CONCISE REPORT

Trends in disease modifying antirheumatic drug prescription in early rheumatoid arthritis are influenced more by hospital setting than patient or disease characteristics

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Objective: To characterise temporal trends and factors associated with the prescription of disease modifying antirheumatic drugs (DMARDs) at the initial consultation in early rheumatoid arthritis (RA).

Methods: Data from 2584 patients with early RA at 19 hospitals were extracted from the Swedish Rheumatoid Arthritis Register for the period 1997–2001. Disease characteristics and DMARD prescription at first consultation with the rheumatologist were investigated using cross tabulation and logistic regression.

Results: DMARD prescriptions, particularly for methotrexate, increased from 1997 to 2001 independently of patient characteristics. Stratification by hospital type showed that patients in district hospitals were less likely to be prescribed DMARDs than those in university hospitals (adjusted odds ratio (OR)=0.53 (95% confidence interval (CI) 0.40 to 0.69), $p<0.001$), independently of confounding factors. Association of the DAS28 with the likelihood of DMARD prescription was greater among patients attending district hospitals (OR=1.65 (1.34 to 2.02), $p<0.001$) than those at university hospitals (OR=1.23 (1.07 to 1.41), $p=0.003$) and county hospitals (OR=1.34 (1.01 to 1.63), $p=0.003$). Interaction testing indicated that the difference was significant ($p=0.007$).

Conclusions: Temporal trends in DMARD prescription indicate an increasingly aggressive approach to disease management among Swedish rheumatologists. However, the association of hospital type with DMARD prescription suggests that the adoption of research findings in clinical care varies considerably.

Although research findings support early and aggressive intervention with disease modifying antirheumatic drugs (DMARDs) in the treatment of rheumatoid arthritis (RA),^{1–4} the integration of these findings into daily clinical practice varies considerably, as reflected in rheumatologists' prescribing habits.^{5–8} In this study we use clinical data from the initial consultation of patients with early RA with rheumatologists to identify temporal trends and to characterise factors associated with the prescription of DMARD.

PATIENTS AND METHODS

Study population

Data were provided by the Swedish Rheumatoid Arthritis Register, a national quality register for early RA, containing

clinical data from initial and follow up consultations. Patients over 15 years of age with RA according to the American College of Rheumatology criteria⁹ and disease duration of less than 1 year qualify as having early RA. Baseline assessments include name, age, sex, symptom onset, and rheumatoid factor (RF) status using local agglutination methods. Each patient is assigned a code number to enable data extraction without disclosing patient identity. Patients give informed consent before inclusion and are free to withdraw from participation in the register at any time. Ethical clearance for the study was obtained from the Karolinska Institute's Research Ethics Committee in Stockholm.

At the first consultation and follow up assessments, the American College of Rheumatology core set of outcomes are compiled and recorded.¹⁰ First consultation defined here includes test results, diagnosis, and prescription of treatment in the weeks immediately after the first visit to the clinic. Patients' pain and general health are quantified on a visual analogue scale (100 mm), and disability is measured by the Swedish version of the Stanford Health Assessment Questionnaire (HAQ).¹¹ Rheumatologists record the following: physician's global assessment of disease activity using a Likert scale (none, low, medium, high, maximal); intended prescriptions for DMARDs, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and analgesics; C reactive protein and erythrocyte sedimentation rates; and the 28 joint count Disease Activity Score for swelling and tenderness (DAS28).¹² Disease activity as measured by the DAS28¹³ is calculated automatically in the database.

All patients with newly diagnosed RA ($n=2584-799$ men, 1785 women) from 19 hospitals that contributed data to the Swedish RA Register for the entire 5 year period, 1997–2001, were analysed. Patients with suspected RA are referred from primary care to rheumatology specialist care. Of the 19 hospitals in this study, eight were university teaching hospitals, six were county, and five were district hospitals.

Statistical analysis

Cross tabulation was used to compare the following characteristics by sex for each of the 5 years: age group, RF, disability (HAQ), and disease duration. Mean values for the DAS28 were compared by sex and year using analysis of variance. The associations of DMARD prescription with age, sex, RF, disease duration, type of hospital attended, and the year of diagnosis were analysed using logistic regression.

Abbreviations: CI, confidence interval; DAS28, 28 joint count Disease Activity Score; DMARD, disease modifying antirheumatic drug; GCs, glucocorticosteroids; HAQ, Health Assessment Questionnaire; OR, odds ratio; RA, rheumatoid arthritis; RF, rheumatoid factor

Figure 1 Changing preferences in the type of DMARD prescribed at first consultation in early RA, 1997–2001.

Prescription patterns for glucocorticosteroids (GCs) were also examined. Simultaneous adjustment was made for all these variables and for the DAS28. The material was then stratified by hospital type and analysed similarly. Logistic regression was used to investigate the interaction of hospital type and the DAS28 for the prescription of DMARDs, with adjustment being made for all confounding factors and for the main effects.

In the adjusted model, all variables, except the DAS28, were modelled as a series of binary dummy variables. The DAS28 was modelled as a continuous measure, such that the odds ratio (OR) refers to the change in the probability of DMARD prescription for each one-unit increase in the DAS28. Patients with at least one missing variable ($n = 259$) were excluded from this analysis. Univariate analysis was used to evaluate the potential confounding effect of the missing data. The unadjusted and adjusted ORs were calculated with the 95% confidence interval (CI). SPSS was used to analyse the data.¹⁴

RESULTS

Patient characteristics

Patients' age, sex, DAS28, HAQ, RF serology, and mean disease duration (6 months) were similar for each of the

5 years and between hospital types. Median HAQ (range) was 1.00 (0–3) for women, 0.88 (0–3) for men and median age was 57 (16–88) years and 63 (18–89) years for women and men, respectively. Mean DAS28 (standard deviation) at inclusion was 5.13 (1.25) for women and 5.07 (1.33) for men.

DMARD prescription patterns

Overall, the proportion of patients prescribed DMARDs—in particular, methotrexate—at the first consultation increased between 1997 and 2001 (fig 1), producing an adjusted OR of 0.43, (95% CI 0.34 to 0.54), $p < 0.001$, but with some variation by hospital type (fig 2). Combinations of DMARDs were prescribed to 31 patients.

Differences in routines for the registration of methotrexate may have confounded these results. If patients were asked to wait for the start of treatment until chest x ray results were known, registration might have been delayed until the first follow up visit. Therefore, we chose to analyse the data again to include methotrexate registered for the first time at follow up. The proportion of patients receiving a DMARD was understandably higher than in the initial analysis, but the variation between district hospital type and university and county hospital types remained, independent of potential confounding factors (table 1). The linear trend for the DAS28 indicates that a higher score was more likely to elicit a DMARD prescription. When methotrexate was included at follow up, patients over 65 years were significantly less likely to receive a DMARD than patients in the 46–55 year age group, regardless of the DAS28 (table 1). No other patient characteristics were associated with DMARD prescription.

Association of the DAS28 with the likelihood of a DMARD prescription appeared to be greater for patients in the district hospital stratum (OR = 1.65 (1.34 to 2.02), $p < 0.001$) than in the university hospital (OR = 1.23 (1.07 to 1.41), $p = 0.003$) or county hospital strata (OR = 1.34 (1.01 to 1.63), $p = 0.003$). Whether association of the DAS28 with DMARD prescription differed between hospital types was tested using the interaction between the DAS28 and hospital type. Interaction of the DAS28 with district hospital type was found more likely to provide patients with a DMARD prescription than interaction between the DAS28 and university hospitals (adjusted OR = 1.37 (1.09 to 1.73), $p = 0.007$). There was no difference between university and county hospitals in this regard (adjusted OR = 1.01 (0.81 to 1.26), $p = 0.938$). The exclusion of patients with missing data did not significantly affect the results of the analysis.

Glucocorticosteroid prescription

GCs were prescribed to 37.9%, 43.3%, and 42.7% of patients in university, county, and district hospitals, respectively. Median dosages were 7.5 mg in university hospitals and 10 mg in both county and district hospitals with no change over the years. Most GCs were prescribed in combination with DMARDs. Patients in county hospitals were more likely than patients in university and district hospitals to be prescribed a GC (OR = 1.25 (1.03 to 1.51), $p = 0.022$). The prescription of GC monotherapy was not generally widespread (6.6% of patients in district hospitals); however, it was more likely in district hospitals (OR = 2.2 (1.42 to 3.41), $p < 0.001$) than in university hospitals.

DISCUSSION

Two main factors—the year of RA diagnosis and hospital type—were associated with the likelihood of being prescribed a DMARD. The increasing proportion of patients with early RA over time prescribed a DMARD at their first consultation appears to reflect changes in prescribing practice rather than any change in the characteristics of the patient population. Similar trends have been reported previously¹⁵; however,

Figure 2 Variation between hospital types in the proportion of patients with early RA to be prescribed a DMARD at first consultation, 1997–2001.

Table 1 Influence of patient and disease characteristics on DMARD prescription at the initial consultation together with the unadjusted and adjusted odd ratios

Characteristics	No (%) with DMARD	No (%) without DMARD	Unadjusted		Adjusted	
			OR (95% CI)	Sig. (p)	OR (95% CI)	Sig. (p)
Type of hospital						
University	1038 (53.0)	168 (45.5)	1.00		1.00	
County	512 (26.1)	82 (22.2)	1.22 (0.94 to 1.60)	0.141	1.05 (0.78 to 1.41)	0.751
District	408 (20.8)	119 (32.2)	0.64 (0.50 to 0.82)	0.000	0.53 (0.40 to 0.69)	0.000
DAS28 at inclusion <i>Linear trend</i>	1958 (100.0)	369 (100.0)	1.28 (1.18 to 1.40)	0.000	1.33 (1.21 to 1.46)	0.000
RF						
Negative	671 (34.3)	130 (35.2)	1.00		1.00	
Positive	1287 (65.7)	239 (64.8)	1.06 (0.85 to 1.32)	0.618	0.94 (0.74 to 1.21)	0.641
Disease duration (months)						
0–3	478 (24.4)	90 (24.4)	1.00		1.00	
4–6	642 (32.8)	120 (32.5)	0.96 (0.73 to 1.27)	0.767	1.08 (0.79 to 1.48)	0.618
7–9	495 (25.3)	91 (24.7)	0.98 (0.73 to 1.32)	0.909	1.14 (0.81 to 1.58)	0.456
10–12	343 (17.6)	68 (18.4)	0.94 (0.68 to 1.30)	0.723	1.06 (0.74 to 1.52)	0.767
Sex						
Male	603 (30.8)	120 (32.5)	1.00		1.00	
Female	1355 (69.2)	249 (67.5)	1.06 (0.85 to 1.32)	0.629	0.98 (0.76 to 1.26)	0.885
Age group						
16–25	64 (3.3)	15 (4.1)	0.76 (0.42 to 1.35)	0.345	0.70 (0.37 to 1.32)	0.273
26–35	141 (7.2)	29 (7.9)	0.82 (0.53 to 1.27)	0.378	0.76 (0.47 to 1.25)	0.281
36–45	208 (10.6)	29 (7.9)	1.12 (0.73 to 1.71)	0.606	1.13 (0.70 to 1.82)	0.616
46–55	425 (21.7)	67 (18.2)	1.00		1.00	
56–65	466 (23.8)	76 (20.6)	1.08 (0.78 to 1.51)	0.636	0.88 (0.61 to 1.26)	0.472
66–75	429 (21.9)	98 (26.6)	0.78 (0.57 to 1.06)	0.112	0.59 (0.42 to 0.84)	0.004
76–85	220 (11.2)	51 (13.8)	0.71 (0.49 to 1.02)	0.065	0.61 (0.43 to 0.93)	0.021
86–95	5 (0.3)	4 (1.1)	0.11 (0.03 to 0.46)	0.003	0.10 (0.02 to 0.45)	0.003
Year of inclusion						
1997	359 (18.3)	119 (32.2)	1.00		1.00	
1998	422 (21.6)	92 (24.9)	1.49 (1.12 to 1.99)	0.006	1.60 (1.17 to 2.20)	0.003
1999	393 (20.1)	49 (13.3)	2.46 (1.77 to 3.43)	0.000	2.76 (1.91 to 3.99)	0.000
2000	394 (20.1)	54 (14.6)	2.41 (1.74 to 3.35)	0.000	2.58 (1.80 to 3.70)	0.000
2001	390 (19.9)	55 (14.9)	2.60 (1.86 to 3.63)	0.000	2.36 (1.65 to 3.38)	0.000
Total	1958 (100.0)	369 (100.0)				

Patients without a DMARD at the initial consultation but prescribed methotrexate at follow up are included in the analysis. Results are adjusted for age, sex, disease duration, RF, hospital type, year of inclusion, and DAS28.

sulfasalazine use did not continue to rise in our population, and methotrexate alone accounted for the increase.

The patients in our study represent the majority of incident cases of early RA from the catchments of the participating hospitals, which are widely dispersed throughout Sweden. Not only are the age, sex, RF, and disease activity (DAS28) distributions of patients constant over the study period but also the associations of DMARD prescription with year were independent of all of these factors. Similarly, variation in prescribing practice between hospitals was independent of patient characteristics, so the lower rate of DMARD prescription in district hospitals is likely to reflect institutional differences in practice. The lack of association between RF status and DMARD prescription indicates again that institutional prescribing practice rather than disease characteristics influences which patients with early RA are prescribed DMARDs at their first consultation. Greater disease activity indicated by a higher DAS28 was more likely to elicit a DMARD prescription, but more so in district hospitals than in the other hospital types. Again, as we were able to adjust for other patient characteristics, these could not account for the variation in association of the DAS28 with DMARD prescription by hospital type. It is of note that the difference between district and university hospitals had almost disappeared by the end of the study period, indicating a more universal approach to DMARD prescription across hospital types.

In conclusion, the temporal trends in DMARD prescription indicate that rheumatologists in this study adopted an increasingly aggressive approach to the treatment of early RA from 1997 to 2001. The influence of hospital type on the prescription of DMARDs suggests that there is room for improvement in the management of early RA. The use of quality and surveillance arthritis registers may help to identify and define areas of unwarranted variation, which may be even more important when considering the increasing use of effective but expensive biological drugs.

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REFERENCES

- 1 **Stenger AA**, Van Leeuwen MA, Houtman PM, Bruyn GA, Speerstra F, Barendsen BC, *et al*. Early effective suppression of inflammation in rheumatoid arthritis reduces radiographic progression. *Br J Rheumatol* 1998;**37**:1157–63.
- 2 **Egsmose C**, Lund B, Borg G, Pettersson H, Berg E, Brodin U, *et al*. Patients with rheumatoid arthritis benefit from early 2nd line therapy: 5 year follow-up of a prospective double blind placebo controlled study. *J Rheumatol* 1995;**12**:2208–13.
- 3 **van der Heijde DM**, Jacobs JW, Bijlsma JW, Heurkens AH, van Booma-Frankfort, van der Veen MJ, *et al*. The effectiveness of early treatment with “second-line” antirheumatic drugs: a randomised controlled trial. *Ann Intern Med* 1996;**124**:699–707.
- 4 **Mottonen T**, Hannonen P, Korpela M, Nissila M, Kautiainen H, Ilonen J, *et al*. Delay to institution of therapy and induction of remission using single-drug or combination-disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. *Arthritis Rheum* 2002;**46**:894–8.
- 5 **Criswell LA**, Henke CJ. What explains the variation among rheumatologists in their use of prednisolone and second line agents for the treatment of rheumatoid arthritis? *J Rheumatol* 1995;**22**:829–35.
- 6 **Saraux A**, Berthelot JM, Chales G, Le HC, Thorel J, Hoang S, *et al*. Second-line drugs used in recent-onset rheumatoid arthritis in Brittany (France). *Joint Bone Spine* 2002;**69**:37–42.
- 7 **Albers JMC**, Paimela L, Kurki P, Eberhardt KB, Emery P, van 't Hof MA, *et al*. Treatment strategy, disease activity, and outcome in four cohorts of patients with early rheumatoid arthritis. *Ann Rheum Dis* 2001;**60**:453–8.
- 8 **Galindo-Rodriguez G**, Avina-Zubieta JA, Fitzgerald A, LeClerq SA, Russell AS, Suarez-Almazor ME. Variations and trends in the prescription of initial second line therapy for patients with rheumatoid arthritis. *J Rheumatol* 1997;**24**:633–8.
- 9 **Arnett FC**, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:315–24.
- 10 **Felson DT**, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, *et al*. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. *Arthritis Rheum* 1993;**36**:729–40.
- 11 **Ekdahl C**, Eberhardt K, Andersson SI, Svensson B. Assessing disability in patients with rheumatoid arthritis. Use of the Swedish version of the Stanford Health Assessment Questionnaire. *Scand J Rheumatol* 1988;**17**:263–71.
- 12 **Prevoo ML**, van Riel PL, van't Hof MA, van Rijswijk MH, van Leeuwen MA, Kuper HH, *et al*. Validity and reliability of joint indices. A longitudinal study in patients with recent onset rheumatoid arthritis. *Br J Rheumatol* 1993;**32**:589–94.
- 13 **Prevoo ML**, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;**38**:44–8.
- 14 **Norusis MJ**. *SPSS user's guide*. Chicago: SPSS Inc, 1998.
- 15 **Aletaha D**, Eberl G, Nell VP, Machold KP, Smolen JS. Practical progress in realisation of early diagnosis and treatment of patients with suspected rheumatoid arthritis: results from two matched questionnaires within three years. *Ann Rheum Dis* 2002;**61**:630–4.