted in patients with RA who were taking biologics to establish perioperative guidelines. Given the potential risk of septic arthritis and the indeterminate effect on wound healing, withholding biologics 1 week before and after surgery may be prudent (39, 40).

Lymphoma

An increased incidence of lymphoma among patients with RA had been reported ranging from 2 to 25-fold, even before the introduction of TNF-α antagonists (41-48). To what extent the disease alone and/or concomitant therapies such as azathioprine and methotrexate (49, 50) may contribute to this increased risk has not been well delineated.

Brown *et al.* (51) reviewed MedWatch reports of 26 cases of lymphoma through December 2000 in patients who were treated with infliximab from May 1999 and in patients treated with etanercept from November 1998. The main indication for treatment was RA, followed by Crohn's disease, and psoriatic arthritis. From these data, a crude extrapolation of the lymphoma incidence for etanercept was 19 cases per 100,000 persons treated. For infliximab, a crude rate of 6.6 cases per 100,000 persons treated was calculated. These rates alone do not indicate an increased risk for developing lymphoma with TNF-α antagonists, because the annual incidence in the general population is 24.8 per 100,000 for men and 17.7 per 100,000 persons for women (52). Furthermore, comparing such rates is difficult due to an imprecise estimation of patient drug exposure used to calculate the incidence rates.

Despite the low rates, salient features in these cases raised concern. Fifty-four percent of the patients developed lymphoma within 8 weeks of initiation of treatment, and regression of lymphoma occurred in 2 patients whose only intervention was discontinuation of medication, one with etanercept and one with infliximab (51). Three deaths occurred, 2 in patients with fulminant recurrence of lymphoma that had been in remission. In an addendum to this article, 68 new cases of "probable/possible" medication-associated lymphoma were reported to MedWatch during November 2001 to September 2002.

Information concerning the risk of lymphoma in patients treated with TNF-α antagonists was reviewed at an Arthritis Advisory Committee meeting in March 2003 (1). Nine cases of lymphoma occurred among 3,389 patients treated with etanercept in clinical trials, including patients in extension studies, treated for a median of 2.2 years, resulting in a standardized incidence ratio of 3.47 (95% CI, 1.58 to 6.59). For infliximab, 4 cases were observed among 555 patients with RA in the ATTRACT trial (standardized incidence ratio, 6.35; 95% CI, 1.73 to 16.26) and 2 cases occurred in Crohn's disease trials (standardized incidence ratio, 8.7; 95% CI, 1.05 to 31.41). For adalimumab, 10 cases were reported over the 24-month clinical trial among 2,468 RA patients (standardized incidence ratio, 5.4; 95% CI, 2.6 to 10.0).

Comparing these incidence ratios is complex because of the absence of definitive information concerning lymphoma incidence ratios in the RA population (41-47). Three studies have been cited frequently to mitigate concerns about potential increased incidences with the biologics. A study by Baecklund *et al.* (44) demonstrated a 25.8-fold increased risk for lymphoma in biologically naïve RA patients with high disease activity. The 95% conference intervals CI for this odds ratio, however, were extremely wide (3.1 to 213.0), suggesting that more data are needed before definitive conclusions may be drawn. A study by Prior *et al.* (42) reported a 23-fold increased risk for lymphoma in RA patients. Because this involved a small patient population

treated at a tertiary referral center, referral bias may have influenced the results. Lastly, in a 1994 study by Wolfe and Fries (53), a correction was made in the incidence death rate for leukemia/lymphoma in RA patients, reducing it from 8.02 to 1.78.

An important concern raised at the FDA Advisory Committee meeting in March 2003 was the absence of lymphoma in comparator groups in clinical trials of etanercept, infliximab, and adalimumab, although this suggests that the biologic agents increase the risk of lymphoma because the control group of RA patients with parallel disease activity not treated with TNF-α antagonists had a lower incidence. One rationale is that the control groups were considerably smaller and were followed only for brief periods. Therefore, the increased number of lymphoma cases in patients treated with TNF-α antagonists could have been the result of chance. Further data, including careful longitudinal assessment of treated patients, are required and are being collected to clarify the risk of lymphoma with TNF-α antagonists (4).

Systemic lupus erythematosus-like syndromes

Systemic lupus erythematosus-like syndromes and autoimmune serology conversion has been described with all the TNF-α antagonists. Of the confirmed cases of etanercept-associated systemic lupus erythematosus (SLE) from November 1998 to February 2002, 12 of 13 patients had complete resolution of symptoms by 1 to 4 months after discontinuation of the biologic agent (54). A caveat is the difficulty in detecting TNF-α antagonist-induced SLE because these features may be misinterpreted as symptoms resulting from RA (55). In a few recently reported cases of drug-induced SLE, patients initially had objective evidence of RA but vague symptoms and serologic findings typical of SLE. Treatment with TNF-α antagonists appeared to lead to the progression of subtle SLE manifestations (56), causing re-evaluation of the original diagnosis of RA.

Although monitoring of autoantibodies may be important, the predictive value of seroconversion while taking biologics for developing SLE still needs to be determined. In a one-year randomized, controlled trial of RA patients treated with infliximab, antinuclear antibodies were detected in 29% of the patients before and in 53% after treatment, and approximately 10% of the patients developed IgM anti-dsDNA antibodies (pre-treatment anti-dsDNA levels were not reported). However, only one patient with all three isotypes (IgG, IgM, and IgA anti-dsDNA) was observed to develop a reversible lupus syndrome (57).

Positive dechallenge and rechallenge cases are the strongest evidence that these TNF-α antagonists induce features of SLE (54,58). One proposed explanation for the development of autoantibodies is that administration of antibodies to TNF-α on the cell surfaces leads to apoptosis releasing nuclear antigens that promote the formation of antinuclear antibodies (57).

Heart failure

Questions have arisen concerning the possibility that TNF-α antagonists may cause new congestive heart failure (CHF) or worsen pre-existing disease (6). In clinical trials of infliximab for CHF, mortality and hospitalizations for heart failure were increased (1). A report from the MedWatch database described 47 cases of heart failure after initiation of TNF-α antagonists (59). These cases included new onset or exacerbations that were diagnosed a median of 3.5 months and 4 months respectively after the initiation of therapy. New-onset heart failure without a known risk factor occurred in 19 (50%) of these patients with a median ejection fraction of 0.2 (range, 0.1 to 0.45). For the 10 patients under age 50, 9 had stopped the TNF-α antagonist and received treatment for heart failure. Three patients completely resolved, 6 patients partially resolved, and one patient died. Despite the temporal association, no definitive conclusions can be made because coincidental occurrence cannot be ruled out with this small number of case series (59).

In response to the FDA warning of cases of heart failure in patients treated with etanercept or infliximab, Wolfe *et al* reviewed their National Data Bank for cases of heart failure in patients with RA. The most relevant information gleaned from this data is that there were no incidents of heart failure in 1,569 patients who were less than 50 years old and treated with TNF-α antagonists. However, heart failure associated with TNF-α antagonists appears to be a rare event, with only 47 cases reported to the FDA among approximately 270,000 patients exposed to TNF-α antagonists. Furthermore, there was a strong temporal association in the cases reported by the FDA, as the 9 patients who had no predisposition to cardiac disease had resolution of their depressed ejection fractions after withdrawal, as well as treatment for heart failure. Detection of cases of heart failure may have been limited, as 8% of their population declined to participate in the study. Approximately 0.017% of the FDA database patients developed heart failure. (60)

Because TNF-α is important for viral clearance (61, 62), a possible explanation for congestive heart failure in patients without a history of heart disease might be that myocardial decompensation is secondary to viral myocarditis. A study with TNF-deficient mice demonstrated decreased survival after infection with encephalomyocarditis virus, resulting from viral defects in clearance from the myocardium (63, 64). Survival improved with the administration of recombinant human TNF-α. These findings suggest that viral myocarditis may develop during treatment with TNF-α antagonists. Further evaluation for viral infection may help characterize new cases of heart failure in patients treated with TNF-α antagonists.

Demyelination

Twenty cases of patients developing neurologic symptoms with accompanying demyelination on MRI scans have been reported to the FDA database as a TNF-α antagonist-associated adverse event (4, 65). Although this complication has been attributed to possible precipitation of a multiple sclerosis-like demyelinating syndrome, a brain biopsy

from one index case demonstrated leukoencephalopathy. The patient's symptoms and progressive lesions on MRI were consistent with progressive multifocal leukoencephalopathy. This report raises an intriguing possibility: namely, that some cases categorized as multiple sclerosis-like demyelinating syndromes could in fact represent progressive multifocal leukoencephalopathy. The organism responsible for progressive multifocal leukoencephalopathy is human JC papovavirus, which can be detected in the cerebrospinal fluid by the polymerase chain reaction (66-69). Cases of "demyelination syndrome" will require careful analysis to determine the etiology of the symptoms, and increased scrutiny is necessary to exclude progressive multi-focal leukoencephalopathy.

Conclusion

The introduction of TNF-antagonists has been a major advance for patients with inflammatory arthritis. The overall safety of these agents appears to be comparable to traditional DMARDs. However, patients may be at a small but increased risk for specific serious adverse events such as tuberculosis, opportunistic infection, and possibly lymphoma. In general, the perception by many patients and physicians that these agents also offer greater therapeutic benefit with respect to symptoms, quality of life and retardation of disease progression, has led to the widely held view that the benefit/risk ratio for TNF-blockers is positive despite a small possibility of an increase in serious adverse events.

Ongoing surveillance is crucial to define accurately the incidences of adverse events, with a particular focus on lymphoma. Pharmaceutical companies, working with the FDA, have developed pharmacovigilance programs to collect data in clinical trials and registries for 3 to 10 years with projected enrollments of 600 to 5000 patients per program (70), in addition to efforts by rheumatologists such as the National Database for Rheumatic Diseases under leadership of Dr. Frederick Wolfe, and the Alberta Pharmacosurveillance Program under leadership of Dr. Walter Maksymowych (71). Voluntary health care professional reporting is also making a key contribution to surveillance via the FDA MedWatch program. Anticipating and identifying complications early should decrease the frequency and severity of adverse events and improve the overall safety of these highly effective agents.

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Case Report: A 51-year-old man was referred for esophagogastroduodenoscopy on the basis of microcytic anemia. The patient's pertinent medical history included end-stage renal disease secondary to polycystic kidney disease leading to cadaveric renal transplantation in 1996, cerebral aneurysm requiring surgical repair, hypertension, and obstructive sleep apnea. Idiopathic angioedema had been diagnosed 11 months earlier on the basis of typical symptoms and normal results on C1 esterase inhibitor and C4 assays performed during the acute episode.

Medications at the time of the procedure were doxazosin, tacrolimus, atenolol, prednisone, erythropoietin, furosemide, hydralazine, and sirolimus. Hydralazine, erythropoietin, and sirolimus had been added within the previous 2 months. The patient had undergone colonoscopy 3 days earlier for the same indication; for that procedure, he received intravenous fentanyl and midazolam. Diverticulosis was noted, and no complications followed the procedure.

At presentation for upper endoscopy, the patient had no unusual symptoms to report. Findings on physical examination performed before the procedure were unremarkable. An experienced endoscopy nurse administered two brief sprays of 20% benzocaine to the oropharynx. Conscious sedation was then administered intravenously (midazolam, 5 mg, and fentanyl, 125 μg). The esophagus was intubated without difficulty. Erosive esophagitis was found at endoscopy, and no biopsies or other interventions were performed.

The initial recovery period was uneventful. However, approximately 1 hour after the procedure concluded, the patient, while in the recovery area, reported dysphagia and swelling of the tongue that rapidly spread to the neck and periorbital area. He did not report pruritus or respiratory symptoms. Physical examination now showed obvious macroglossia, periorbital and labial edema, and nonpitting edema of the neck. Nasopharyngoscopy showed mild pharyngeal edema. The patient rapidly improved after taking H_1- and H_2-blockers in combination with intravenous steroids. He recovered without incident and was doing well when seen in follow-up 1 week later.

Conclusion: This case of angioedema occurring in the context of upper endoscopy was probably due to administration of topical benzocaine spray. Although midazolam was thought to be the cause in the only other known reported case of angioedema during upper endoscopy, the authors did not report on the use of topical anesthetics (1). Our patient received both midazolam and fentanyl on several previous occasions without adverse sequelae.

This case report raises two important issues. First, clinicians and patients should be aware of this potential complication. Primary care physicians referring patients for upper endoscopy should inform the gastrointestinal consultant of this relevant medical history if it is present. Likewise, the endoscopist and patient should remain vigilant for symptoms suggestive of angioedema following the procedure. It is also important to note that the development of symptoms may be delayed, as suggested by their onset nearly 1 hour after endoscopy in our patient. Second, as was recently suggested by Gunaratnam and associates (5), endoscopists should reconsider the routine administration of benzocaine. Topical anesthesia could be provided with viscous lidocaine or possibly even abandoned altogether in patients receiving intravenous sedation.

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Severe Neutropenia and Thrombocytopenia Associated with Infliximab

TO THE EDITOR: *Background:* Infliximab, a monoclonal anti–tumor necrosis factor (TNF)-α antibody, has recently been approved for treatment of rheumatoid arthritis (1, 2). To date, therapy with this drug has been associated with few adverse events (3–5).

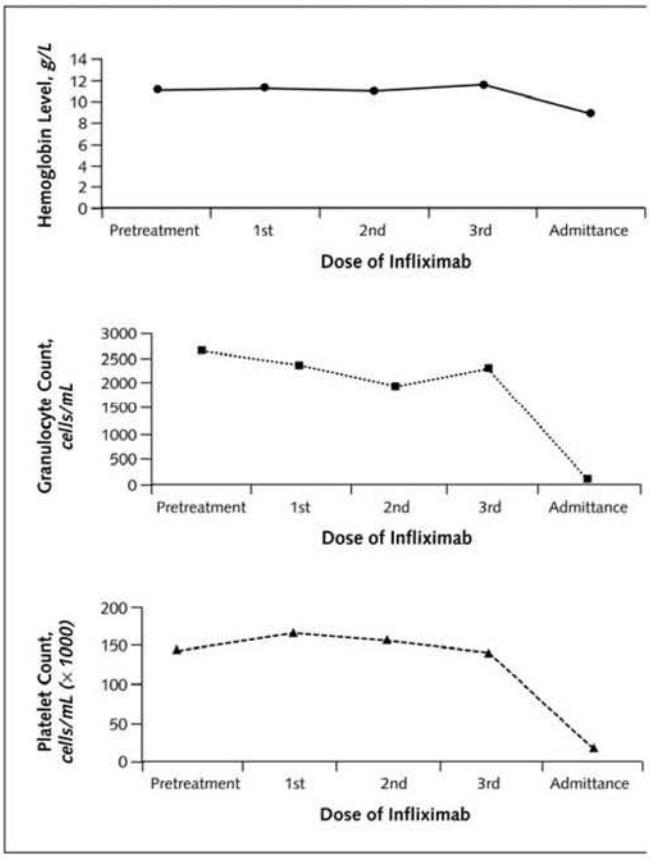
Objective: To describe a patient who developed severe neutropenia and thrombocytopenia after administration of infliximab.

Case Report: A 60-year-old woman had developed rheumatoid arthritis in her forties. She had received many drugs, including nonsteroidal anti-inflammatory drugs, steroids, chloroquine, cyclophosphamide, and methotrexate (up to 15 mg/wk), with good hematologic tolerance but poor clinical results. The disease progressed markedly, and by the beginning of 2001, the patient required assistance with activities of daily living. She was receiving indomethacin, 150 mg/d, and 6-methylprednisolone, 12 mg/d; treatment with immunosuppressive drugs had been discontinued several months before. In June 2001, intravenous infliximab was started (after 1-month pretreatment with methotrexate, 7.5 mg/wk) at doses of 3 mg/kg of body weight at weeks 0, 2, and 6, and every 8 weeks thereafter. Following the second dose of infliximab, the patient improved markedly. Blood cell counts, assessed before each dose of infliximab, remained normal.

One week after the third infliximab dose, the patient was admitted to the hospital because of fever, chills, and skin hemorrhages. Profound neutropenia and thrombocytopenia were noted (**Figure**), and bone marrow examination indicated hypoplasia. Methotrexate and infliximab therapies were discontinued, and cefepime and granulocyte macrophage colony-stimulating factor were started. The cytopenias recovered in 10 days. Results of microbiological examinations were negative. Later, results of initial and repeated laboratory studies and tests for other causes of cytopenia (systemic lupus erythematosus, parvovirus, Epstein–Barr virus, cytomegalovirus, and many others) were found to be negative, and subsequent monthly blood cell counts remained normal. Four months later, the patient's arthritis worsened, and treatment with flufenomide was started.

Conclusion: Infliximab is a monoclonal anti–TNF-α antibody and represents one of the latest and most promising advances for treating inflammatory diseases that are refractory to current standard therapy. To date, infliximab has been used to treat rheumatoid arthritis (1) and Crohn disease (6). Main adverse effects reported by

Figure. **Blood cell counts before and during treatment with infliximab.**



To convert hemoglobin values to g/L, multiply by 10. To convert platelet counts and granulocyte counts to $\times 10^9$ cells/L, multiply by 0.001.

pharmaceutical companies and medical journals are hypersensitive reactions (3), development of antinuclear antibodies (3), possibly lymphoproliferative disorders (3), and reactivation of latent tuberculosis (4, 5). Serious hematologic reactions have been reported in patients treated with etanercept (7), a recombinant human TNF-α receptor that renders TNF biologically inactive. However, to our knowledge, no previous infliximab-related hematologic toxicity has been reported. In our patient, treatment with methotrexate could have played a role in the development of the cytopenias, but two facts argue against this. First, the patient had received methotrexate in the past, even at higher doses, with good hematologic tolerance, and second, the total dose that she received was too low to induce neutropenia.

The causal relation between TNF-α blockade and bone marrow hypoplasia is unclear. However, since TNF-α exerts its physiologic and immune functions through its ability to regulate some proinflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-8, and granulocyte macrophage colony-stimulating factor, it is theoretically conceivable that its blockade could induce bone marrow failure by blocking stem-cell differentiation (8). In fact, early trials of infliximab documented a rapid decrease in levels of IL-1β, IL-6, and TNF-α R1 and R2, all of which are cytokines that play a role in stem-cell differentiation. Therefore, we think that neutropenia and thrombocytopenia in our patient were probably due to infliximab, or were at least related to the combination of infliximab and methotrexate, and should be added to the adverse effects of this drug. Although this is an anecdotal case report, clinicians and patients should be aware that new-onset fever in a patient beginning a treatment regimen containing infliximab requires a complete blood cell count to exclude neutropenia.

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