EXTENDED REPORT

Results from a nationwide postmarketing cohort study of patients in Sweden treated with etanercept

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Objectives: To describe a nationwide system for postmarketing follow up of new antirheumatic drugs in Sweden, and to analyse safety and effectiveness in an etanercept treated patient cohort.
Methods: Etanercept became available in Sweden for prescribing on a named patient basis in 1999. All patients treated were included in a follow up of intensified adverse event reporting and recording of clinical outcome during 24 months, according to the EULAR core set.
Results: The mean (SD) disease activity score (DAS 28) value at inclusion among 820 patients recruited on a named patient basis during year 1 was 5.99 (1.19). After two years, 21% (n = 172) of these patients had discontinued the treatment. Of the remaining 648 patients, 68% (n = 442) responded to the treatment. However, in 55% of the responders, the disease activity was intermediate or high (mean DAS 28, 3.37 (1.20)). In all, 540 adverse events were reported in 421 adverse drug reaction (ADR) reports, in 294 patients. The events in 80 reports (19%) were serious. Twenty two per cent of the events were infections, of which 24% (n = 29) were serious. The incidence of serious adverse events remained constant over time.
Conclusions: At start of etanercept treatment, patients had high disease activity. Activity remained high in a large proportion of the responding patients. Although serious ADRs occurred during late phases of treatment, no unexpected safety problems arose. No specific indicators of ADR risk were found. The monitoring system that was established may be useful in future postmarketing surveillance.

It is becoming increasingly evident that new drugs, although approved for marketing, must be monitored for safety, effectiveness, and costs in the everyday clinical setting. Fast track approval of new drugs means that long term safety data are lacking at the time of marketing.[1] In addition, several of the rapidly approved drugs have novel pharmacological characteristics (for example, antibodies, receptor inhibitors, viral vectors, anti-sense therapies, and gene modifications), and the risk of cancer and other late complications has not been fully assessed. In patients with rheumatoid arthritis treated with tumour necrosis factor α (TNFα) blockers, the risk of lymphoma has been of particular interest.[2]

Several of the new drugs are expensive. At the time of approval, neither their costs nor their long term cost-effectiveness is known. Health care authorities responsible for reimbursement are demanding this information.[3] The regulatory agencies have tried to compensate for the limited safety and effectiveness information present at the time of approval by making their decisions conditional on various postmarketing monitoring requirements.[4] This was the case with the TNFα blocker etanercept, where the approval in the European Union was linked to a long term follow up requirement.

The safety of approved drugs is commonly monitored in adverse drug reaction (ADR) spontaneous reporting systems, postmarketing surveys, and through event monitoring in clinical databases. The various national spontaneous ADR reporting systems suffer from a substantial underreporting.[5] Complementary systems to collect information about effectiveness and adverse drug reactions are thus needed. Postmarketing surveys are typically designed as a continuation of clinical trials, with a reduced set of variables but with monitoring of a large number of patients. The experiences have so far seldom been evaluated. Extracting adverse events from clinical databases has previously mainly been carried out in research projects. High rates of false positive findings are common.[6] Typically these methods yield comparatively few ADR findings, and provide very little information about the patient, the disease, or the effectiveness of the drug.

Despite the general recognition of a need to enhance the postapproval follow up of drugs, it is unclear who is liable—health care professionals, industries, or regulatory agencies. Recently, regulatory agencies have declared their ambition to ameliorate the situation. This is manifested by a recent position paper from the European Agency for the Evaluation of Medicinal Products (EMEA) head of agencies group.[7] More comprehensive data than those emerging from conventional ADR monitoring systems are thus needed to serve patients, clinicians, and regulatory authorities.

Several conditions that prevailed when the TNF blockers were introduced in Sweden in 1999 enabled a pilot project to be undertaken on comprehensive patient monitoring:

- TNF blockers were already available before marketing, with prescribing controlled by the Swedish Medical Products Agency (MPA) on a named patient basis.
- All patients with rheumatoid arthritis were treated at a similar level of health care—that is, by rheumatology specialists.
- The Swedish Society of Rheumatology maintained a nationwide monitoring registry of incident rheumatoid arthritis patients. Various regional registries have developed these reporting systems further. Contributing to

Abbreviations: ADR, adverse drug reaction; CPMP, Committee for Propriety Medicinal Products; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; EMEA, European Agency for the Evaluation of Medicinal Products; EULAR, European League Against Rheumatism; HAQ, health assessment questionnaire; ICH, International Conference on Harmonisation; MPA, Swedish Medical Products Agency

Table 1 Patient characteristics and concomitant drug treatment at entry

Variable	First year (n = 820)	Years 2–4 (n = 253)	Entire cohort (n = 1073)
Female sex	627 (76.5%)	195 (77.1%)	822 (76.6%)
Age (years), mean	52.3	51.0	52.0
HAQ, mean score	1.64	1.50	1.62
Missing	33 (4.0%)	40 (15.8%)	73 (6.8%)
DAS 28, mean	6.0	5.7	5.9
Missing	56 (6.8%)	53 (20.9%)	109 (10.2%)
C reactive protein (mg/l), mean	48	36	45
Missing	28 (3.4%)	38 (15.0%)	66 (6.2%)
ESR (mm/h), mean	47	39	45
Missing	39 (4.8%)	47 (18.6%)	86 (8.0%)
Doctor's global assessment			
No disease activity	2 (0.2%)	4 (1.6%)	6 (0.6%)
Low disease activity	47 (5.7%)	18 (7.1%)	65 (6.1%)
Moderate disease activity	338 (41.2%)	91 (36.0%)	429 (40.0%)
High disease activity	379 (46.2%)	97 (38.3%)	476 (44.4%)
Maximum disease activity	18 (2.2%)	5 (2.0%)	23 (2.1%)
Missing	36 (4.4%)	38 (15.0%)	74 (6.9%)
Concomitant drug treatment*			
DMARD none	377 (46.0%)	110 (43.5%)	487 (45.4%)
One	372 (45.4%)	97 (38.3%)	469 (43.7%)
Two	60 (7.3%)	12 (4.7%)	72 (6.7%)
Three	2 (0.2%)	2 (0.8%)	4 (0.4%)
Methotrexate	339 (41.3%)	91 (36.0%)	430 (40.1%)
Sulfasalazine	46 (5.6%)	10 (4.0%)	56 (5.2%)
Ciclosporin	36 (4.4%)	9 (3.6%)	45 (4.2%)
Azathioprine	21 (2.6%)	4 (1.6%)	25 (2.3%)
Chloroquine/hydroxychloroquine	18 (2.2%)	6 (2.4%)	24 (2.2%)
Reumacon® (CPH 82)	16 (2.0%)	1 (0.4%)	17 (1.6%)
Sodium aurothiomalate	7 (0.9%)	0	7 (0.7%)
Auranofin	5 (0.6%)	0	5 (0.5%)
Other DMARD	10 (1.2%)	6 (2.4%)	16 (1.5%)
Missing	9 (1.1%)	32 (12.7%)	41 (3.8%)
Corticosteroids	779 (95.0%)	242 (95.7%)	1021 (95.2%)
Non-aspirin NSAIDs	779 (95.0%)	242 (95.7%)	1021 (95.2%)
Other analgesics	738 (90.0%)	231 (91.3%)	969 (90.3%)

Values are n (%) or mean, as indicated.
*Reported drug treatment during the first three months of follow up.
DAS, disease activity score; DMARD, disease modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; NSAID, non-steroidal anti-inflammatory drug.

these databases has familiarised all Swedish rheumatologists with a common system of clinical follow up with centralised data reporting.

- Committee for Propriety Medicinal Products (CPMP) approval for marketing was conditional on specific, detailed follow up activities, and there was drug company interest in supporting expanded monitoring.
- The MPA was prepared to support the project within its programme to develop new tools for postmarketing follow up.

Our aim in this paper was to report the design and findings of a nationwide comprehensive monitoring system for patients with rheumatoid arthritis treated with etanercept between 1999 and 2003.

METHODS

Inclusion of patients

The patients included had active rheumatoid arthritis, as evaluated by the attending physician, and had previously been treated with at least one disease modifying antirheumatic drug (DMARD) in addition to methotrexate. In early 1999, when the follow up was initiated, etanercept was not yet approved on the Swedish market and treatment was only available on a named patient basis. All the 820 patients included during the first year received the treatment after application and approval of the MPA. Later, when etanercept was approved and marketed, the supply of the drug was limited; thus only 253 patients initiated etanercept treatment during years 2 to 4. Etanercept was given subcutaneously twice weekly in a standard dose of 25 mg. Every patient could be identified by the Swedish system of a unique personal number, which can also be used to link each patient to other national registries such as the cancer registry, the inpatient registry, and so on. Patients were informed about the registration and consented to it.

Assessment of effectiveness

Patients recruited during the first year were included in the assessment of treatment effects (fig 1). Examinations were scheduled at 0, 3, 6, 12, 18, and 24 months after inclusion. Disease activity was measured by C reactive protein, erythrocyte sedimentation rate (ESR), the health assessment questionnaire (HAQ), the number of swollen and tender joints, and the patient's and doctor's global assessment of disease. In addition, disease activity scores (DAS 28), the European league against rheumatism (EULAR) response criteria, and the American College of Rheumatology criterion of improvement (ACR 20) were calculated.[8 9] Descriptive statistics were calculated using SAS statistical software. Student's *t* test was used in comparisons of means.

Assessment of safety

Patients recruited during years 1 to 4 were included in the assessment of treatment safety (fig 1). Reports on adverse drug reactions (ADR) were categorised as mild, moderate, or serious. Serious reactions were classified according to the ICH standard.[10] Causality was primarily assessed by the reporting physician. Expertise from the MPA pharmacovigilance department was involved in the final assessment and classification of all ADR reports. Reporting was in

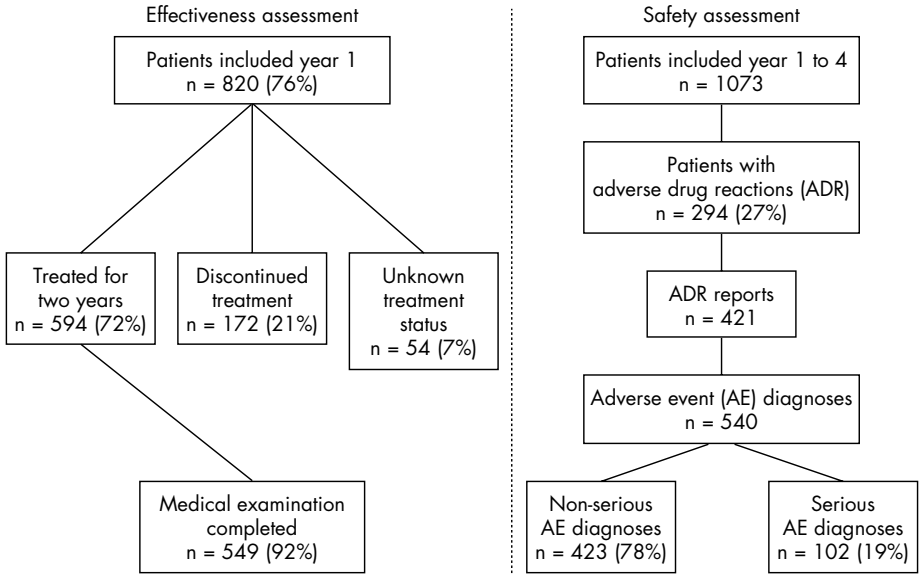

Figure 1 Distribution of patients in the assessment of safety and effectiveness.

conjunction with an adverse event, and the action taken—that is, if the drug treatment was discontinued or modified—was reported by the physician. The specific adverse event diagnoses reported were recorded according to the Swedish MPA ADR diagnosis classification which corresponds to the Medical Dictionary for Regulatory Activities (MedDRA) guidelines.[11]

Data collection

The reporting of data was initially compulsory for all prescribers and was linked to approval by the MPA, which secured a high initial reporting compliance. The already established registries for monitoring incident cases of rheumatoid arthritis also formed a platform for this national reporting system. Thus the majority of Swedish rheumatologists were accustomed to a standard procedure of regularly reporting clinical data, which was also used for the TNF blocker follow up. The project was organised by the Swedish Society of Rheumatology and was led by a steering committee (the ARTIS group) nominated by the society. The MPA was a formal participant and was represented within the steering committee.

Table 3 Seriousness of adverse events in 294 patients with reported events

Adverse events	n (%)
Non-serious reports	
Mildly serious	110 (37.4%)
Moderately serious	104 (35.4%)
Serious reports	
Serious	66 (22.4%)
Life threatening	7 (2.4%)
Lethal	3 (1.0%)
Report of seriousness missing	4 (1.4%)

The pharmaceutical company (Wyeth Pharmaceutical) had the opportunity to give input to the initial monitoring protocol. As the reporting was based on an agency request, the reports were sent to the MPA. The analyses of data were made at the Unit of Clinical Epidemiology at Karolinska Institute. An agreement was made with the company which allowed the sharing of adverse event data to be used in the

Table 2 Disease activity, treatment response, and disease improvement among patients included during the first year of follow up*

	Entry	3 Months	6 Months	12 Months	24 Months
Treatment response†					
No response	–	150 (19.1%)	123 (17.6%)	90 (14.7%)	75 (14.5%)
Moderate response	–	443 (56.4%)	361 (51.7%)	308 (50.2%)	243 (47.0%)
Good response	–	192 (24.5%)	215 (30.8%)	215 (35.1%)	199 (38.5%)
Disease activity score‡					
Inactive disease	6 (0.8%)	115 (16.5%)	119 (19.2%)	133 (23.9%)	125 (26.6%)
Low activity	6 (0.8%)	68 (9.8%)	81 (13.0%)	69 (12.4%)	63 (13.4%)
Intermediate activity	151 (19.8%)	376 (54.0%)	317 (51.0%)	279 (50.2%)	219 (46.6%)
High activity	601 (78.7%)	137 (19.7%)	104 (16.7%)	75 (13.5%)	63 (13.4%)

Values are n (%).
*At 24 months' follow up, 172 (21%) had ceased the treatment.
†Treatment response defined by the EULAR criteria, in relation to disease activity score at entry. At 24 months' follow up information on treatment response was missing for 131 of 648 patients.
‡Disease activity score (DAS 28). *Inactive disease*, DAS 28 value <2.6; *low*, 2.6 to 3.2; *intermediate*, >3.2 to 5.1; *high*, >5.1. At 24 months' follow up, disease activity was missing for 178 of 648 patients.

company's periodic safety update reports. This arrangement was in line with the European Agency for the Evaluation of Medical Products (EMEA) committee for proprietary medicinal products (CPMP) request at the time of marketing approval for a follow up registry.

RESULTS

Of the 1073 subjects in the cohort of etanercept treated patients, 820 patients (76%) were included during the first study year and 253 patients during years 2 to 4. There was a female majority (77%) and the mean (SD) age of the patients was 52 (13.5) years (table 1). Clinical assessment of the seriousness of the patients' disease at entry generally indicated severe illness, with mean (SD) HAQ of 1.62 (0.63), DAS 28, 5.9 (1.2), C reactive protein 45 (39) mg/l, and ESR 45 (28) mm/hour (table 1). No significant difference in the number of swollen or tender joints between the 109 subjects (10%) with a missing DAS 28 value at entry and the subjects with complete information on DAS 28 was seen ($p = 0.36$ and 0.30, respectively). During the study period, generally decreasing disease activity was seen. The decrease in the mean DAS 28 entry value was statistically significant though small (0.2 units per year). Half the patients were treated with at least one DMARD in addition to etanercept. Methotrexate was prescribed in 40% of the patients. The use of corticosteroids and analgesics was generally substantial—more than 95% of the patients used corticosteroids (table 1).

Among the patients included during the first year of the study (n = 820), 72% were treated with etanercept for at least two years (n = 594), and the medical examination was completed in 67% (n = 549) (fig 1). Treatment status was unknown for 54 patients (7%) lost to follow up. The treatment was discontinued in 172 patients (21%) within two years. Poor treatment effect was reported in 67 patients (39%) and 59 (34%) ended the treatment because of an adverse event. In 26% (n = 44), the reason for discontinuation was not reported. The total observation time for etanercept treatment was 2694 patient-years.

Table 4 Adverse event diagnoses (n = 540) in 421 reports grouped according to organ system disorder and seriousness*

Organ system disorder	Non-serious (n = 423)	Serious (n = 102)	Total (n = 540)
Skin	122 (28.8%)	8 (7.8%)	134 (24.8%)
Infection resistance mechanism†	66 (15.6%)	20 (19.6%)	90 (16.7%)
Respiratory system	62 (14.7%)	10 (9.8%)	74 (13.7%)
General	61 (14.4%)	8 (7.8%)	70 (13.0%)
Neurological	19 (4.5%)	9 (8.8%)	29 (5.4%)
Gastrointestinal	25 (5.9%)	3 (2.9%)	28 (5.2%)
Cardiovascular	11 (2.6%)	15 (14.7%)	26 (4.8%)
Haematological	8 (1.9%)	9 (8.8%)	17 (3.2%)
Musculoskeletal	11 (2.6%)	1 (1.0%)	12 (2.2%)
Neoplasms	0	11 (10.8%)	11 (2.0%)
Vision/eye	10 (2.4%)	1 (1.0%)	11 (2.0%)
Female reproductive	6 (1.4%)	1 (1.0%)	8 (1.5%)
Urinary system	4 (1.0%)	2 (2.0%)	7 (1.3%)
Metabolic	3 (0.7%)	2 (2.0%)	5 (0.9%)
Psychiatric	4 (1.0%)	1 (1.0%)	5 (0.9%)
Hearing/vestibular	4 (1.0%)	0	4 (0.7%)
Liver/biliary	2 (0.5%)	1 (1.0%)	3 (0.6%)
Odontological	2 (0.5%)	0	3 (0.6%)
Drug related collagenosis	2 (0.5%)	0	2 (0.4%)
Endocrine	1 (0.2%)	0	1 (0.2%)

Values are n (%).
*Organ system disorder according to the Swedish Medical Products Agency diagnostic classification. Seriousness missing in 15 diagnoses (2.8%).
†Includes increased infection susceptibility and opportunistic infections.

After two years of follow up, among the 648 patients included during the first year and for whom there was no information that the treatment had been discontinued, 442 (68%) had responded according to the EULAR criteria. Among 517 (80%) of these patients with known treatment response during two years of therapy, 39% and 47% had a good and a moderate response, respectively (table 2). However, in 55% of the responding patients, the DAS 28 indicated persisting intermediate or high disease activity (mean (SD) DAS 28, 3.4 (1.2)). No response was seen in 75 patients (15%). In 65% of the patients, the disease had improved in relation to activity at treatment start according to the ACR 20 response criterion (data not shown). Despite clinical response, the disease activity score (DAS 28) indicated intermediate or high activity in 60% of the patients (table 2).

All the 1073 patients were included in the etanercept treatment safety assessment. In 27% of the patients (n = 294), at least one ADR report was recorded (421 ADR reports; mean 1.5 report per patient; median 1; range 1 to 6). The 421 reports comprised 540 adverse event diagnoses (mean 1.8 diagnoses per patient; median 1; range 1 to 7) (fig 1). Nineteen per cent of the ADR reports (n = 80) were

Table 5 Serious events during etanercept treatment within selected diagnostic groups

Adverse event	n	/1000 patient-years*
Infections		
Sepsis	8	3.0
Pneumonia	8	3.0
Osteitis	3	1.1
Infectious arthritis	2	0.7
Soft tissue abscess	2	0.7
Gastroenteritis	2	0.7
Recurrent fever	1	0.4
Skin inflammation	1	0.4
Encephalitis	1	0.4
Cardiovascular disorders		
Myocardial infarction	5	1.9
Pulmonary oedema	2	0.7
Angina pectoris	2	0.7
Coronary artery disorder	1	0.4
Tachycardia	1	0.4
Asystole	1	0.4
Heart failure	1	0.4
Venous thrombosis	1	0.4
Other vascular disorder	1	0.4
Haematological disorders		
Leucopenia	4	1.5
Thrombocytopenia	2	0.7
Pancytopenia	1	0.4
Myelodysplastic syndrome	1	0.4
Other haematological disorders	1	0.4
Neoplasms		
Lymphoma	3	1.1
Benign respiratory tract neoplasm	2	0.7
Unspecified liver neoplasm	1	0.4
Primary liver cancer	1	0.4
Benign gastrointestinal neoplasm	1	0.4
Ovarian cancer	1	0.4
Cervical cancer	1	0.4
Rectal cancer	1	0.4
Neurological disorders		
Paraesthesiae	2	0.7
Subarachnoid haemorrhage	2	0.7
Cerebral infarction	1	0.4
Facial paresis	1	0.4
Dysarthria	1	0.4
Headache	1	0.4

*Total observation time was 2693.6 patient-years.

categorised as serious, and 79% (n = 331) were non-serious. Seriousness was not recorded in 10 reports (2%). The serious ADR reports included 19% (n = 102) of the adverse event diagnoses, and 78% (n = 423) of the diagnoses were recorded in reports classified as non-serious. Seventy six of the patients (7%) in the cohort experienced at least one serious event, whereas 114 (11%) had events exclusively classified as non-serious (table 3). Serious adverse events were reported to be associated with the death of three patients treated with etanercept. The causes of death were lymphoma, cardiac arrest, and enteritis.

The distribution of 540 adverse event diagnoses in 421 ADR reports is presented in table 4, grouped by diagnosis according to the Swedish MPA adverse event diagnosis classification. Overall, adverse events classified as skin disorders were the most commonly reported, with infections coming second. According to the Swedish MPA classification, infections fell within several different diagnostic groups. However, 22% (n = 120) of all reported adverse event diagnoses were infections and 24% (n = 29) of the infections were classified as serious (data not shown).

The detailed adverse event diagnoses in the groups classified as neoplasms, infections, and cardiovascular, haematological, and neurological disorders, stated in reports to be categorised as serious, are presented in table 5, along with the estimated incidence rate.

Among the patients experiencing a non-serious adverse event, more than 60% of the first events occurred within six months of the start of etanercept treatment. In contrast, the serious adverse events were more evenly distributed over time (fig 2). The median latency to the first non-serious ADR report among patients experiencing only non-serious adverse events was three months. The corresponding median latency among patients with at least one serious ADR report was 14.5 months (table 6). In 76% and 74% of the patients with non-serious and serious adverse events, respectively, the disease activity was intermediate or high by the time of the ADR report. Considering the disease activity at the start of etanercept treatment, 63% and 66% of the patients with non-serious and serious adverse events, respectively, had responded to the treatment when the event occurred (table 6). In patients with serious adverse events, a greater proportion experienced a good response and a smaller proportion had not responded to the treatment at all.

DISCUSSION

In summary, the magnitude of the clinical effectiveness in this nationwide postmarketing cohort study is similar to the efficacy reported in the previous randomised controlled

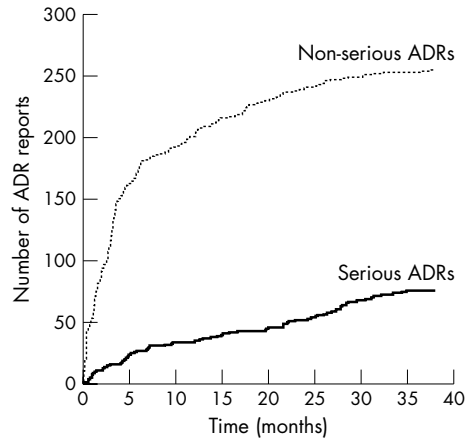

Figure 2 Cumulative number of first adverse drug reaction (ADR) reports by seriousness.

Table 6 Patient characteristics, overall treatment response, and treatment effectiveness at the time of adverse events by highest reported seriousness*

Variable	Serious (n = 76)	Non-serious (n = 214)	No event (n = 779)	All patients (n = 1073)
Female	59 (77.6%)	173 (80.8%)	587 (75.4%)	822 (76.6%)
Age (years)				
Mean	55.4	50.9	52.0	52.0
Median	55.5	52	53	53
Interquartile range	48.5 to 66	42 to 59	44 to 61	44 to 61
Overall treatment response†				
No response	3 (4.0%)	18 (8.4%)	56 (7.2%)	77 (7.25)
Moderate response	33 (43.4%)	66 (30.8%)	237 (30.4%)	338 (31.5%)
Good response	26 (34.2%)	94 (43.9%)	328 (42.1%)	449 (41.9%)
Missing	14 (18.4%)	36 (16.8%)	158 (20.3%)	209 (19.5%)
Latency to adverse event (months)				
Mean	15.1	5.9		
Median	14.5	3.0		
Interquartile range	4.3 to 26.4	1.2 to 6.2		
Disease activity when adverse event occurred‡				
Inactive disease	16 (21.1%)	25 (11.7%)		
Low activity	3 (4.0%)	15 (7.0%)		
Intermediate activity	33 (43.4%)	104 (48.6%)		
High activity	23 (30.3%)	58 (27.1%)		
Missing	1 (1.3%)	12 (5.6%)		
Response when adverse event occurred†				
No response	8 (10.5%)	32 (15.0%)		
Moderate response	34 (44.7%)	99 (46.3%)		
Good response	16 (21.1%)	36 (16.8%)		
Missing	18 (23.7%)	47 (22.0%)		
Methotrexate when adverse event occurred†	17 (22.4%)	73 (34.1%)		
Missing	5 (6.6%)	3 (1.4%)		

Values are n (%) unless stated otherwise.
*Seriousness was missing in reports of four patients.
†Treatment response as defined by the EULAR criteria, in relation to disease activity at start of etanercept treatment.
‡Disease activity score for the 28-joint indices (DAS 28).

trials.[12] The pattern of adverse events is also similar.[13] Analysis of concomitant drug treatment showed a high proportion of corticosteroid users, whereas concomitant use of methotrexate was restricted to 40%. Notwithstanding the large proportion of patients responding to the treatment, a considerable number still had active disease after two years of etanercept treatment. TNF inhibitor treatment should perhaps have been discontinued earlier in such treatment resistant patients. Treatment duration appeared important for the occurrence of serious ADRs as the median latency was 14.5 months. One objective of the intense monitoring was to determine whether specific patterns of patient characteristics and treatment response could be detected as early indicators of later ADRs. However, there was no clear pattern in disease activity or treatment response in patients suffering serious ADRs. In addition, the incidence of serious ADRs was evenly distributed over the follow up period.

When monitoring any approved drug, the expected number of ADRs is typically low. Thus different priorities must be balanced when considering efforts to improve the value of the information collected in monitoring systems. These systems may be compared with any diagnostic method, and the performance of these tools can be evaluated by conventional epidemiological methods. Given the very low incidence of ADRs, even with the high hypothetical sensitivity and specificity of these systems, the positive predictive value of any reported finding is low.[14] Consequently, only a few ADRs actually reported will eventually be found to be truly positive. Moreover, it seems unlikely that neither spontaneous ADR reporting systems nor clinical database surveillance would approach this high degree of accuracy. In addition, very little information on other important factors is readily available, and no adequate patient group for comparison is present.

A more detailed postmarketing monitoring of a cohort like ours might thus be worthwhile, even with few unexpected findings after two years. First, the consistent results are so far reassuring to patients, their doctors, the authorities, and drug companies. Second, the ADRs detected may be evaluated against clinical effectiveness in a large number of patients. Third, if these patient cohorts are maintained and adverse drug monitoring continued, more experience will be accumulated about long term treatment effectiveness and also about the risk of late ADRs.

The most common means of ADR monitoring are national spontaneous reporting systems, postmarketing surveys, and clinical databases for adverse event monitoring.[15] Obtaining data only from the national spontaneous reporting system would, in our view, not have provided the information, the analysis, and the results we are able to present here. At best, it would only yield stray observations of ADRs. Consequently, these systems will seldom collect enough cases to ascertain whether the reported ADRs are consistent or just random observations. These systems were implemented to serve as a standardised reporting procedure for any and all unexpected ADRs, for all patients, for all diseases, and for all drugs. Each ADR report may contain several ADR diagnoses, and only sparse information is available about the patient, the clinical history, and the treatment, including response to therapy. When evaluating these reports, no information is available about patients with similar characteristics who have not experienced ADRs. On the other hand, the cost of this system is low. Each year in Sweden (population 8.9 million), only about 3500 ADR reports are filed.[16] This may be compared to the annual 1.5 million hospital admissions, about 26 million outpatient visits to physicians, and a drug budget of about €2000 million.[17]

Our study was carried out within an established professional network already engaged in regular monitoring of treatment and disease activity in patients with rheumatoid arthritis, with reporting of regionally collected data.[18] However, patient data were also merged with information on all ADRs, including additional information on action taken and the course of the event. This enabled a more comprehensive analysis of patients with serious and non-serious events, including comparisons with patients without any reported ADRs. The collaboration with the Swedish Medical Products Agency from the start, as part of an initiative to develop and test new methods for pharmacovigilance, facilitated the study. Furthermore, all patients were identified by their unique personal identification number which will allow future studies of the patient's disease history by linkage to Swedish national health care registries of inpatient care, cancers, and causes of death.

In spite of these advantages, the ''real life character'' of our postmarketing cohort study had several important shortcomings, principally the absence of a control group, a multitude of different combinations and doses of treatment with other DMARDs, and insufficient information on disease history at the time when the patients were included. However, the severity of the patients' disease, as evaluated by the DAS 28 and HAQ values at the time of inclusion, indicated that all patients had severe and long standing rheumatoid arthritis. For some outcomes, the amount of missing data was unacceptably high. Some events may have been managed primarily at levels of health care other than rheumatology clinics and thus were not reported.

In summary, this project has highlighted the possibilities as well as the problems linked to the monitoring of newly approved drugs in a ''real life setting.'' The project shows that the medical profession is able to establish and pursue national drug monitoring programmes. Improvements in data logistics and support to participating clinics are needed to ensure the quality and adequacy of the information for scientific as well as regulatory purposes. Thus, projects like this one may be of great value in complementing the existing systems of drug surveillance.

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