Treatment of Psoriatic Arthritis and Rheumatoid Arthritis with Disease Modifying Drugs — Comparison of Drugs and Adverse Reactions

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ABSTRACT. ***Objective.*** Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are chronic inflammatory diseases of the musculoskeletal system. Although it seems likely that these conditions have a different pathogenesis, the drugs used to treat them are the same. Our study used a cross-sectional clinical database to compare drug use and side-effect profile in these 2 diseases.

Methods. The CASPAR study collected data on 588 patients with PsA and 536 controls, 70% of whom had RA. Data on disease modifying drug treatments used over the whole illness were recorded, together with their outcomes, including adverse events, for RA and PsA.

Results. For both diseases methotrexate (MTX) was the most frequently used disease modifying drug (39% of patients with PsA, 30% with RA), with over 70% of patients in both diseases still taking the drug. Other drugs were used with the following frequencies in PsA and RA, respectively: sulfasalazine 22%/13%, gold salts 7%/11%, antimalarial drugs 5%/14%, corticosteroids 10%/17%, and anti-tumor necrosis factor (TNF) drugs 6%/5%. Compared to RA, cyclosporine and anti-TNF agents were less likely to be ineffective in PsA. Compared to RA, subjects with PsA were less likely to be taking MTX and more likely to be taking anti-TNF agents. Hepatotoxicity with MTX was more common in PsA, and pulmonary toxicity with MTX was found more often in RA.

Conclusion. These data provide insight into prescribing patterns of disease modifying drugs in RA and PsA in a large international cohort, together with the differential adverse events of these drugs between these diseases. (First Release Jan 15 2008; J Rheumatol 2008;35:472–6)

Key Indexing Terms:
PSORIATIC ARTHRITIS RHEUMATOID ARTHRITIS ADVERSE EFFECTS
DISEASE MODIFYING DRUGS TREATMENT ANTI-TUMOR NECROSIS FACTOR DRUGS

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis. Recent developments have seen the proposal of new internationally agreed classification criteria[1] and a review of evidence for the efficacy of disease modifying drugs[2]. Consistent with the recent upsurge in interest in this condition, the best quality evidence for treatment efficacy is for the more recently introduced pharmaceuticals, leflunomide and anti-tumor necrosis factor (TNF) drugs. Low-dose weekly oral or systemic methotrexate (MTX) is widely used to treat PsA, yet the evidence base for the use of it is poor, graded as at best level B for polyarticular disease in the recent review[3]. Further, treatment trials are constrained in ways that may detract from the use of the drug in everyday practice — patients entered into trials are often a very select group with little comorbidity[4], which confounds extrapolation of drug use to a wide spectrum of patients.

There is also the question of the differential adverse event profile for each of the drugs used to treat PsA and rheumatoid arthritis (RA). For example, hepatotoxicity with MTX is regarded as more frequent when this drug is used to treat psoriasis and PsA than when it is used in RA[5]. The reverse is true for pulmonary complications of MTX use, which may reflect the more frequent involvement of the lung in RA[6]. The published data to support these assertions are relatively limited and lack appropriate control of possible confounding factors such as preexisting lung disease and alcohol consumption.

The CASPAR study (ClASsification criteria for Psoriatic ARthritis) collected clinical, radiological, and laboratory data on 588 patients with physician-diagnosed PsA and 536 controls with other inflammatory arthritis, 70% of whom had

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Supported by the European League Against Rheumatism, Barnsley District NHS Trust, Groote Schuur Hospital, Cape Town, South Africa; Department of Medical Sciences, University Hospital, Uppsala, Sweden; Krembil Foundation; St. Vincent's University Hospital Radiology Department, Dublin, Ireland; Inkosi Albert Luthuli Central Hospital, Durban, South Africa; El Ayachi Hospital, Salé, Morocco; National Psoriasis Foundation, USA; The Foundation for Scientific Research of the Belgian Society of Rheumatology; and Arthritis New Zealand. Dr. Taylor was supported by a Dorothy Eden Fellowship, Arthritis New Zealand.

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Accepted for publication October 24, 2007.

RA[1]. The CASPAR study also provided an opportunity to review the use of disease modifying drugs across a wide spectrum of patients from an international cohort. The aim of this study was, therefore, to examine the disease modifying drugs used and their efficacy and adverse event profile in patients with PsA, and to compare these with drugs used in patients diagnosed with RA.

MATERIALS AND METHODS

Ethical approval for this study was obtained at each of the contributing study sites. Consecutive clinic attendees with physician-diagnosed PsA were enrolled into the study by 30 rheumatology clinics in 13 countries. Controls were the next clinic attendee with inflammatory arthritis. It was prespecified that at least 50% of controls were to have RA to reflect the disease distribution seen in normal rheumatological practice. Data were recorded onto standardized forms and included demographic and clinical data as described[1]. In addition, data on disease modifying treatment were recorded. The sequence (first drug used, second drug, and so on) and outcome (whether still taking, or if discontinued, giving the reason why) were recorded for each drug, to a maximum of 7, including drug combinations. Details of start and stop dates and the indications for each drug were not recorded on the proforma, but as the data were recorded by rheumatologists, it was assumed that the disease modifying treatment was given for the arthritis rather than the skin.

Data forms were sent to the coordinating site, where they were entered into an SPSS database. Data entry accuracy was checked on a random sample of 10% of cases and the appropriateness of the diagnostic label was checked on a further sample of 10% by a quality control committee.

Statistical analysis. The relationship between disease, drug, and outcome (Table 1) was examined using Loglinear analysis in SPSS v 15.0. Two models were examined. First, a log-linear model that predicted the numbers as displayed in the cells of a table of outcome by drug by disease, using this to determine the association of disease and treatment with outcome. Four categories were used for outcome: adverse effect, ineffective, remission, and still taking. The saturated model, that is, with all main effects, 2-way interactions, and the 3-way interaction, was fitted using a test of partial associations for the effect of components of the model. Second, a log-linear model specifically predicting the cell counts of a table of side-effect by drug by disease, using this to determine the association of disease and drug with side-effect. Much of this analysis was invalid because of sparse data, so the statistical analysis concentrated on MTX.

RESULTS

Data were collected prospectively from 588 consecutive clinic attendees with PsA and 536 control patients, as described. Control patients had RA (n = 384), ankylosing spondylitis (n = 72), undifferentiated arthritis (n = 38), connective tissue disorders (n = 14), and other diseases (n = 28). Subsequent analysis focused on drug outcomes in patients with PsA and RA only. The disease duration for PsA and RA was similar, but patients with PsA were younger and more likely to be male than patients with RA. Demographic variables and further clinical data are given in Table 2.

Psoriatic arthritis. Table 3 details the drugs used in PsA, by sequence and drug. No drug therapy was recorded for 70 (12%) cases. Across all sequences MTX was the most frequently used drug (39% of all drugs used), followed by sulfasalazine (22%). The proportion of patients receiving anti-TNF drugs increased with each sequence, reflecting the time over which these patients had been treated and the use of these drugs after "conventional" disease modifying drugs.

In the 404 patients where drugs were still being taken, drug combinations were used in 92 (23%) cases. In the majority of cases 2 drugs were combined, the drug combinations most frequently used being MTX/sulfasalazine (33 cases), MTX/steroids (22 cases), and MTX/anti-TNF (16 cases). In 9 cases, triple therapy was employed — MTX was used in all of these in various combinations that also included cyclosporine, sulfasalazine, antimalarials, and anti-TNF drugs.

Rheumatoid arthritis. Table 4 details the drugs used in RA, by sequence and drug. No drug therapy was recorded for 9 (2%)

Table 1. Outcome of taking a disease modifying drug. Numbers represent cases (percentages) within each vertical column based on the (horizontal) totals in Tables 2 and 3. The totals of figures in the vertical columns do not equal the totals in Tables 2 and 3 because of missing data.

	AZA		CYC		AM		GST		LEF		MTX		CS		SSZ		TNF	
	PsA	RA	PsA	RA	PsA	RA	PsA	RA	PsA	RA	PsA	RA	PsA	RA	PsA	RA	PsA	RA
Hepatic	1 (4)	0	0	0	0	0	1 (1)	1 (< 1)	4 (11)	1 (2)	32 (7)	12 (4)	0	0	8 (3)	4 (2)	0	0
CNS	0	0	2 (4)	0	0	1 (< 1)	0	1 (< 1)	1 (< 1)	0	3 (1)	1 (< 1)	0	2 (1)	4 (2)	1 (< 1)	0	0
Respiratory	0	0	0	0	0	0	0	0	0	1 (2)	5 (1)	15 (4)	0	0	1 (< 1)	1 (< 1)	0	0
Renal	0	0	9 (16)	5 (11)	0	0	2 (3)	6 (5)	0	0	2 (< 1)	1 (< 1)	0	0	1 (< 1)	0	0	0
Skin	0	0	0	0	6 (12)	5 (3)	12 (16)	17 (15)	1 (3)	4 (9)	4 (2)	7 (2)	0	0	18 (7)	6 (4)	0	2 (2)
Blood	0	0	1 (2)	0	0	0	0	2 (2)	0	0	5 (1)	1 (< 1)	0	0	4 (2)	3 (2)	0	0
Gastrointestinal	2 (8)	0	4 (7)	0	0	4 (3)	0	0	1 (3)	4 (9)	11 (2)	4 (1)	0	0	10 (4)	8 (6)	0	0
Drug-induced LE or vasculitis	0	1 (6)	0	0	0	0	0	0	0	0	0	0	0	0	2 (1)	2 (1)	0	0
Infection	0	0	0	0	0	0	0	0	0	0	0	1 (< 1)	0	0	0	0	1 (2)	0
Ocular	0	0	0	0	2 (4)	3 (2)	0	0	0	0	0	0	0	0	0	0	0	0
Ineffective	8 (29)	6 (35)	13 (23)	16 (36)	16 (31)	60 (39)	33 (44)	49 (42)	8 (21)	12 (26)	40 (9)	32 (10)	10 (9)	7 (4)	70 (28)	55 (39)	2 (3)	8 (15)
Remission	1 (4)	1 (6)	3 (5)	1 (2)	4 (8)	2 (1)	2 (3)	3 (3)	0	0	7 (2)	1 (< 1)	6 (5)	10 (5)	9 (4)	2 (1)	1 (2)	0
Still taking	10 (36)	5 (29)	19 (33)	7 (16)	16 (31)	52 (34)	4 (5)	9 (8)	19 (50)	16 (35)	256 (59)	234 (70)	36 (32)	107 (58)	96 (38)	40 (28)	59 (91)	35 (64)

AZA: azathioprine; CYC: cyclosporine; AM: antimalarial; GST: gold salts; LEF: leflunomide; MTX: methotrexate; CS: corticosteroids; SSZ: sulfasalazine; TNF: anti-TNF drug; LE: lupus erythematosus; CNS: central nervous system.

Table 2. Patient characteristics.

	PsA, n = 588	RA, n = 384
Age, yrs, mean (SE)	50.3 (0.54)	58.0 (0.68)
Disease duration arthritis, yrs, mean (SE)	12.5 (0.40)	12.4 (0.51)
Disease duration psoriasis, yrs, mean (SE)	19.5 (0.53)	17.8 (8.4)*
Male sex, N (%)	306 (52)	111 (29)
Caucasian ethnicity, N (%)	511 (88)	318 (83)
RF-positive, N (%)	27 (4.6)	292 (76)
Clinical phenotype, N (%)		
Oligoarthritis	76 (13)	15 (4)
Polyarthritis	372 (63)	363 (94)
Spinal involvement	82 (14)	0
Distal interphalangeal joint predominant	23 (4)	0
Arthritis mutilans	16 (3)	5 (1)
Not defined	19 (3)	1 (< 1)

* 5 cases had incidental psoriasis.

cases. Across all sequences MTX was the most frequently used drug (30% of all drugs used), followed by corticosteroids (17%), antimalarials (14%), and sulfasalazine (13%). The proportion of patients receiving anti-TNF drugs again increased with each sequence.

In the 315 patients where drugs were still being taken, drug combinations were used in 143 (45%) cases. In the majority of cases 2 drugs were combined, the drug combinations most frequently used being MTX/corticosteroids (74 cases), MTX/antimalarials (33 cases), MTX/sulfasalazine (22 cases), and MTX/anti-TNF (13 cases). In 26 cases triple therapy was employed, the most common combination being antimalarials/MTX/corticosteroids (12 cases).

PsA and RA compared. Table 1 gives the treatment outcome by disease and drug. The majority of patients were still taking MTX and anti-TNF drugs and, although few were recorded as being in remission, these 2 drugs had the lowest percentages of discontinuation for inefficacy. The adverse event profile differed between drugs and diseases. Some drug adverse

Table 3. Psoriatic arthritis: drugs used to treat by drug and order in which the drug was given. Figures are numbers (percentage within each sequence). Some drugs were given in combination (drug combinations are given in the text).

	Order Given					
Drug	First	Second	Third	Fourth	Fifth to 7th	Totals
Azathioprine	2 (< 1)	9 (3)	9 (6)	5 (7)	3 (6)	28 (2)
Cyclosporine	14 (3)	29 (9)	5 (3)	7 (9)	2 (4)	57 (5)
Antimalarials	20 (4)	17 (5)	7 (5)	4 (5)	4 (8)	52 (5)
Gold salts	43 (8)	16 (5)	10 (7)	4 (5)	2 (4)	75 (7)
Leflunomide	1 (< 1)	9 (3)	13 (9)	14 (19)	1 (2)	38 (3)
Methotrexate	205 (39)	155 (48)	42 (29)	15 (19)	16 (30)	433 (39)
Corticosteroids	56 (11)	25 (8)	20 (14)	7 (9)	6 (11)	114 (10)
Sulfasalazine	175 (34)	45 (14)	18 (13)	6 (8)	6 (11)	250 (22)
Anti-TNF drugs	5 (< 1)	15 (5)	20 (14)	12 (16)	13 (25)	65 (6)
Totals	521	320	144	74	53	1112 (100)

Table 4. Rheumatoid arthritis: drugs used to treat by drug and order in which the drug was given. Figures are numbers (percentage within each sequence). Some drugs were given in combination (drug combinations are given in the text).

	Order Given					
Drug	First	Second	Third	Fourth	Fifth to 7th	Totals
Azathioprine	2 (< 1)	4 (1)	1 (< 1)	3 (3)	7 (7)	17 (2)
Cyclosporine	10 (3)	11 (4)	12 (6)	4 (4)	7 (7)	44 (4)
Antimalarials	61 (15)	53 (17)	27 (14)	4 (4)	9 (10)	154 (14)
Gold salts	48 (12)	34 (11)	18 (9)	12 (12)	5 (5)	117 (11)
Leflunomide	2 (< 1)	5 (2)	10 (5)	17 (18)	12 (13)	46 (4)
Methotrexate	115 (29)	113 (37)	69 (35)	22 (23)	16 (17)	335 (30)
Corticosteroids	85 (21)	44 (14)	30 (15)	12 (12)	14 (15)	185 (17)
Sulfasalazine	75 (19)	30 (10)	20 (10)	11 (11)	5 (5)	141 (13)
Anti-TNF drugs	2 (< 1)	12 (4)	10 (5)	12 (12)	19 (20)	55 (5)
Totals	400	306	197	97	94	1104 (100)

events were common to both diseases. These included discontinuation due to renal problems with cyclosporine and gold salts and discontinuation due to skin reactions with antimalarials and gold salts.

In order to allow for recall bias, the adverse event profile was analyzed separately for each drug sequence, but no substantial differences in adverse event profile were seen for either disease. Similarly, as drug combinations may also affect the adverse event profile, a separate analysis of drugs used singly or in combination was performed, but again no substantial differences in adverse event profile were found.

The first statistical model showed that all effects were significant, including the 3-way interaction. The model that excluded the 3-way interaction term had a likelihood ratio chi-square of 37.21 (df 24; p = 0.042), indicating that only the full (saturated) model adequately fitted the observed data. A significant 3-way interaction effect meant that the distribution of outcome was different for different drugs and this difference was different for the 2 diseases. To determine which specific drug-outcome combinations were different in PsA compared to RA, we compared the standardized residuals between the models with and without the 3-way interaction term. Combinations for which the standardized residual was greater than 1.96 indicated statistical significance at the 5% level. The following drug-outcome combinations were statistically significant: cyclosporine and ineffective (standardized residual 2.08; occurred more often in RA); MTX and still taking (standardized residual 2.05; occurred more often in RA); anti-TNF and ineffective (standardized residual 2.28; occurred more often in RA); and anti-TNF and still taking (standardized residual 2.34; occurred more often in PsA). Overall, drugs were less likely to be ineffective in PsA (22%) compared to RA (27.3%), but more likely to be stopped because of side-effects (17.6% vs 14.2%; both differences statistically significant at 5% level).

The second analysis focused on the differential toxicity of MTX. Although the differential hepatotoxicity seen with PsA and RA was maintained for both leflunomide and MTX, the pulmonary toxicity seen with MTX was confined to the patients with RA. The parameter estimates from the log-linear model did not show statistically significant effects for individual side-effects because the cell counts were too small. So the categories were collapsed into "hepatitis" or "other" to show that this side-effect is more common from MTX in PsA compared to RA (OR 2.67, 95% CI 1.16 to 6.14) and into "respiratory" or "other" to show this side-effect is less common in PsA compared to RA (OR 0.16, 95% CI 0.05 to 0.48).

Although the number of patients receiving anti-TNF drugs was comparatively small there was a suggestion of less efficacy in RA compared to PsA. However, anti-TNF drugs are by far the best tolerated and the most efficacious (as indicated by number of withdrawals for lack of effect and number continuing the drug) among those reported across both diseases. Corticosteroids in RA are a close second to anti-TNF drugs. These associations were not examined statistically as the cell frequencies were too small.

DISCUSSION

The strengths of this database are in the wide international collaboration, the relatively large numbers of patients, and the fact that these were consecutive, unselected patients treated in everyday practice. The results show that MTX was the most frequently used disease modifying drug for both PsA and RA. Further, once started, it was continued in the majority of cases, with very few people discontinuing the drug for lack of efficacy. This is testimony to its efficacy and tolerability in both diseases. However, evidence of MTX efficacy in PsA from appropriately conducted clinical trials is sparse and relies on anecdotal and open-label studies[3]. Such studies have shown evidence of efficacy in arthritis, enthesitis, and dactylitis, with good effect sizes using standard measures[7]. MTX also remains the drug of first choice in PsA because it is also efficacious for treating plaque psoriasis[8].

The data from Table 1 suggest that, although MTX is infrequently discontinued for reasons of inefficacy in both diseases, it was more often discontinued in PsA compared to RA, primarily for reasons of toxicity. The same considerations apply to the use of gold salts and corticosteroids. A recent metaanalysis found that patients with psoriasis taking MTX were more likely than patients with RA to have advanced histological changes on liver biopsy (7.7% vs 2.7%; p = 0.003) and histologic progression (33.1% vs 24.3%; p = 0.02)[5]. Although there was a higher prevalence of hepatotoxicity due to MTX and leflunomide in PsA, our study was unable to address the reasons for this. A greater alcohol intake and higher prevalence of obesity, with a greater degree of hepatic steatosis, have been adduced as an explanation, but further studies are needed. None of the anti-TNF drugs were discontinued for hepatotoxicity, although new data suggest that hepatotoxicity with the new biologic drugs is also greater in patients with psoriasis and PsA compared to RA[9]. The relatively uncommon pulmonary adverse events in people with PsA treated with MTX have been previously described, but again, controlling for appropriate confounders such as preexisting pulmonary disease was not performed[6].

Discontinuation of drug for cutaneous reactions is well recognized for such drugs as antimalarials and gold salts, and it is interesting that this was a more frequent adverse event in PsA, albeit it was not statistically significant. Moreover, rheumatologists providing cases to this cohort only seldom used antimalarials in PsA, despite evidence that the drug can be given safely in PsA[10]. Anti-TNF drugs were discontinued due to cutaneous reactions in 2 cases, both with RA. It is not possible to tell from these data whether this was an injection site reaction or induced palmo-plantar psoriasis, a recently described adverse event of anti-TNF drugs in RA[11].

The weaknesses of this study are the lack of precise infor-

mation on drug outcomes in terms of both response criteria and adverse events, the lack of details on drug doses, and the retrospective property of the data. Drug doses may influence the likelihood of adverse events so that if, for example, larger doses of MTX were used in PsA, this would give the impression of a higher adverse event profile for this condition, although the data in Table 1 would not support this (apart from the liver, noted above). The data also lack information on the precise reason that each disease modifying drug was started. For example, both cyclosporine and MTX could have been started for the skin, rather than the joint, disease. As stated, all the proformas were completed by rheumatologists and therefore our supposition was that the disease modifying drugs were most likely to have been given for the joint disease, albeit with the skin disease in mind. However, whatever the indication for the drug, this is unlikely to have influenced the adverse event profile. A further weakness concerns the heterogeneity of PsA — for example, is sulfasalazine more effective for the entheseal component of this disease? Although data on enthesitis were collected, it is not possible to say whether this feature was predominant or was just a related feature, thus confounding subgroup analysis on this basis.

Our data confirmed the tolerability and presumed efficacy of MTX and anti-TNF drugs in PsA and RA in an international cohort of patients selected consecutively and treated in everyday practice. The evidence provides some insight into prescribing patterns and the differential adverse events of pharmaceuticals between these diseases.

APPENDIX

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