The safety of biologic agents in early rheumatoid arthritis

A. Kavanaugh[1], E.C. Keystone[2]

[1]Division of Rheumatology, Allergy, and Immunology, The University of California, San Diego, California, USA;
[2]The Rebecca MacDonald Centre for Arthritis and Autoimmune Disease, Mount Sinai Hospital, The University of Toronto, Canada.

Arthur Kavanaugh, MD, Director, Center for Innovative Therapy, Professor of Medicine; Edward C. Keystone, MD, Professor of Medicine.

Please address correspondence to: Arthur Kavanaugh, MD, Center for Innovative Therapy, UCSD, Division of Rheumatology, Allergy, Immunology, 9500 Gilman Drive, La Jolla, CA 92093-0943, USA.

ABSTRACT

Accompanying the excitement surrounding the prominent efficacy of biologic agents in rheumatoid arthritis (RA) has been concern regarding potential adverse effects. Data from clinical trials and pharmacovigilance has provided an assessment of their safety in patients with established RA. As biologic agents are utilized in patients with earlier disease, optimal determination of the risk/benefit will depend on continued careful monitoring, collection, reporting and analysis of safety information.

Introduction

Among the most important advances in the treatment of patients with rheumatoid arthritis (RA) in recent years has been the introduction of biologic agents. In particular, inhibitors of the key pro-inflammatory cytokine TNF have proven effective in reducing signs and symptoms of disease, improving the functional status of affected patients, and inhibiting the progression of structural damage. The clinical efficacy of the TNF inhibitors was initially documented in clinical trials of RA patients who had had the most severe, refractory disease.

The availability of these agents in the clinic coincided with a paradigm shift in the treatment approach to RA, with earlier and more frequent utilization of aggressive regimens. Since their introduction, the use of TNF inhibitors has expanded, with greater use in diverse populations of RA patients, as well as in other immune-driven systemic inflammatory conditions. In animal models of autoimmune disease, introduction of immunomodulatory therapies either prior to or soon after disease initiation is nearly universally much more effective in controlling the disease process than delayed therapy. By extrapolation to human disease, there has been great excitement surrounding the potential treatment of early RA with biologic agents.

As of 2003, three TNF inhibitors had been approved for clinical use worldwide: etanercept, infliximab, and adalimumab (Table I), as well as one IL-1 inhibitor, anakinra (IL-1ra). Many other biologic agents are currently in development. These agents received regulatory approval on the basis of their efficacy and tolerability in a number of controlled clinical trials, mostly of patients with longstanding, severe RA. In early RA, a successful study of etanercept has been completed, leading to regulatory approval for this indication (1). Similarly designed, large clinical trials of infliximab and adalimumab in early RA were completed in the spring of 2003, and the results are eagerly awaited.

The excitement surrounding the introduction of TNF inhibitors into the clinic has been accompanied by caution re-

Table I. Characteristics of TNF antagonists.

	Infliximab	Etanercept	Adalimumab
Structure	Chimeric mAb	TNFRII / IgG1 Fc fusion protein	Human mAb
Binding target(s)	TNF-	TNF-, Lymphotoxin	TNF-
Binding affinity	1.8×10^9	10^{10}	2.3×10^{10}
Half-life	8 – 9.5 days	4 – 5 days	12 – 14 days
In vitro complement-mediated cell lysis	+	—	+
Dose interval	q56 days	q3-4 days	q7-14 days
Efficacy in Crohn's	+	—	?
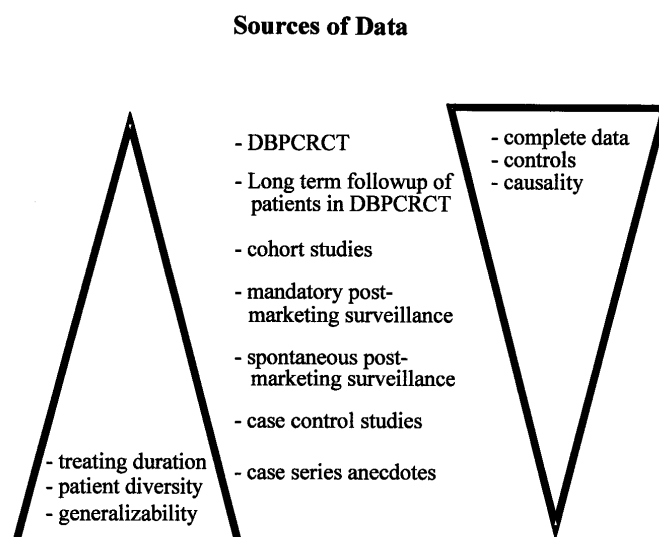
Sources of Data

Fig. 1. Sources of safety data: strengths and weaknesses.

garding the potential safety profile of these agents. As potent modulators of the immune response, biologic agents may adversely affect host immunosurveillance, potentially leading to decreased resistance to infection or increased risk of malignancy. While data on the safety of these agents from controlled clinical trials provides some reassurance, the numbers of patients in those trials were relatively small and the length of followup relatively short. Therefore, post-marketing surveillance with the collection of further long-term data is critical to identify important safety information concerning the biologic agents. Already to date, important safety information concerning the safety of biologically agents has emerged from postmarketing surveillance, but collection of further long-term data is critical over long periods.

Methodological issues concerning safety data

Safety data from patients with refractory RA is germane to each patient with RA. However, certain considerations for patients with early disease may differentially impact the safety data for biologic agents as well as the risk/benefit ratio governing their use. For example, as will be reviewed below, adverse events such as infections and lymphoma have been observed to occur at a greater frequency among RA patients with the most severe refractory

disease. Assigning attribution of such side effects to treatment is therefore difficult, particularly for biologic agents, which have been used most extensively in that group of patients.

As these agents are introduced earlier in the disease course, might these side effects be expected to occur less commonly? Indeed, if persistent disease activity is effectively prevented by early intervention with these agents, the association of these events with RA disease may be abrogated. Similarly, patients with earlier disease, as a group, could be expected to be younger, and thereby have less comorbidity and tissue damage than the patients with long-standing refractory disease. These factors too could decrease the risk of adverse events such as infections. Along with the potentially greater chance to achieve disease remission, this provides some of the rationale for early aggressive treatment. Indeed, the possibility of greater clinical efficacy could alter the risk/benefit considerations in favor of more aggressive treatment.

However, the reverse could also be possible. Part of the rationale for initially testing TNF inhibitors among patients with the most refractory disease was that many of the patients had literally failed every other therapeutic option, and still had extremely active disease. Thus, they had 'nothing (or little) to lose' in trying these new unproven agents. For patients with early RA, the

consequences of an adverse event may be magnified by their occurrence in a younger, hitherto healthier person. Also, spontaneous remission is possible in very early disease. These considerations should be kept in mind as safety data concerning biologic agents is reviewed.

Sources of safety data

Simply stated, there is no single perfect source of data to assess the long-term safety of novel therapeutic agents. Potential sources that might provide relevant information include: a) double-blind, placebo controlled, randomized clinical trials (DBPCRCT) and other clinical trials; b) long-term open label follow up of patients from DBPCRCT; c) cohort studies; d) mandated or regulated post-marketing surveillance (e.g. registries); e) spontaneous post-marketing surveillance; f) case control studies; g) case series and individual anecdotes. For each source of data there are certain biases that critically affect their reliability and extrapolability of the data (Fig. 1). Periodic reviews, such as those mandated by regulatory agencies, can integrate information from these varied sources.

For many clinicians, it has become an aphorism that the "best" data comes from DBPCRCT. Comprehensiveness of the data collection and the presence of a comparison or control population impart data from such trials substantial internal validity among other advantages. Data completeness permits an accurate assessment of the frequency of adverse events. In other circumstances, such as spontaneous reports, the 'denominator' of patients exposed may not be readily known, making the incidence difficult to determine. In addition, with thorough data collection, unexpected adverse events that might be overlooked in less formal analyses may be identified. As noted above, patients with RA and other rheumatic diseases may experience certain outcomes such as infection more frequently than the general population (2-5). Thus, the presence of a control group may be the most important advantage of data from controlled clinical trials (6).

Despite these advantages, some limita-

tions exist to data regarding safety obtained from trials. There is an ascertainment bias inherent in the enrollment of patients into research studies (7, 8). Study patients tend to be homogeneous as regards stage and activity of disease. Moreover, such patients may have less comorbidity, generally achieve greater compliance with visits and treatments, and use fewer concomitant medications as compared with unselected groups of patients with the same disease. Thus, study patients may not be representative of the overall heterogeneous population of patients. This could have a substantial impact on the occurrence and/or the severity of certain side effects. Clinical trials also tend to be relatively short in duration and limited in size, and important yet uncommon toxicities may be missed. Thus, data from sources other than that clinical trials may have greater generalizability or external validity. Such data, typically obtained after approval, are critical for comprehensive safety assessment.

The collection of data on therapies after they have been marketed is often referred to as 'pharmacovigilance' (9). Procedures for accruing pharmacovigilance data have been established worldwide, for example the US FDA MedWatch program (10, 11). In different locales, reporting of safety data may be voluntary or obligatory. In some countries, requisite registries of all patients receiving treatment with novel medicines such as biologic agents has been established (11). There are strengths and limitations inherent in post-marketing adverse event reporting that impact their ultimate utility (Table II). Much of the value of such reports relates to the ease with which information can be obtained from numerous exposures in heterogeneous patient populations. This optimizes the generalizability of the data and allows collection of uncommon toxicities. Such information can also be rapidly shared, allowing swift regulatory action that might obviate greater exposure and harm.

As with all research approaches, pharmacovigilance data includes disadvantages which may limit their utility. Compared to data from clinical trials,

pharmacovigilance information tends to be much less complete and less verifiable. Even in registries, the nature or extent of the adverse event and the presence of relevant comorbidities or concomitant medications may not be complete or entirely accurate. Particularly for spontaneous reports, underreporting is a concern (12). It has been estimated that fewer than 1% of serious adverse drug reactions are directly reported to the FDA (13). Factors such as the seriousness or the presumed relatedness of the event affect the likelihood of whether an adverse event will be reported, thereby introducing ascertainment bias. In the British spontaneous reporting system, it has been estimated that approximately 2-4% of non-serious adverse events are reported, compared to 10% of serious events (14). In an observational British study, 9% of non-serious adverse events, and 23% of serious adverse events were reported (15). Another study several years later showed consistent levels of reporting of non-serious adverse events (9%) but greater reporting of serious adverse events (53%), suggesting that reporting behavior may vary (16).

Two other factors that affecting the likelihood that an adverse drug reaction will be reported are the duration of time a medication has been on the market, and the type of adverse reaction that occurred. A peak in the number of adverse events reported has been shown to occur near the end of the second year that a drug has been on the market; this is followed by a sharp decline in reporting (17). Sometimes called the 'Weber effect', it has been suggested that this may relate to physicians' initial lack of familiarity with a medication and growing comfort over time. Physicians are more likely to report unanticipated adverse events, such as those not in-

cluded on the package labeling for the medication (16).

Post-marketing cohort studies provide more rigorous controlled data than spontaneous reports; however such studies are costly and therefore often smaller in size (18). Formal registries, to the extent that data collection is complete, are potentially a powerful source of safety data. Nonetheless, as patients with similar disease characteristics are not randomly allocated to different treatments, attribution of specific adverse events to a given therapy may be tenuous.

Long-term safety of TNF inhibitors

During clinical trials of the TNF inhibitors in patients with refractory RA, a number of toxicities were noted. For example, the numbers of reports for infections (e.g. upper respiratory infections) tended to be somewhat higher among patients treated with TNF inhibitors compared with placebo. However, the numbers of patients with serious infections was similar (Table III). In the study of etanercept in patients with early RA, infection and serious infec-

Table II. Spontaneous post-marketing surveillance: Strengths and limitations.

Strengths
- rapid identification of adverse events
- detection of rare events
- long-term followup
- identification of risk factors for adverse events
- assessment of safety in large, diverse populations

Limitations
- underreporting
- unverifiable data (diagnoses, duplicate reports)
- incomplete data (comorbidity, concomitant medications)
- ascertainment bias
- causality difficult to establish

Table III. Serious infection rates in clinical trials*.

	Etanercept	Infliximab	Adalimumab
Pt exposure (pt-yrs)	8336	2458	4870
TNF antagonist	0.04**	0.03	0.04
Placebo	0.04	0.03	0.02

* Presented at FDA Arthritis Advisory Committee Meeting March 2003
** Incidence (patient-years)

Table IV. Mycobacterium tuberculosis in RA patients treated with TNF antagonists[†].

	Etanercept	Infliximab	Adalimumab*
Approximate numbers of patients treated	150,000	200,000	2,500
Approximate patient-years of exposure	230,000	230,000	4,900
TB reports	38	172	13
Distribution: use of agents			
USA	90%	64%	60%
Outside USA	10%	36%	40%
Distribution TB cases			
USA	20 (52%)	55 (32%)	3 (23%)
Outside USA	18 (48%)	117 (68%)	10 (67%)
Time to onset of TB	1 to 22 months (Median 11.2)	75% by 6 weeks; 97% by 7 months	3 to 8 months
Extrapulmonary/miliary involvement	50%	45%	40%

[†] Data through 4th quarter 2002; *all data for adalimumab is from clinical trials.

tion rates were comparable among those receiving etanercept or methotrexate (1). As one method to extend safety information derived from controlled trials with TNF inhibitors, the manufacturers have collected post-trial data on patients who participated in studies (19, 20). Similar trends for infection were noted.

Serious infections, including tuberculosis
Pharmacovigilance data concerning biologic agents have been an area of great interest among clinicians. Since their introduction, the US FDA has twice convened panels to examine the safety of TNF inhibitors. In January of 2001, after a number of reports of *Mycobacterium tuberculosis* (TB) infection among patients treated with infliximab had been received, the manufacturer issued a "Dear Doctor" letter alerting clinicians to this outcome, and urging appropriate caution be taken.
Driven by considerations of infectious and other adverse events related to the use of TNF inhibitors, the FDA convened a meeting of the Arthritis Advisory Committee in August 2001. At the time of that meeting, 84 cases of TB had been observed among patients receiving infliximab, out of approximately 170,00 patient years of exposure, and 11 cases of TB among patients treated with etanercept, out of 104,000 patient-years of exposure. Notably, only 1 case of TB had been seen up to that time in the clinical trials of infliximab, and none with etanercept, highlighting the need for pharmacovigilance data. Updated data through August 2002 is shown (Table IV). For adalimumab, which initially received approval 12/31/02 in the United States, 13 cases of TB were seen in clinical trials. Among infliximab treated patients who developed TB, 75% developed infection within the first 2 months of treatment, and 97% within the first 6 months, suggesting that this represented reactivation of latent tuberculosis (21). About 25% of patients presented with features of disseminated tuberculosis, and roughly half had extrapulmonary involvement; much higher percentages than those seen among the general population. Interestingly, while the number of TB cases with etanercept is lower, a similar distribution in terms of extrapulmonary cases was observed.
Considering the specific role of TNF in limiting tuberculosis infections in animal models (22, 23), it might be anticipated that inhibition of TNF in RA patients could be associated with increased risk of infection. Interestingly, even though more than two-thirds of all patients receiving treatment with infliximab worldwide reside in the United States, roughly 80% of the cases of TB occurred outside of the United States, most in countries with a higher rate of TB among the general population. In addition to TB, other opportunistic infections have been observed, highlighting the need for clinician vigilance.

Lymphoproliferative malignancies
Among potential adverse events related to the use of immunosuppressive medications, the development of malignancy is also of concern. For solid tumors exclusive of non-melanoma skin cancers, data for both etanercept and infliximab from longer term followup of clinical trial patients reveal an incidence of approximately 0.007 cases per patient year of followup (19, 20). To provide a frame of reference, the number of solid organ malignancies that would be expected for during followup of an aged matched cohort can be obtained from the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute of the United States (24). Solid organ tumors observed during followup of patients treated in clinical trials with etanercept and infliximab closely approximate the number expected from the SEER database.
Analysis of the risks of developing lymphoproliferative tumors is somewhat more complex in studies of RA, because the incidence of tumors such as lymphoma is increased from 2- to 20-fold among RA patients (25-27). Moreover, the risk of developing lymphoma has been shown to correlate with the severity and activity of disease, as well as with exposure to immunosuppressive medications. The RA patients enrolled in many of the trials of TNF inhibitors were patients with severe active disease that was typically refractory to other treatments, including immunosuppressive agents.
In March 2003, the US FDA convened a meeting to update safety concerns regarding TNF inhibitors, specifically focusing on the issue of neoplasia and lymphoma in RA patients receiving these agents. Safety data from controlled clinical trials (blinded and open label studies) were presented for all 3 drugs; post-marketing safety data are

Table V. Neoplasia and lymphoma incidence rates in RA patients on TNF inhibitors.

Randomized controlled: RA trials and open-label extension RA trials combined.

	Etanercept	Infliximab	Adalimumab
Patients / (patient-years)	3389 / (8336)	1298 / (2458)	2468 / (4870)
Number of lymphomas observed	6 → 9	4	10
Hodgkins/Non-Hodgkins lymphoma	33% / 66%	23% / 75%	10% / 99%
Number of lymphomas expected	2.59	0.63	1.8
SIR lymphoma	2.31 → 3.47	6.35	5.42
Time to lymphoma onset (range)	90 weeks (1-200)	(30 – 82 weeks)	77 weeks (8-181)
Number of malignancies observed (including lymphomas)	55	21	46
Number of malignancies expected	56.2	19.25	45.82
SIR malignancy	0.98	1.1	1.0

Postmarketing studies (Adverse Event Reporting System; AERS)

	Etanercept	Infliximab	Adalimumab
Number	>150,000	365,000[+]	
(Patient-years)	(> 230,000)	(554,000)[+]	No
AERS Lymphoma Reports	70	95	data available
RA lymphoma rate: No./100 pt-yrs	0.03*	0.017*	(drug approved
Time to lymphoma	14 ±12 mos. (1.4 - 39.5)	312 days (27 - 731 d)	12/31/02)

*Normal population rate is estimated to be 0.03/100 pt-yrs; [+] includes RA and Crohn's patients.

available for etanercept and infliximab (Table V; from the ACR Hotline, May 2003; available at www.rheumatology.org). No increased risk of malignancy overall was seen (Standardized incidence ratio [SIR] 0.98-1.1). Observed lymphoma SIRs ranged from 2.31 – 6.35, with wide and overlapping 95% confidence intervals. These data do not permit inter-drug comparison for lymphoma rates, owing to different trial designs and patient characteristics. The data suggest that lymphoma rates in RA patients who take TNF inhibitors are elevated, but it is not known if this exceeds the risk that would be expected from RA alone. In post-marketing surveillance (> 515,000 patient-years use), about 160 RA patients treated with TNF inhibitors have been reported to develop lymphoma. The crude reporting rate in the post-marketing era is roughly 2 to 3 cases per 10,000 patient-years of drug exposure, which approximates that of the general population. However, there is often substantial under-reporting in post-marketing surveillance.

Other safety concerns

Based on *ex vivo* and animal model data suggesting a central role for TNF in the pathogenesis of congestive heart failure (CHF) several trials of TNF inhibitors were initiated. Surprisingly, not only were these agents ineffective, but there was a suggestion that subsets of treated patients fared worse (Table VI). In one study (Renaissance) there was a trend towards worse outcome among CHF patients with milder CHF (NYHA class II) treated with etanercept. There are several caveats that are

Table VI. Clinical trials of TNF antagonists in CHF.

ATTACH trial	Placebo n = 48	Infliximab 5mg/kg n = 50	Infliximab 10 mg/kg n = 51		**Etanercept RENAISSANCE trial**	**Etanercept RECOVER trial**
				No. of patients	925 (NYHC 2-4)	1123 (NYHC 2-4
Hospitalization 0 - 28 weeks	5 (10%)	3 (6%)	11 (21)%	Rx Etanercept 25 mg	BIW, TIW	BIW, QWK
				Duration f/u	Median 12.7 mos.	Median 5.7 mos.
Death 0 - 28 weeks	0	1 (2%)	3 (6%)	Risk ratio compared	1.1*	1.0
0 - 52 weeks	4 (8%)	4 (8%)	8 (16%)	with placebo		

* Presented at FDA Arthritis Advisory Committee Meeting March 2003; ** adjusted for covariates.

relevant to interpretation of these data *vis-à-vis* RA patients. RA patients were not included in these trials, and patients with CHF were typically excluded from RA trials. Adalimumab has not been studied in CHF, although neither it nor future TNF inhibitors will likely be tested for that indication in the near future. Nevertheless, caution is indicated in the consideration of using these agents in patients with underlying CHF. Other adverse effects potentially related to the use of TNF inhibitors include demyelinating diseases, elevations in liver function tests, and abnormalities in blood cell lines. As of October 2002, 17 cases of multiple sclerosis (MS) and 11 cases of optic neuritis had been reported among patients receiving etanercept; cases have also been observed with inflximab and adalimumab. Whether these relatively small numbers of observed cases exceeds the number that might be expected remains unknown, as the actual prevalence of these demyelinating conditions in patients with RA remains uncertain. However, given the exacerbations of disease that had been observed during a previous study of a different TNF inhibitor (lenercept) in patients with MS, consideration of the possiblity of demyelinating disease as an adverse effect would seem prudent during TNF therapy. Of relevance to patients with early RA, several cases of demyelinating disease occurred among younger and relatively healthier RA patients, in distinction to several other adverse events noted during TNF inhibitor therapy.

Conclusions

The introduction of biologic agents, particularly TNF inhibitors, has initiated a new era in the therapy of RA. There has been tremendous excitement surrounding not only the clinical efficacy of these agents, but also the potential ability of such therapies to attenuate structural damage and improve functional status for patients. This has spawned considerable interest in the use of these agents in early RA, in the hopes of achieving greater clinical efficacy and preventing damage and disa-

bility. Accompanying the enthusiasm for their potent efficacy has been caution regarding the potential long-term safety of these powerful immunomodulators. The introduction of biologic agents into the clinic has highlighted the necessity for long-term monitoring of novel therapies, and for ascertainment of safety data from heterogeneous groups of patients. Regarding safety, there may be differences in the occurrence of adverse effects or in the risk/benefit considerations surrounding the use of biologic agents in patients with early RA compared to those with more established disease. Thus, assiduous collection of long-term safety information will be crucial in patients with early RA who are treated with biologic agents.

References

1. BATHON J, MARTIN R, FLEISCHMANN R, *et al.*: A comparison of etanercept and methotrexate in patient with early rheumatoid arthritis. *N Engl J Med* 2000; 343: 1586-93.
2. DORAN M,GABRIEL S: Infections in rheumatoid arthritis – A new phenomenon? *J Rheumatol* 2001; 28: 1942-3.
3. HERNANDEZ-CRUZ B, SIFUENTES-OSORNIO J, ROSALES P, DIAZ-JOUANEN E: *Mycobacterium tuberculosis* infection in patients with systemic rheumatic diseases. A case series. *Clin Exp Rheumatol* 1999; 17: 289-96.
4. MATTESON E, HICKEY AM MAGUIRE A, *et al.*: Occurrence of neoplasia in patients with rheumatoid arthritis enrolled in a DMARD registry. *J Rheumatol* 1991; 18: 809-14.
5. GRIDLEY G, MCLAUGHLIN J, EKBOM A, *et al.*: Incidence of cancer among patients with rheumatoid arthritis. *J Natl Cancer Institute* 1993; 85: 307-11.
6. VAN DEN BORNE B, LANDEWE R, HOUKES I, *et al.*: No increased risk of malignancies and mortality in cyclosporin A-treated patients with rheumatoid arthritis. *Arthritis Rheum* 1998; 41: 1930-7.
7. ROBINSON D, WOERNER M, POLLACK S, LERNER G: SUBJECT selection biases in clinical trials: data from a multicenter schizophrenia treatment study. *J Clin Psychophar macol* 1996; 16: 170-6.
8. TEJEDA H, GREEN S, TRIMBLE E, *et al.*: Representation of African-Americans, Hispanics and whites in National Cancer Institute cancer treatment trials. *J Natl Can Instit* 1996; 88: 812-6.
9. ROUTLEDGE P: 150 years of pharmacovigilance. *Lancet* 1998; 351: 1200-1.
10. KESSLER D: Introducing MedWatch: A new approach to reporting medication and device adverse effects and product problems. *JAMA* 1993; 269: 2765-8.
11. MEYBOOM R, EGBERTS A, GRIBNAU F, HEKSTER Y: Pharmacovigilance in perspec-

tive. *Drug Safety* 1999; 21: 429-47.
12. ELAND IA, BELTON KJ, VAN GROOTHEEST AC, MEINERS AP, RAWLINS MD, STRICKER BH: Attitudinal survey of voluntary reporting of adverse drug reactions. *Br J Clin Pharma col* 1999; 48: 623-7.
13. SCOTT H, ROSENBAUM S, WATERS W, *et al.*: Rhode Island physicians' recognition and reporting of adverse drug reactions. *R I Med J* 1987; 70: 311-6.
14. RAWLINS MD: Pharmacovigilance: paradise lost, regained, or postponed ? *J R Coll Physi cians Lond* 1995; 29: 41-9.
15. MARTIN RM, KAPOOR KV, WILTON LV, MANN RD: Underreporting of suspected adverse drug reactions to newly marketed ("black triangle") drugs in general practice: observational study. *BMJ* 1998; 317: 119-20.
16. HEELEY E, RILEY J, LAYTON D, WILTON L, SHAKIR S: Prescription-event monitoring and reporting of adverse drug reactions. *Lancet* 2001; 358: 1872-3.
17. WEBER J: Epidemiology of adverse reactions to nonsteroidal antiinflammatory drugs. *Adv Inflam Res* 1984; 6: 1-7.
18. MacDONALS T, MORANT S, ROBINSON G, *et al.*: Association of upper gastrointestinal toxicity of non-steroidal anti-inflammatory drugs with continued exposure: A cohort study. *BMJ* 1997; 315: 1333-7
19. SCHAIBLE T: Long term safety of infliximab. *Can J Gastroenterol* 2000; 14 (Suppl. C): 29C-32C.
20. MORELAND L, COHEN S, BAUMGARTNER S, *et al.*: Longterm safety and efficacy of etanercept in patients with rheumatoid arthritis. *J Rheumatol* 2001; 28: 1238-44.
21. KEANE J, GERSHON S, WISE R, *et al.*: Tuberculosis associated with infliximab, a tumor necrosis factor -neutralizing agent. *N Engl J Med* 2001; 345: 1098-104.
22. MOHAN V, SCANGA C,YU K, *et al.*: Effects of tumor necrosis factor alpha on host immune responses in chronic persistent tuberculosis: possible role for limiting pathology. *Infection Immunity* 2001; 69: 1847-55.
23. SENALDI G, YIN S, SHAKLEE CL, PIGUET PF, MAK TW, ULICH TR: *Corynebacterium parvum*- and *Mycobacterium bovis* bacillus Calmette-Guerin-induced granuloma formation is inhibited in TNF receptor I (TNF-RI) knockout mice and by treatment with soluble TNF-RI. *J Immunol* 1996; 157: 5022-6.
24. NATIONAL CANCER INSTITUTE: *Surveillance, Epidemiology, and End Results (SEER) Database.* Kosary 1995, SEER Stat for Windows 95/NT; 1997.
25. BAECKLUND E, EKBOM A, SPAREN P, FELTELIUS N, KLARESKOG L: Disease activity and risk of lymphoma in patients with rheumatoid arthritis: Nested case-control study. *BMJ* 1998; 317: 180-1.
26. GRIDLEY G, MCLAUGHLIN JK, EKBOM A, *et al.*: Incidence of cancer among patients with rheumatoid arthritis. *J Natl Cancer Inst* 1993; 85: 307-11.
27. ASTEN P, BARRETT J, SYMMONS D: Risk of developing certain malignancies is related to duration of immunosuppressive drug exposure in patients with rheumatic diseases. *J Rheumatol* 1999; 26: 1705-14.