CONCISE REPORT

Toxicity profiles of traditional disease modifying antirheumatic drugs for rheumatoid arthritis

D Aletaha, T Kapral, J S Smolen

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Background: The progression of rheumatoid arthritis (RA) can be retarded or halted by disease modifying antirheumatic drugs (DMARDs). Next to inefficacy, toxicity limits their use.

Objective: To explore the toxicity profiles of DMARDs in daily life.

Patients and methods: Five hundred and ninety three patients with RA charts (>2300 patient years of treatment) were reviewed at two rheumatology outpatient clinics. All recorded data on toxicity and reasons for stopping treatment were collected.

Results: Adverse events were common reasons for treatment discontinuation (42% of treatments). In 70% they were subjectively reported at the clinical visit, while substantial laboratory abnormalities were seen relatively rarely (9% of treatments: abnormal liver function tests in 5%; haematological abnormalities in 3%; impaired renal function in 1%). No single case of retinopathy from antimalarial drugs (that is, an incidence of <0.3 events/1000 patient years) was found, although eye examinations by the specialists were abnormal 30 times per 1000 patient years, mostly revealing keratopathy. Most commonly reported symptoms per 1000 patient years were nausea (54 events), abdominal pain (37 events), and rashes (34 events). Adverse events were more likely to occur with increasing number of consecutive DMARD courses.

Conclusion: The first DMARD course in a patient seems to be safer than the consecutive ones. In addition, the incidence of adverse events (AEs) seems to be similar for high and low dose treatment. Data are also provided on types and incidence of AEs that are consistent with previous studies in other countries and different settings.

Rheumatoid arthritis (RA) is a chronic disease that will cause disability and increased mortality if not treated efficiently.^{1–3} Drug treatment of RA mainly consists of three therapeutic approaches: non-steroidal anti-inflammatory drugs, which are symptomatic agents and have an important role in the relief of pain and other symptoms caused by inflammation, but are not generally associated with improvement of laboratory surrogates of inflammation in RA, such as C reactive protein or erythrocyte sedimentation rate^{4,5}; corticosteroids, which have a great anti-inflammatory potential in patients with RA,^{6,7} although adverse effects limit their long term use⁸; and agents that have the potential to prevent joint destruction, the disease modifying antirheumatic drugs (DMARDs). However, the ability of DMARDs to prevent joint damage, disability, and disease related mortality^{2,8,9} is not only limited by their frequently insufficient efficacy, but also by potentially considerable toxicity.^{10–12}

In this study we aimed at determining the types and incidences of adverse events (AEs), to compare these with

results of previous studies, and to estimate the proportion of patients in whom AEs lead to treatment discontinuation.

METHODS

The study subjects were a convenient sample of all patients with RA attending the outpatient clinics at two rheumatology departments in the Vienna area—the Vienna General Hospital and the Lainz Hospital. Both are specialised referral centres as seen in other parts of Europe or the United States. Sampling was performed in a consecutive manner, limiting inclusion only to patients who were receiving at least one course of DMARD treatment (either terminated or still continuing), and had at least one follow up examination after initiation of DMARD treatment. Data were extracted from the files in 1999; files of all patients with RA who were seen in the outpatient clinics after 1993 were available in the archives (also those of patients who were lost to follow up or had died). Only charts of patients who did not have a visit after 1993 were not available for analysis.

Five hundred and ninety three patients were identified. Of these, 477 women (80%) and 116 men (20%) received 1319 courses of DMARDs during the time of observation, which dated back to the 1970s for many patients. The number of DMARDs used in an individual patient with RA ranged from 1 to 10 (median 2). Rheumatoid factor at first presentation was positive in 64% of patients. The patients' mean (SD) age at the time of onset of symptoms was 44.7 (14.9) years and the mean period of follow up was 13.6 (9.3) years. The median lag time from onset of symptoms according to the history to the first DMARD was nine months (maximum two years) for those patients who received their first DMARD at one of the study hospitals. In both clinics, patients with RA are seen regularly (generally every three months) by doctors in training who already have at least one year's experience in rheumatology and are closely supervised by a senior rheumatologist.

For the purpose of this study, all AEs documented in the charts at each patient visit (upon general questioning by the doctor or self reported) were extracted and recorded. The relation between symptoms and drug treatment at the time of evaluation was rated by consensus as certain, probable, possible, or unlikely. This included the evaluation of any documented objective tests or examinations to verify subjective symptoms. Also the plausibility of association of the AE and DMARD treatment was determined for the type of DMARD employed, the temporal occurrence in conjunction with its application or resolution after DMARD discontinuation, and the presence of comorbidity and comedication. The

Abbreviations: AEs, adverse effects; AM, antimalarial drugs; AZA, azathioprine; DMARDs, disease modifying antirheumatic drugs; D-Pen, D-penicillamine; MTX, methotrexate; OG, oral gold; PG, parenteral gold; RA, rheumatoid arthritis; SSZ, sulfasalazine

Adverse events	All	MTX	SSZ	CG	PG	OG	D-Pen	AZA	CSA	Comb.	Time to adverse event in months (Mean (SEM))
No =	1319	389	267	285	109	68	65	25	31	80	
Years at risk:	2378	751	428	536	218	130	164	56	27	67	
General											
Weight loss	2	3		4							8.5 (2.5)
Fatigue	6	13	5		5		6				9.7 (3.2)
Sweating	4	3	7	2			6		73	15	3.1 (1.0)
Gastrointestinal											
Nausea	54	75	82	28	5	8	37	90	73	119	7.0 (1.0)
Vomiting	10	15	9		9		12	18	37	45	7.3 (2.7)
Abdominal pain	37	39	65	22	9	15	37	54	37	60	11.5 (1.7)
Diarrhoea	21	20	37	6	9	69	18		73	15	16.6 (5.1)
Anorexia	3	4	2	4						15	4.2 (2.1)
Skin											
Rash	34	17	37	17	120	54	37		73	15	10.2 (1.8)
Pruritus	18	12	19	11	64	15	18		37		11.0 (2.3)
Alopecia	18	40	2	7		23	18		37	15	14.4 (3.0)
Oedema	4	7	2	2	9				37		11.1 (3.2)
Flush	2	3	2		5						6.3 (3.3)
Haematoma	2	1	2				12				6.1 (2.9)
Erythema/sun sensitivity	3	1		9							32.5 (12.6)
Dermatitis/eczema	2	4		2		8					17.0 (11.8)
Neuropsychiatric											
Psychiatric	3	4	5	2					37	15	5.9 (2.1)
Sleep disturbance	5	4	12	4						15	13.6 (4.6)
Headache	15	23	16	9	5		18		37	15	18.4 (7.0)
Dizziness/vertigo	13	20	19	7	5		6	18	37	15	16.2 (7.3)
Other neurological	8	7	14	6	5		6		37	15	9.4 (3.8)
ENT/ophthalmological											
Stomatitis/mucosal ulcers	18	29			46	8	12	36	73	60	8.9 (2.0)
Altered taste	4		2	4	9		18			15	9.2 (7.1)
Blurred vision	5	4		17						15	27.5 (17.3)
Pathological eye examination	9	4		30		8				15	15.2 (4.0)
Infections											
Dysuria	2	1		2		8	6				9.1 (5.5)
Urinary tract infection	22	37	19	7	14	15	18		73	45	17.5 (3.9)
Respiratory infections	18	33	9	6	5		31	18		45	17.7 (3.3)
Other infections with fever	21	39	19		23	8	18			75	12.4 (2.2)

1–10 events/1000 patient years

11–50 events/1000 patient years

51–120 events/1000 patient years

Figure 1 Major symptoms in patients taking DMARDs (events/1000 patient years).

results of this adjudication process were then reviewed independently for accuracy by the senior author. AEs rated as “certain” or “probable” were regarded as “DMARD related”. These events were classified into 29 categories and six subgroups according to previous publications^{10 11} and the OMERACT Revised Rheumatology Toxicity Grading Index.¹³

Data were analysed (Mann-Whitney U test, χ^2 test) using version 10.0 of the Statistical Package for the Social Sciences (SPSS) for the microcomputer.

RESULTS

DMARD treatments and years at risk

A total of 2378 patient years of DMARD treatment were analysed comprising the following treatments (abbreviation, number, and rounded proportion of patient years in parentheses): antimalarial drugs (AM, 536 patient years, 22.5%), auranofin (OG, 131 patient years, 5.5%), aurothiomalate (PG, 218 patient years, 9.2%), azathioprine (AZA, 56 patient years, 2.4%), cyclosporin A (CyA, 27 patient years, 1.1%), D-penicillamine (D-Pen, 164 patient years, 6.9%), methotrexate (MTX, 751 patient years, 31.6%), sulfasalazine (SSZ, 428

patient years, 18.0%). Combination treatments of different DMARDs (Comb, 67 patient years, 2.8%) mostly included MTX (in 75%), AM, and SSZ (53% each). For better comparison with other studies,^{10 11} the incidence of encountered AEs is given in events/1000 patient years by extrapolation (see later).

Signs and symptoms related to DMARD toxicity

AEs were the most common reasons for stopping DMARD treatment—namely, in a total of 249 (42.0%) of the patients, followed by inefficacy (in 217 (36.6%)), remissions (in 19 (3.2%)), and various other reasons, such as surgery, planned pregnancy, and non-compliance (in 108 (18.2%)). As expected, the incidence of AEs the patients presented with, or reported, was much higher than the discontinuation rate. However, about 71% of DMARD terminations due to AEs were caused by subjective symptoms of the patients, and in the remainder DMARD discontinuation was triggered by objective signs or laboratory abnormalities.

Figure 1 shows the incidence of AEs in events per 1000 patient years in this patient group for every DMARD. Figure 2

	1	2	3	4	5
All DMARDs	Nausea (54)	Abd. pain (37)	Rash (34)	Urinary inf. (22)	Diarrhoea; infections/ fever (21)
Methotrexate	Nausea (75)	Alopecia (40)	Abd. pain, infections/fever (39)		Urinary infection (37)
Sulfasalazine	Nausea (82)	Abd. pain (65)	Diarrhoea; rash (37)		
Antimalarial drugs	Eye symptoms (30)	Nausea (28)	Abd. pain (22)	Rash; blurred vision (17)	
Parenteral gold	Rash (120)	Pruritus (64)	Stomatitis, mucosal ulcers (46)	Infections/ fever (23)	Urinary infection (14)
Oral gold	Diarrhoea (69)	Rash (54)	Alopecia (23)	Pruritus; urinary infection; Abd. pain (15)	
D-Penicillamine	Rash; abdominal pain; nausea (37)			Respiratory (15)	
Azathioprine	Nausea (90)	Abd. pain (54)	Stomatitis, mucosal ulcers (36)	Respiratory; vomiting; vertigo (18)	
Cyclosporin A	Nausea; stomatitis; mucosal ulcers; rash; diarrhoea; urinary infection; sweat (73)				
Combinations	Nausea (119)	Infections/ fever (75)	Stomatitis, mucosal ulcers; abdominal pain (60)		

Figure 2 Ranking of major symptoms in patients treated with various DMARDs. Incidence in events/1000 patient years is given in parentheses).

shows the ranking of the major AEs. Nausea was the most commonly encountered AE due to DMARD treatments, followed by abdominal pain, and rashes. These were also the AEs that most commonly led to discontinuation.

The number of different AEs encountered for each DMARD course ranged from 0 to 4. In 58% of treatments, no subjective AEs were registered, while there was one reported problem in 33%, and two to four problems in 9% of the treatments. There were no significant differences in types and numbers of AE for high dose (≥ 12.5 mg/week, $n=89$) compared with low dose (≤ 10 mg/week, $n=285$) MTX, and high dose (≥ 2 g/day, $n=184$) compared with low dose (≤ 1.5 g/day, $n=62$) SSZ (Mann-Whitney-U test, data not shown). When consecutive DMARD courses in individual patients were examined, it was found that the proportion of treatments without any AE was higher for the first treatments (62%) than the second treatments (54%; $p<0.01$, χ^2 test statistics) or all other courses together (55%, $p<0.01$). This evaluation assumes that the larger contribution of chloroquine to first courses (32.0%) compared with consecutive ones (13.9%) has no major impact on the results. However, it has to be borne in mind that potentially more toxic DMARDs, like MTX and SSZ, had been used in increasing proportion in consecutive courses (45.1% of first, 55.1% of second, 60.3% of third courses).

The mean time to an AE from the start of treatment was shortest for sweating (3.1 months) and anorexia (4.2 months) and longest for erythema or sun sensitivity (32.5 months) and blurred vision (27.5 months) (fig 1).

Antimalarial drugs and the eye

Regular consultations by specialists—that is, 1–4 ophthalmological examinations a year, have only been performed for patients receiving AM. Interestingly, no case of retinopathy was seen during 285 courses and 536 patient years of chloroquine treatment, suggesting an incidence of $<0.4\%$ of treatments (that is, <0.3 events/1000 patient years). Abnormal results of the eye examinations by specialists (including Amsler grid test, slit lamp examination, and fundoscopy in most cases) mostly showed keratopathies and were seen with an incidence of 3%. Subjective symptoms were reported by the

patients 17 times per 1000 patient years (mostly blurred vision).

Laboratory abnormalities

Abnormal laboratory results (that is, values exceeding the limits of normal as defined by the laboratories that performed the tests) were common, especially shortly after initiation of DMARD treatments. More pronounced abnormalities were seen quite rarely: in 5.0% of all treatments aspartate aminotransferase or alanine aminotransferase levels were ≥ 40 U/l, in 0.8% creatinine levels were ≥ 120 $\mu\text{mol/l}$ or a protein excretion of ≥ 0.5 g/24 h was present. In 3.0% there was a considerable decrease in erythrocytes, leucocytes ($\leq 3.5 \times 10^9/\text{l}$ for both), or platelets ($\leq 100 \times 10^9/\text{l}$).

We also explored a potential correlation between these laboratory abnormalities and congruent clinical symptoms. An abnormal value was considered correlated with a clinical symptom if it was felt associated by clinical judgment and the symptom occurred within the time frame (± 4 weeks) of the laboratory abnormality. Even with this relaxed approach, a correlation was considered possible in only 5.7% of patients.

DISCUSSION

AEs are a major concern in traditional DMARD treatment and are well known. The dilemma of having powerful drug treatments available, on the one hand, and facing serious toxicity, on the other, is not uncommon in medicine. For many years it has been felt that the chronic and non-fatal nature of RA narrows the therapeutic space between risk and benefit (pyramid approach). In this analysis we determined not only the different types of AE, but also their actual incidence in a “real life” setting of about 600 patients with RA from two middle-European clinics and approximately 2400 patient years of treatment with DMARDs.

Nausea, abdominal pain, and rashes were the most commonly encountered AE. The lag periods to the onset of individual AEs were different, which may partly be reflected by dose increases later in the course of DMARD treatment (for example, nausea with increasing doses of MTX). Furthermore, it cannot be assumed that washout periods were considered before a new DMARD treatment was started, and thus in the early phase of a new DMARD AEs might

potentially be still due to the previous DMARD or the transient combination of both drugs. The use of folates was not evaluated here (however, <10% of the patients taking MTX received folates).

Three further subanalyses were performed in the dataset. Firstly, we examined the incidence of AEs in groups receiving a high and a low dose of MTX and SSZ. Interestingly, the rates of AE were similar in the groups receiving different doses. This paradox is likely to be associated with a higher proportion of patients receiving low dose treatments stopping treatment early because of AEs. Vice versa, the application of high dose treatment implies a good tolerability of low doses. Secondly, from our database the incidence of chloroquine retinopathy can be estimated as very low (<0.3 events per 1000 patient years). Recent studies have only discussed hydroxychloroquine retinopathy with an even lower estimation of incidence.¹⁴⁻¹⁶ Thirdly, we tested if the patient's clinical symptoms might be useful for predicting laboratory abnormalities. As in previous studies,¹⁷ we found no correlation of laboratory abnormalities (as objective measures) with clinical symptoms (subjective) of the patient.

Fries *et al* presented results from a chronic disease databank (the ARAMIS Post-Marketing Surveillance Program) in the US (AEs are given in events/1000 patient years) in the early 1990s.¹⁰ The incidences of 18 categories of AE were compared step by step individually for each of the following DMARDs: MTX, AM, OG, PG, D-Pen, and AZA. Interestingly, 55% of the reported incidences from both studies were in the same categories as given in the key to figure 1 (no event/1–10 events/11–50 events/>51 events per 1000 patient years), in 12% the incidences were identical. In addition, our database provides toxicity data on SSZ and combination treatments (which were heterogeneous). In contrast with these consistent results, we also observed apparently lower toxicity of OG compounds and AZA. However, this might be related to the lower number of these DMARDs in our dataset and the less frequent use in more recent years, which may underestimate the incidence of rare AEs.

Data were extracted from doctors' notes in the patient files, and therefore have to be interpreted with caution owing to potentially subjective and inconsistent recording, despite many other merits. Also, patients may either fail to report spontaneously certain AEs, such as mood changes during treatment with SSZ, because they are not easily recognised as AEs; or underreport AEs owing to their satisfaction with treatment; or sometimes be suggestive concerning a potential relationship of AEs and medication—for example, if it is mentioned on the patient information label. Once an AE is recorded, a further issue is the adjudication of the recorded events to the actual treatment and the distinction from other potential causes. Scoring methods, such as the Naranjo score¹⁸ have been developed to estimate the probability of an AE and its relation to treatment. The adjudication process in the present study included all items of the Naranjo score that are available in retrospective analysis. It should also be mentioned that about 9% of patients were rechallenged with the same DMARD type, and one third of these were rechallenged after a previous discontinuation due to an AE, and that this may also bias towards higher frequency of AEs. In conclusion, the discussed limitations seem to be more patient-specific and doctor-specific than dependent on characteristics that have been used in the analyses (such as different types of DMARDs or first v later DMARDs). Moreover, despite these potential limitations, there was remarkable consistency with the results from previous studies.

Another issue of interest relates to our observation that initial DMARD courses were the safest, as we found significantly fewer AEs than in subsequent courses. This may be related to

the practice of prescribing safer drugs at the start of treatment in a new patient, a trend that has been shown for our patients only to a small degree. Also it may constitute one factor among several others why initial DMARD treatments, which are usually given early, are more successful than later ones. In fact, we and others observed that first DMARD courses were maintained longer than subsequent ones,^{19,20} a finding that may reflect both the somewhat better efficacy and lower toxicity of first courses.

With the exception of MTX, traditional DMARDs are likely to be used in decreasing frequencies and/or for decreasing periods of time after the availability of the new generations of DMARDs.²¹⁻²³ Thus this dataset can serve as a basis for comparison of the toxicity of these new DMARDs with the traditional ones in the near future. It will be important to accumulate such data, and to compare them with datasets as presented here, for better understanding of the benefit and risk profile of these new agents.

Authors' affiliations

D Aletaha, T Kapral, J S Smolen, Division of Rheumatology, Department of Internal Medicine III, University of Vienna, Austria

Correspondence to: Dr D Aletaha, Division of Rheumatology, Department of Internal Medicine III, University of Vienna, Vienna General Hospital, Waehringer Guertel 18–20, A-1090 Vienna, Austria; Daniel.Aletaha@akh-wien.ac.at

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UNUSUAL AND MEMORABLE.....

Case Number 26: Systemic idiopathic fibrosis associated with aortitis

Series editor: Gary D Wright

A 41 year old woman presented with an eight month history of general weakness, relapsing pericardial effusion, vertigo symptoms, and a more recent history of dyspnoea. Routine laboratory tests were normal except for a raised C reactive protein concentration (69 mg/l), a leucocytosis (up to $13.3 \times 10^9/l$), and a dysproteinaemia (raised α_2 and γ globulin fractions). Autoantibody tests showed positive rheumatoid factor and negative antinuclear antibody. An idiopathic fibrosclerotic process was suggested by an x ray and magnetic resonance imaging (MRI) examination that showed an increase in heart size, signs of congestion, a thickening of both renal fasciae (up to 15 mm), and a homogeneous and/or nodular mass around the aorta (fig 1A). The diagnosis of a combined mediastinal and retroperitoneal fibrosis was confirmed by biopsy. Moreover, MR angiography of the descending aorta demonstrated the following signs of infrarenal

Figure 1 Magnetic resonance imaging showing the thickening of both fasciae (A), a homogeneous and/or nodular mass around the aorta (A), and signs of infrarenal aortitis.

aortitis (fig 1B): (a) stenosis (30–40% lumen reduction); (b) thickening and structural abnormalities of the vessel wall with contrast enhancement.

Combined prednisolone/cyclophosphamide treatment was started. A recent follow up visit (four months later) showed no radiological signs of further progression.

O Schultz, S Schuchmann, G-R Burmester, F Buttgerit

Department of Rheumatology and Clinical Immunology, Charité University Hospital, D-10117 Berlin, Germany

Correspondence to: Professor F Buttgerit; frank.buttgerit@charite.de