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Adverse reactions to disease-modifying anti-rheumatic drugs in clinical practice

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Summary

We analysed computerized records of disease-modifying anti-rheumatic drug (DMARD) monotherapy to determine how long rheumatoid arthritis (RA) patients continued on five commonly prescribed DMARDs, and the incidence and time-course of adverse drug reactions (ADRs) they experienced. We studied the records for 3923 courses of DMARDs given to a cohort of 2170 patients monitored for a total of 9378 treatment-years. Methotrexate (MTX) was the DMARD most likely to be continued long-term; $<45\%$ of patients had discontinued the drug after 96 months. For the other DMARDs, the time until 50% discontinued due to ADRs or inefficacy was 43.3 months for sulphasalazine (SAS), 33.9 months for D-penicillamine (DPN) and 26 months for myocrisin. Most monitored ADRs requiring drug discontinuation were seen early in therapy, with a median time to onset of <6 months; the important exceptions to this were haematological ADRs to MTX, where the median delay to neutropenia was 16.9 months, and that to thrombocytopenia was 9.4 months. Monitored ADRs (identified by blood or urine tests) were seen least frequently with SAS (one ADR in every 35 patient-years of monitoring) but this apparent advantage was offset by a high incidence of gastrointestinal ADRs and inefficacy. Overall, one toxicity reaction requiring drug discontinuation was identified for every 15.9 patient-years of monitoring.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by progressive joint erosion that accumulates over a period of years, resulting in significant disability,[1] morbidity[2] and increased mortality[3,4] among sufferers. Various 'second-line' or disease-modifying anti-rheumatic drugs (DMARDs) have been used over the last 50 years to provide symptomatic relief, reduce disease activity and disability, and to prevent radiological progression.[5] All of these drugs show significant toxicity, such that their use requires regular monitoring,[6,7] although there is disagreement as to the exact nature and duration of monitoring required.[8] Monitoring schedules have significant cost and resource implications. Many rheumatologists believe that if a patient has been taking a DMARD at stable dosage for a long period of time, then the risk of toxicity is likely to be low, and hence monitoring need not be as rigorous.[9,10] There is little direct evidence available to support this view, as most prospective studies of DMARD toxicity are short-term,[11] and undertaken in selected patients monitored under drug trial protocols. Long-term outcomes in clinical practice are much poorer[12,13] than clinical trial data would suggest, and late adverse drug reactions (ADRs) do occur.[14] Long-term data derived from unselected patients seen in everyday clinical practice would provide the most useful information for planning DMARD treatment regimens in the out-patient setting. Cross-sectional studies of current clinic attenders are, however, vulnerable to left censorship bias, whereby the clinic population represents a self-selected group of patients, and those who die or

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who are lost to follow-up are under-represented.[15] Registries of all patients who have ever attended, together with high-quality records of such patients, are required to avoid this problem.

We are fortunate to have such a register: the computerized database we have been using to assist in DMARD monitoring at our unit since 1986. This affords us an opportunity to study not only the frequency of ADRs but also the time-course over which they occur, and hence target drug monitoring to the periods of greatest risk. In this study, all RA patients commencing DMARD monotherapy in our clinic since 1986 were followed according to standardized protocols to determine: (i) how long patients stay on DMARD monotherapy; (ii) the incidence of monitored ADRs with each DMARD; and (iii) the time-course to onset of monitored ADRs with different DMARDs.

Methods

The DIAMOND (Diagnostic and Monitoring Database) programme was written by one of us (MFS) and runs across a local area network of PCs available throughout the Rheumatology Department. Drug histories, blood test results and clinical correspondence files for each patient can be accessed over the system, which is linked to the main hospital pathology database. The software was designed primarily as a DMARD therapy record and planning aid; the database does not include measures of function or disease activity other than ESR and haemoglobin level. Patients are enrolled on to the database when first starting a monitored DMARD, and their clinical diagnosis is recorded at this time and then modified as necessary.

All patients on DMARD therapy attend nurse-run drug monitor clinics, weekly for the first month of treatment and monthly thereafter, for as long as the DMARD is continued. Monitoring is only relaxed for patients on SAS, who attend 3- to 6-monthly after the first 6 months. A report is produced for each clinic identifying patients whose results do not fall within defined normal parameters, or where there is a worrying trend (for example, three sequential falls in platelet count within the normal range). These warning thresholds were defined by a consensus of four consultant rheumatologists in the unit, and have been described elsewhere.[16] The report is reviewed by the supervising physician, who decides whether DMARD doses should be changed or stopped, or further investigations arranged. Lists of patients overdue for monitoring appointments are automatically produced, who can then be contacted by the Rheumatology nurse; very few patients are lost to follow-up. In a small number of cases (49/4374 courses of therapy: ~1.1%), responsibility for monitoring has been passed to the GP, but the majority of courses of DMARDs initiated in our unit are monitored directly by us for their entire duration.

For this study, we analysed all records on the database as of 1 November 1999. Inclusion and exclusion criteria and data analysis are described below.

Inclusion criteria

(i) Patients with a clinical diagnosis of rheumatoid arthritis. (ii) Courses of DMARDs (SAS, MTX, DPN, myocrisin and auranofin) started since 1986. (iii) Second or subsequent courses of DMARDs where the initial course had been started since 1986 (and was therefore included). (iv) Courses of cyclophosphamide and azathioprine (AZP) were included in the secondary ADR incidence and time-courses analysis only, to show comparative toxicity.

Exclusion criteria

(i) Patients with a clinical diagnosis other than rheumatoid arthritis. (ii) Courses of DMARDs started prior to 1986. (iii) Second and subsequent courses of DMARDs where the initial course had been started prior to 1986 (and was therefore not eligible for inclusion). (iv) Courses of cyclosporin A (insufficient numbers for meaningful analysis). (v) Courses of cyclophosphamide and AZP were excluded from the primary survival analysis due to insufficient numbers, but included in the secondary analysis (as explained above). (vi) Courses of antimalarial DMARDs (hydroxychloroquine or chloroquine), as these are not monitored by blood tests and hence not included on the database. (vii) courses of combination therapy (see below).

Combination therapy

For the purposes of this study, we only analysed courses of DMARD monotherapy. Courses of two or more DMARDs started simultaneously were excluded. Where a second DMARD was used as 'add in' therapy, the course of the first DMARD was only analysed up until that point, and then treated as a treatment failure due to inefficacy. The course of the second 'added in' DMARD was excluded from analysis if the period for which two DMARDs were being taken concurrently exceeded one month. This was to allow analysis of courses of

therapy where there was a short period of overlap during which an earlier DMARD was tailed off.

Data analysis

The DIAMOND database does not contain detailed statistical analysis tools. A copy of the database was transferred to Microsoft Access 2000 for data mining. Statistical analyses used SPSS v. 9.0 and GraphPad Prism v. 3.00 for Windows was used for calculating the confidence limits of Kaplan-Meier survival curves by Greenwood's method.

ADRs analysed in this study were those leading to DMARD discontinuation; reactions that led to dose changes were not included.

For the purpose of Kaplan-Meier survival analysis, ADRs that led to a hiatus in therapy of $\leqslant 3$ months were ignored, the two courses of therapy being analysed as one course. Courses of therapy interrupted for >3 months were analysed as separate courses.

For ADR incidence and time-course analysis, any ADRs resulting in discontinuation were included, even if the drug was later restarted within a few days. This was because we were interested in the incidence of all ADRs severe enough to require drug discontinuation.

Results

Kaplan-Meier survival curves

Threr were 2170 RA patients suitable for analysis (Table 1).These patients received in total 4374 courses of DMARD therapy; 11 126 treatment-years of monitoring. Of these, 451 courses of therapy concerned combination DMARD treatment (327 where a second drug was 'added in' and 114 courses where two or more drugs were started simultaneously), and were excluded, leaving 3923 courses of therapy covering 9378 treatment-years of monitoring. Numbers of patients exposed to each drug and duration of therapy are shown in Table 2. Figure 1 shows the changes in DMARD prescribing rates over the study period.

Of the 3923 courses of therapy, 1487 were ongoing at the time of analysis. The reasons given for definitive DMARD discontinuation in the other 2436 courses are shown in Table 3. Of note is that monitoring was discontinued in only 0.7% because the patient had left the district; in a further 1.7% responsibility for monitoring was handed over to the GP.

Kaplan-Meier survival curves were plotted for each drug to compare rates of discontinuation over time. The Kaplan-Meier method estimates the probability of a defined event occurring by a given time, in the presence of cases in the studied population where the defined event does not occur (known as censored cases).[17] For our purposes, these included courses of DMARD therapy continuing at the time of analysis and courses where the drug was discontinued for a reason other than the defined event. We plotted curves comparing discontinuation rates due to ADRs only (Figure 2**a**). To estimate the overall probability of remaining

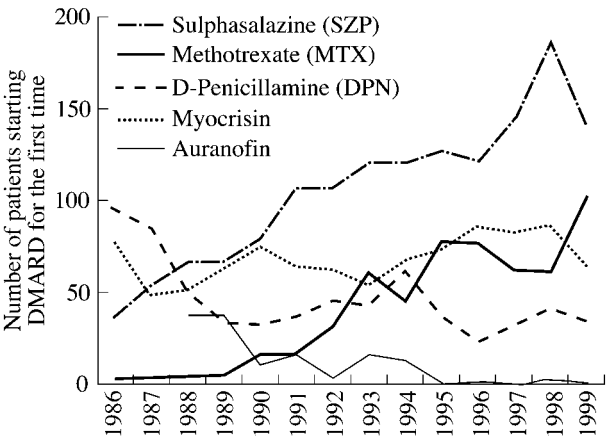

Figure 1. Change in DMARD prescribing rates 1986–99. Database analysed as of 1 November 1999, so data for 1999 only represents 11 months accumulation.

Table 1 Patient characteristics

	Male	Female
Number	799	1371
Mean age (±SD) at database entry (years)	58.1 (±11.3)	58.1 (±12.5)
Mean duration of RA at database entry (years) [range, median]	5.9 (±7.9) [0–46, 5]	6.8 (±8.6) [0–52, 5]
Mean time on monitored therapy (years)	5.0 (±4.1)	5.6 (±4.2)
Number still on monitored therapy (%)	510 (63.8%)	868 (63.3%)
Number deceased (%)	138 (17.3%)	175 (12.8%)

Data are for 1 November 1999, when the database was analysed.

Table 2 Numbers of patients exposed to each drug and years of monitoring

Drug	Patients exposed (*n*)*	Courses of therapy	Years monitored
Sulphasalazine	1321	1426	3158
Myocrisin	862	957	2308
D-Penicillamine	582	646	1889
Methotrexate	551	591	1402
Auranofin	128	135	310
Azathioprine	85	88	187
Cyclophosphamide	68	80	124
Totals		3923	9378

*Most patients were exposed to more than one drug. Courses of DMARD therapy given in combination have been excluded.

Table 3 Reason for DMARD monotherapy discontinuation in 2436 courses of completed therapy

Reason for drug discontinuation	Number of courses	%
Inefficacy	483	19.9
Changed to combination therapy	327	13.5
Abdominal pain, diarrhoea, nausea or vomiting/mouth ulcers	286	11.8
Skin rash/pruritus	260	10.8
Patient deceased	188	7.7
Blood dyscrasia	144	5.9
Other reason/protocol	136	5.5
None given	115	4.7
Proteinuria/haematuria/renal impairment	101	4.1
Other ADR	94	3.9
Patient unhappy about continuing monitoring	76	3.1
GP undertaking monitoring/ Patient moved district	60	2.4
Liver function abnormalities	46	1.9
Intercurrent infection/illness	43	1.7
Non-compliance with therapy/ patient misunderstanding	20	0.8
Clinically improved	17	0.7
Pneumonitis	16	0.7
SLE	10	0.4
Myasthenia gravis	8	0.3
Pregnancy	6	0.2
Totals	2436	100

on the drug long-term, further curves were plotted where discontinuation due to drug inefficacy as well as ADRs were the defined events (Figure 2**b**). Paired DMARD survival curves were compared by log rank test (Tables 4 and 5).

MTX was the DMARD least likely to be discontinued due to ADR, followed by SAS. There were no differences between myocrisin, auranofin and DPN in terms of ADRs (Figure 2**a**, Table 4). The survival curves tended to plateau after 48–60 months, which probably reflects a decline in ADR rate in patients on long-term monotherapy.

When discontinuations due to inefficacy are included (Figure 2**b**, Table 5), the curves no longer plateau. This reflects late discontinuations due to loss of efficacy, or addition of other DMARDs in combination—which we treated as discontinuation for analysis purposes. MTX was superior to all the other drugs in the long-term. SAS was statistically better than the other DMARDs, but the survival curves for SAS, myocrisin and DPN were very close, and the difference might not be clinically significant. Auranofin was inferior to all the other drugs, and although there were fewer patients in the auranofin group, the 95%CIs for the survival curves showed that this was a significant clinical difference.

Table 6 shows median DMARD survival times—the time by which only 50% of patients remain on a given DMARD, the rest having discontinued either due to ADRs or inefficacy. Although

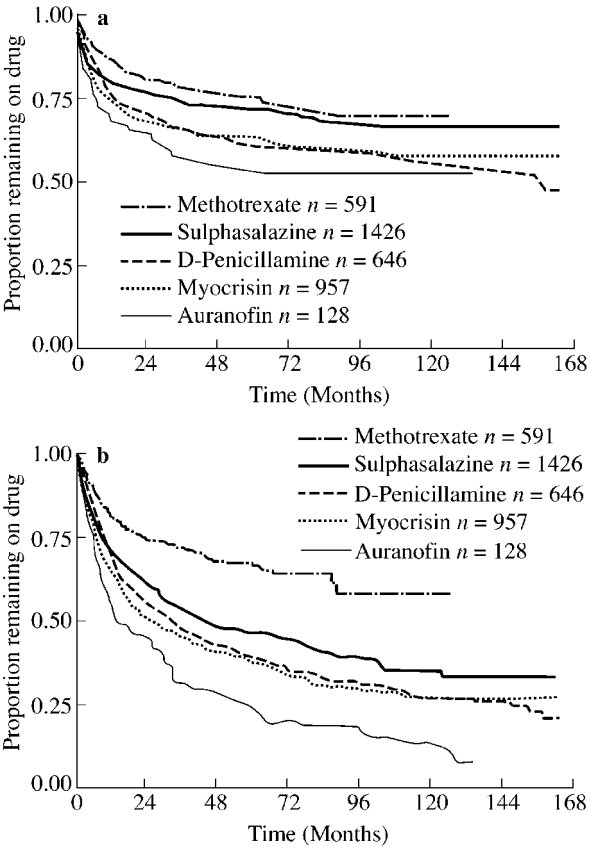

Figure 2. (**a**) DMARD discontinuations for ADRs only. (**b**) DMARD discontinuations for ADRs and inefficacy.

Table 4 Comparison of survival curves in Figure 2**a**

	SAS	DPN	Myocrisin	Auranofin
MTX	$\chi^2 = 6.45$ $p < 0.01$	$\chi^2 = 18.0$ $p < 0.0001$	$\chi^2 = 24.8$ $p < 0.0001$	$\chi^2 = 22.1$ $p < 0.0001$
SAS		$\chi^2 = 6.14$ $p < 0.01$	$\chi^2 = 10.6$ $p < 0.001$	$\chi^2 = 10.3$ $p < 0.001$
DPN			$\chi^2 = 0.25$ $p = 0.6$ NS	$\chi^2 = 3.23$ $p < 0.07$ NS
Myocrisin				$\chi^2 = 2.13$ $p < 0.15$ NS

The Kaplan-Meier survival curve for the DMARD in the left-hand column is compared with the curve for the DMARD in the top row. Numbers in the intersecting box are the χ^2 statistic and p value for the logrank test comparing these two curves.

Table 5 Comparison of survival curves in Figure 2**b**

	SAS	DPN	Myocrisin	Auranofin
MTX	$\chi^2 = 45.7$ $p < 0.0001$	$\chi^2 = 60.1$ $p < 0.0001$	$\chi^2 = 85.1$ $p < 0.0001$	$\chi^2 = 88.6$ $p < 0.0001$
SAS		$\chi^2 = 4.12$ $p < 0.04$	$\chi^2 = 13.4$ $p < 0.0002$	$\chi^2 = 29.0$ $p < 0.0001$
DPN			$\chi^2 = 1.4$ $p = 0.24$ NS	$\chi^2 = 16.9$ $p < 0.0001$
Myocrisin				$\chi^2 = 11.2$ $p < 0.0008$

The Kaplan-Meier survival curve for the DMARD in the left-hand column is compared with the curve for the DMARD in the top row. Numbers in the intersecting box are the χ^2 statistic and p value for the logrank test comparing these two curves.

Table 6 Median survival time of courses of DMARD therapy (discontinuations due to ADRs and inefficacy)

Drug	Median survival time in months (95% CI)
Sulphasalazine	43.3 (30.8–55.6)
Methotrexate	$>96^*$
D-Penicillamine	33.9 (25.7–40.2)
Myocrisin	26.0 (19.9–32.1)
Auranofin	14.7 (3.8–25.6)
Azathioprine	13.1 (0–29.1)

*Median survival time was not calculable for MTX, as <45% of patients had discontinued therapy at 96 months. Mean survival time was 85.7 (95%CI 79.7–91.7 months; limited to 125.7) months.

median survival for SAS (43.3 months) was better than for either DPN (33.9 months) or myocrisin (26.0 months), the 95%CIs overlap. Median survival time was not calculable for MTX, as at the time of analysis fewer than 45% of eligible patients had discontinued therapy; we estimate it to be >96 months.

Incidence of adverse reactions

Table 7 shows the incidence of the principal monitored toxicities as a function of the number of years for which each drug was monitored. The overall incidence was 591 monitored ADRs requiring drug discontinuation in 9378 years of monitoring—one per 15.9 treatment-years.

Oral cyclophosphamide was the most toxic DMARD, with one ADR observed for every 5.6 years of monitoring. The least toxic agent was SAS, with one discontinuation due to monitored ADR every 35.1 treatment-years, and not MTX as might have been expected (one monitored ADR per 16.1 treatment-years). This apparent paradox is explained by the high rate of SAS discontinuation from other ADRs, principally skin rashes and gastrointestinal reactions, which were not monitored for by blood or urine tests (Table 8). MTX was much better tolerated in this respect.

Significant neutropenic reactions were equally common with MTX and SAS (one reaction per 58.4 years of monitoring for MTX, one per 67.2 years for SAS), although the former was much more likely to disturb liver function (one reaction per

Table 7 Incidence of monitored toxicities requiring drug discontinuation

Drug	Total years monitored	Monitored Adverse Drug Reaction requiring discontinuation													
		Neutropenia		Low platelets		Haematuria		Proteinuria		Liver function abnormality		Pulmonary reaction		Totals	
		ADRs	Years/ADR	ADRs	Years/ADR	ADRs	Years/ADR	ADRs	Years/ADR	ADRs	Years/ADR	ADRs	Years/ADR	ADRs	Years/ADR
Sulphasalazine	3158	47	67.2	18	175	2	1579	3	1053	20	158	–	–	90	35.1
Methotrexate	1402	24	58.4	13	108	–	–	2	701	35	40.1	13	108	87	16.1
D-Penicillamine	1889	16	118	120	15.7	8	236	67	28.2	1	188	1	188	213	8.9
Myocrisin	2308	25	92.3	48	48.1	4	577	64	36.1	10	231	2	1154	153	15.1
Auranofin	310	2	155	4	77.5	1	310	5	62.0	–	–	1	310	13	23.8
Cyclophosphamide	124	10	12.4	9	13.8	3	41.4	–	–	–	–	–	–	22	5.6
Azathioprine	187	4	46.7	4	46.7	–	–	–	–	5	37.4	–	–	13	14.4
Totals	9378	128	73.3	216	43.4	18	521	141	66.5	71	552	17	552	591	15.9

40.1 years for MTX, only one per 158 years for SAS). Incidence of proteinuria was similar for DPN (one per 28.2 years) and myocrisin (one per 36.1 years).

Table 8 shows incidence figures for other side-effects, not monitored by blood tests but commonly leading to drug discontinuation. The most important figures here are the high incidences of gastrointestinal reactions with SAS (one per 16.5 years) and skin rashes with myocrisin (one per 11 years). Auranofin's principal toxicity was gastrointestinal upset (one per 7.4 years); by contrast, myocrisin was the best tolerated drug for gastrointestinal ADRs, with only one ADR every 64.1 years. Of the DMARDs analysed, MTX was least likely to cause skin rashes, with only one ADR every 117 years. Data for rates of intercurrent illness and death are provided for comparison; attribution is uncertain, as patients with more severe disease and hence a poorer prognosis were likely to be taking more toxic drugs. The high rate of discontinuations due to intercurrent illness seen with MTX, second only to cyclophosphamide, is interesting. This may represent perceived risk among physicians, who might be more likely to stop MTX in a patient with sepsis than to stop myocrisin.

Time-course of adverse reactions

Duration of courses of SAS, MTX, DPN and myocrisin discontinued due to monitored toxicities are shown in Figure 3. Most monitored ADRs with SAS occurred early; median times to onset of neutropenia, thrombocytopenia and liver function test (LFT) abnormality were 2.1, 1.4 and 1.9 months respectively. This contrasts with MTX, where the corresponding values were 16.9, 9.4 and 5.6 months. Of the 24 neutropenic ADRs to MTX, 14 occurred after the patient had been on the drug for >12 months; all of these patients were on a stable dose of MTX, with no dose increases for at least six months previously. Mean dose at the time of neutropenia in these patients was 12.3 mg (range 5–20 mg) weekly.

Pneumonitis was given as the reason for discontinuation in 13 courses of MTX: median delay was 3.0 months (range 3 weeks to 45 months). On inspection of the notes, the late reaction at 45 months was reclassified as an asthma attack; the longest delay experienced after starting MTX until a true pneumonitis in our cohort was 12 months.

The incidence of proteinuria was similar with DPN and myocrisin, but occurs earlier with the latter drug: median delay was 5.4 months for myocrisin compared with 8.8 months for DPN.

The unusual autoimmune phenomena seen with DPN all occurred relatively late: median delay for myasthenic reactions (eight cases) was 11.0 months (range 7.2–30.5) and for DPN-induced SLE (nine cases) the median delay was 22.7 months (range 5.1–36.7 months; data not shown in Figure 3). There was one case of SAS-induced SLE, developing after 28.5 months.

Discussion

We believe this is the largest observational study of DMARD toxicity reported in the UK to date. The patients included had clinical diagnoses of rheumatoid arthritis, and are an unselected sample of clinic attenders at a single unit. This is a pragmatic study, and its strength is that its findings were observed in a 'real world' population rather than a research context. This is what happens in clinical practice when 2000 patients with rheumatoid arthritis are given DMARD therapy and monitored diligently by a number of physicians and nurses for over a decade in a District General Hospital Rheumatology clinic.

That MTX is better tolerated than other DMARDs is not a new finding, but the magnitude of the difference shown in our population is larger than in most previous series. Our study provides evidence that this advantage continues over a longer period of time than previously reported. Pincus *et al.*[18] (1992) found median survival times of >60 months for MTX; our data shows median survival of >96 months. The other DMARDs used in our cohort also showed longer median survival times than in their study: for example, 26 months for myocrisin and 34 months for DPN, compared with 25 months and 21 months, respectively. It is doubtful whether these small differences are clinically significant.

SAS was not in current use in the US in 1992, so we looked to the UK for comparative data. Situnayake *et al.* (1987)[19] found that only 19% of patients on SAS continued therapy for 5 years; in our population the proportion was 46%. In the same study, 17% of patients remained on DPN and 8% on intramuscular gold after 5 years; among our patients the proportions were 38% and 37%, respectively. Wolfe *et al.* (1990)[20] also showed slightly shorter survival figures to our own, with 50% of patients still on MTX at 54 months, on myocrisin at 20 months and on DPN at 22 months.

There may be several explanations for why our observed survival times are longer than those previously reported. Situnayake *et al.* used the time elapsed until first discontinuation in their life table analysis, even if the DMARD was discontinued only for a short time; on the other hand, Wolfe *et al.* allowed short interruptions of up to 4 weeks. In Pincus *et al.*, a DMARD could be stopped for up to 6 months before being considered as two separate courses of therapy. In our study, we limited any break in DMARD therapy to 3 months before assuming a significant discontinuation had occurred. This methodological difference might account for some of the observed difference in survival times between the different studies. In other respects, our study population appears to be similar to theirs in terms of age at inclusion—although the cohort of Pincus *et al.* had a longer mean disease duration (12.1 years vs. 6.4 ± 8.3 years in our cohort).

The high incidence of monitored ADRs with DPN (one every 8.9 years) was due to the excess of thrombocytopenic reactions. This was unexpected: by contrast, Comer *et al.*[9] (1995) in a series of 390 RA patients monitored in three London hospitals for 1560 patient years, found only one thrombocytopenic reaction in every 156 years of treatment with DPN; we found one in every

Table 8 Incidence of other toxicities requiring drug discontinuation

Drug	Total years monitored	Reason for discontinuation							
		Skin rash		GI upset		Intercurrent illness		Death	
		ADRs	Years/ADR	ADRs	Years/ADR	ADRs	Years/ADR	ADRs	Years/ADR
Sulphasalazine	3 158	95	33.2	192	16.4	9	351	29	109
Methotrexate	1 402	12	117	35	40.1	31	45.2	32	43.8
D-Penicillamine	1 889	61	31.0	74	25.5	7	270	53	35.6
Myocrisin	2 308	209	11.0	36	64.1	14	165	58	39.8
Auranofin	310	19	16.3	42	7.4	3	103	5	62
Cyclophosphamide	124	1	124	10	12.4	9	13.8	9	13.8
Azathioprine	187	4	46.8	6	31.2	3	62.3	6	31.2
Totals	9 378	401	23.4	395	23.7	76	123	192	48.8

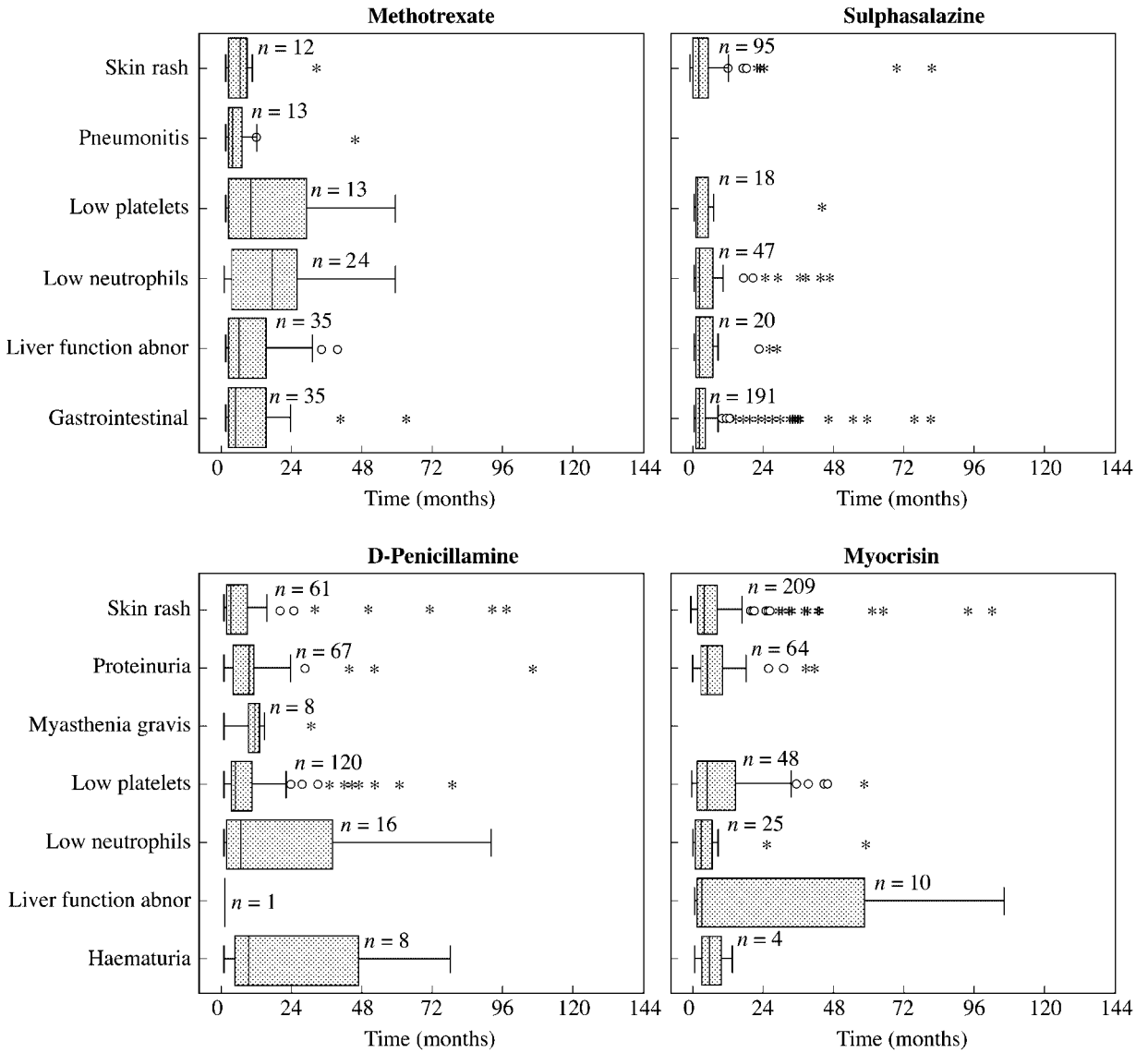

Figure 3. Time spread of monitored ADRs to MTX, SZP, DPN and myocrisin. Boxes represent the interquartile range (IQR). Vertical line is the median ADR. Whiskers show the largest and smallest values within 1.5 IQRs. Circles show outliers falling $>1/5$ and <3 IQRs from the median, asterisks extreme values >3 IQRs from the median.

15.7 years. The discrepancy is large and hard to explain; we included all such reactions, and some transient reactions might have been missed in a less rigorous clinical setting. Of the 120 thrombocytopenic ADRs observed, only 31 of these led to drug discontinuation for a period of 3 months or more, but this remains equivalent to a rate of one ADR per 60.9 years, almost treble that reported by Comer.

Specialist Rheumatology nurse support

We are fortunate in having a dedicated team of specialist Rheumatology nursing staff, who administer the DMARD monitoring clinics on a day-to-day basis. Much of the data entry is done by these nurses, and a secondary role of the DIAMOND database is to act as a communications tool between the medical and nursing staff. They have a key role in patient education, both about rheumatic diseases and what to expect from DMARD therapy; they also run a telephone helpline for patients on DMARDs. We feel that this intensive support helps to keep patients compliant with DMARD therapy in the face of minor symptoms that might otherwise result in unnecessary discontinuation.

Clinical effectiveness

Rheumatoid arthritis is a chronic disease, and any DMARD that is used to treat RA must be tolerable in the long-term to be effective. Although newer agents such as leflunomide show promise of efficacy, long-term clinical effectiveness data is

(as yet) lacking. Observational studies such as this one, although unable to provide hard evidence of clinical efficacy (due to the lack of control groups, randomization and disease activity criteria) do provide an estimate of clinical effectiveness—the probability that a patient will discontinue treatment before therapy is likely to show any benefit at all. On this basis, MTX is the drug with the greatest potential to be effective, because patients are more likely to tolerate it long-term.

Implications for DMARD monitoring

The ADR time-course analysis shows that the majority of ADRs occur early in therapy, supporting the common practice of monitoring more closely during this period. This implies that most ADRs represent hypersensitivity to the relevant DMARD. The clear exception is MTX: whereas pneumonitic (presumed hypersensitivity) reactions with this drug are seen early (median delay to onset only 3 months), neutropenic and thrombocytopenic reactions occurred much later. Late haematological reactions to MTX occurred when the drug was at a steady dosage, implying they are due to a cumulative effect rather than to dose changes. The implication for DMARD monitoring is clear: whereas monitoring intervals for most DMARDs may be relaxed after the first 12 months, MTX must continue to be monitored in the long term, even when the patient has been well on a stable drug dose for many months.

Potential sources of bias

Our data was collected prospectively to assist with monitoring of DMARD therapy in clinical practice, and not with research *per se*. Similarly, the reasons given for drug discontinuation do not imply that specified thresholds for cell counts or transaminase levels had been exceeded, but that the judgement of the supervising clinician in the clinical context was that the drug should be stopped. Our patients were not rigorously rechallenged with each DMARD to verify that the drug had been responsible for the observed reaction, and they may have been taking other medications, particularly NSAIDs or corticosteroids, that may have affected observed toxicity.

Physicians' beliefs are a probable source of bias in non-randomized and uncontrolled observational studies. This effect is particularly hard to tease out where so many physicians and nurses have been involved in making therapeutic decisions, as in our cohort. The incidence of potentially serious ADRs, such as neutropenia or abnormal liver function, is less likely to be altered by practitioner bias than the incidence of 'minor' ADRs such as alopecia with MTX or dysgeusia with DPN. For example, if a patient discontinues MTX claiming that it has caused their alopecia, but the physician reviewing the patient does not believe that MTX causes this side-effect, this might be coded on the database as non-compliance rather than as an ADR. More importantly, physicians might be biased to discontinue MTX earlier in a dyspnoeic patient, and code this as pneumonitis, than in patients who develop similar symptoms on myocrisin or DPN. In patients with pre-existing chest conditions, such decisions are particularly difficult and subjective. Where measured indices, such as neutrophil or platelet counts are concerned, the physician's decisions are more transparent, and the conclusions that can be drawn have a more solid basis.

In the primary analysis, we took no account of whether the course of DMARD therapy was the first that a patient had received, or whether it was a second or third trial of the same drug. Arguably, for second and subsequent courses of the same DMARD, the patient has a higher risk of ADR recurrence. To examine this hypothesis, we plotted further survival curves comparing discontinuation rates due to ADRs for first and subsequent courses for each DMARD (data not shown). Logrank test χ^2 statistics comparing the curves for each drug varied from 0.106 to 1.63; none reached statistical significance.

In our patients with mild non-erosive disease, the antimalarial DMARDs hydroxychloroquine and chloroquine are sometimes used as initial therapy, only switching to monitored DMARDs when these drugs fail to be effective. Thus, some of the patients included in the database have already failed one DMARD prior to inclusion (i.e. they are a group selected for DMARD failure). If this were to produce a systematic bias, we would expect it to *increase* the rate of subsequent monitored DMARD failure, so the low rates of discontinuation can not be explained on this basis.

Rather than being 'naive' patients with early disease, these patients had a median prior duration of RA of 5 years. It is possible that their prior treatment (not known) could have affected the results.

Use of NSAIDs and corticosteroids was not controlled for in our cohort and could potentially have influenced observed rates of DMARD efficacy and ADRs. There may be systematic biases in terms of which DMARDs are given with corticosteroids: certainly, most patients on AZP and cyclophosphamide receive corticosteroids, but it is unclear whether patients on MTX, myocrisin or

DPN receive equal exposure. Pincus *et al*.[17] found that patients on both MTX and low-dose prednisolone had better long-term drug continuation than those on MTX alone; there was no effect on the discontinuation rates of the other DMARDs studied.

Utley *et al*. have recently questioned the validity of Kaplan-Meier plots when applied to drug studies in rheumatology.[21] They argue that the underlying assumptions upon which Kaplan-Meier analysis depend may not hold, particularly when recruitment into a study takes place over an extended time period. For example, we cannot assume that a (hypothetical) patient recruited in 1989 and started on MTX experiences the same ADR hazard as a patient recruited in 1999. Similarly, two patients recruited in 1989 and started on MTX, one immediately and one 5 years later after unsuccessful treatment with two other DMARDs, may not experience the same hazard of discontinuation from ADRs or inefficacy. Intuitively, it seems unlikely that these assumptions will hold. At the very least, improvements in our practice over the last 13 years ensure that patients we see in our clinics today start DMARDs earlier in their disease, receive folic acid with their MTX[22] and are provided with appropriate information, reassurance and ready access to a telephone helpline.

The distinction between a statistically different survival curve and a meaningful clinical difference is a key point. Whether the underlying reasons are purely pharmacological or not, courses of MTX given in our clinical cohort were clearly continued for longer than other DMARDs. The slight differences seen between SAS, myocrisin and DPN are less likely to be of clinical relevance despite their 'statistical significance'. We have tried to present incidence and time-course data unadorned, and point out only the clear clinical differences in our experience of monitoring these drugs.

Conclusions

MTX was the best tolerated DMARD long-term, with fewer than 45% of patients having discontinued therapy after 96 months. Sulphasalazine had the lowest incidence of monitored ADRs requiring drug discontinuation, but in survival analyses came second to MTX in long-term tolerability, due to a higher incidence of other ADRs and more discontinuations due to inefficacy. Monitored ADRs occurred early in therapy, so monitoring should be concentrated on this period; however late reactions do occur, particularly with MTX. Other, more unusual, late reactions include abnormal liver function tests with myocrisin and autoimmune phenomena with DPN.

Consistent DMARD monitoring in large numbers of patients is facilitated by dedicated computer monitoring systems, which help not only with early recognition of potential toxicity but also with patient follow-up and compliance. Our data indicate that deployment of such a system, with intensive monitoring and ease of patient access to specialist rheumatology nurse expertise, optimizes DMARD continuation in the long-term.

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