Concise report

First-line DMARD choice in early rheumatoid arthritis—do prognostic factors play a role?

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Abstract

Objective. To examine if prognostic factors predict the choice of first DMARD for patients with RA.

Methods. Details of 616 patients with early RA were collected from 16 centres in the UK Early Rheumatoid Arthritis Network (ERAN). Logistic regression was used to identify whether HAQ score, swollen joint count (SJC), nodules, RF, ESR, CRP and erosions on radiographs were associated with the choice of first DMARD treatment.

Results. Of 616 patients, 547 (88%) were started on a DMARD, 253 (46%) on MTX, 230 (42%) on SSZ, 47 (9%) on other DMARD monotherapies and 17 (3%) on combination DMARD therapy (CoT). SSZ was started less frequently in patients with positive RF ($P=0.018; OR 0.59; 95\% CI 0.38, 0.91$) and high SJC ($P=0.02; OR 0.95; 95\% CI 0.91, 0.99$). MTX was favoured in patients with high SJC ($P=0.002; OR 1.07; 95\% CI 1.02, 1.11$). Non-prescription of DMARDs was associated with old age ($P=0.02; OR 0.98; 95\% CI 0.96, 0.99$) and low HAQ score ($P=0.009; OR 0.80; 95\% CI 0.68, 0.95$). None of the variables predicted CoT. All other variables and the hospital where the patient was treated were not independently associated with the choice of DMARD.

Conclusions. When choosing DMARD monotherapy in early RA, rheumatologists in ERAN seem to preferentially prescribe MTX for patients with a poor prognosis and SSZ for patients with good prognosis. No DMARDs were used in older patients or in those with a low HAQ.

Key words: Rheumatoid arthritis, DMARD choice, Prognostic factors.

Introduction

RA is an inflammatory arthritis characterized by synovial tissue inflammation that leads to structural damage and disability. There are several treatment options available, which include glucocorticoids, DMARDs and biologics given alone as monotherapy or in a variety of combinations. Recent evidence has shown that early treatment is important in reducing the rate of progression of erosions and decreasing disability [1–5]. There is no uniform agreement among rheumatologists on the best first-line DMARD in early RA, and there is considerable inter-individual variation in drug prescription [4].

Patients with early RA have a variable prognosis, and current guidelines recommend more intensive treatment for patients who are expected to have a worse prognosis [5]. Previous studies in early RA have identified important prognostic factors [6]. Risk factors for radiographic damage include positive RF, presence of anti-CCP antibodies and features of strong disease activity, such as a high swollen joint count (SJC) or CRP at onset. Predictors indicative of disability in early RA include RF
positivity and a raised HAQ score and erosive disease at diagnosis. While these observations are derived from outcomes in population studies, it is unknown whether the presence or absence of any of these predictors of prognosis influences the choice of DMARD treatment in current rheumatological practice.

The Early Rheumatoid Arthritis Network (ERAN) is a group of centres in the UK and Eire with an interest in treatment and outcome in patients with early RA. A standardized dataset including demographic, comorbidity, disease activity and outcome data is collected prospectively on newly diagnosed RA patients at first presentation and regularly thereafter. The choice of treatment and model of care (i.e. follow-up frequency, thresholds to escalate therapy and access to the multidisciplinary team) is left entirely to the discretion of the individual centres. Participating centres are distributed across the UK and Eire, and may be more representative of current clinical practice than single centre studies. We have utilized the ERAN database to examine whether any of the prognostic factors described above are associated with choice of first DMARD prescribed for patients with early RA.

Patients and methods

ERAN registry for early RA

An inception cohort of 616 patients with RA was identified, recruited in 16 ERAN centres between 2004 and 2006. Patients are enrolled in the ERAN registry if they meet the following inclusion criteria: (i) symptom duration <12 months at the time of presentation; and (ii) diagnosed as having RA by a consultant rheumatologist (fulfillment of the ACR 1987 diagnostic criteria is not required). The study was approved by the Trent Research Ethics Committee (REC) and written consent was obtained.

Clinical and laboratory assessments

Standardized case report forms are completed at first presentation, 3–6 months, 1 year and annually thereafter. Details recorded include centre number, age and sex of the patients, initial DMARD used, presence of RF, erosions on radiographs, presence of nodules, SJC and tender joint count (TJC), ESR, 28 joint disease activity (DAS28) score, CRP and HAQ score. All the observations were recorded locally and source data verification was undertaken by an experienced nurse practitioner who visited each centre regularly. Use of combination DMARD therapy as first-line treatment is defined if the patient is started on two or more DMARDs simultaneously or within the first 3 months of first DMARD use.

Statistical analysis

Characteristics of patients treated with MTX, SSZ and combination therapy (CoT) or no DMARD at all were compared. Predictors of DMARD choice were determined by logistic regression and expressed as odds ratios (ORs) and 95% CIs. Calculations were made using SPSS version 17 software (SPSS, Chicago, IL, USA).

Table 1 Demographic, clinical and laboratory characteristics and disease activity scores

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Age, mean (range), years</td>
<td>56 (19–106)</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>425 (69%)</td>
</tr>
<tr>
<td>Positive RF,a n (%)</td>
<td>308 (50%)</td>
</tr>
<tr>
<td>Presence of erosions,a n (%)</td>
<td>160 (26%)</td>
</tr>
<tr>
<td>SJC,b mean (range)</td>
<td>6 (0–57)</td>
</tr>
<tr>
<td>TJC,b mean (range)</td>
<td>8 (0–57)</td>
</tr>
<tr>
<td>ESR, mean (range), mm/hb</td>
<td>31 (1–124)</td>
</tr>
<tr>
<td>CRP, mean (range), mg/lb</td>
<td>25 (0–248)</td>
</tr>
<tr>
<td>HAQ score,b mean (range)</td>
<td>1.1 (0–3)</td>
</tr>
<tr>
<td>DAS28,b mean (range)</td>
<td>4.7 (0.1–10.8)</td>
</tr>
</tbody>
</table>

aPresence or absence of RF and erosions was not recorded in 87 and 60 patients, respectively. bSJC was recorded in 615 patients. TJC in 614, ESR in 549, CRP in 370, HAQ score in 603 and DAS in 472.

Results

Demographics and other baseline characteristics of the study group

A total of 616 patients were diagnosed as having early RA during this period. Demographic features, clinical features and disease activity scores including DAS28 and HAQ score are shown in Table 1.

DMARD choice

Out of 616 patients, 547 (88%) were started on a DMARD; 253 (46%) of these patients were started on MTX as monotherapy, 230 (42%) on SSZ as monotherapy, 17 (3%) on CoT and the remaining 47 (9%) on other DMARDs as monotherapy.

Association of specific DMARDs with prognostic factors

SSZ was started less frequently in patients with positive RF (P = 0.018; OR 0.59; 95% CI 0.38, 0.91) and high SJC (P = 0.02; OR 0.98; 95% CI 0.96, 0.99) and low HAQ score (P = 0.009; OR 0.80; 95% CI 0.68, 0.95) (Table 2). The R² was 0.67. None of the variables predicted CoT, but the number of patients in this group was very small. Presence or absence of all the remaining prognostic factors and the hospital where the patient was treated had no significant association with first DMARD choice.

Discussion

In this cohort of 616 newly diagnosed patients from ERAN, the majority (88%) were treated first with DMARD monotherapy; MTX in 46% and SSZ in 42%. We found that
patients with the recognized poor prognostic factor of a high SJC were given MTX significantly more frequently, whereas those with the good prognostic factors of a negative RF and low SJC were significantly more likely to receive SSZ. We did not find any significant variation in practice between different centres from where the patients were recruited. Our results show that ~12% of the patients with early RA were not started on a DMARD, and this option was significantly more likely in those with good physical function (low HAQ) and old age. Only a small percentage of patients were given first-line CoT, in spite of the evidence that combination DMARD therapy is superior to monotherapy when treating some groups of patients with active RA [7–10].

These findings are similar to other recent observational studies from the European Union, which showed that MTX is used as a single therapy in a significantly higher proportion than other DMARDs [11, 12]. A similar trend is also noted in the UK, where MTX has displaced other DMARDs, especially SSZ, as agent of first choice [13]. This might be due to a variety of reasons. MTX is perceived to have advantages over other DMARDs, and in a US survey >90% of rheumatologists rated MTX as ‘good or excellent’ at 1 year [14]. It is well tolerated long term [11] and adherence over time compares favourably with SSZ and HCQ, particularly with respect to withdrawals due to inefficacy [15, 16]. There is also evidence that MTX is more efficacious than SSZ in suppressing the progression of erosions [17]. Finally, non-MTX DMARDs have less impact on important comorbidities such as cardiovascular disease [18].

Although MTX is the most favoured drug, our findings showed that SSZ is still the first-choice DMARD in a large proportion of patients. This might be due to several factors. One is an assumption by some rheumatologists that SSZ is safer than MTX. Other factors favouring SSZ might include the need for less intensive monitoring compared with MTX, its safety in pregnancy and relative hepatic safety compared with MTX or LEF in patients who are not willing to reduce alcohol consumption.

Our findings suggest that in addition to these various practical, pragmatic and hypothetical advantages of MTX and SSZ in different situations, some prognostic factors were significantly associated with first-line choice of SSZ or MTX. This has also been noted in other studies, which report that patients with high disease activity were given MTX therapy more often than other DMARDs, whereas those with low activity were more likely to receive SSZ [19].

The SJC stands out in our study as the most predictive factor in the choice of first-line DMARD. Fautrel et al. [20] report predictors of second-line DMARD use (after inadequate response for MTX) among French rheumatologists, based on hypothetical vignettes. Interestingly, they also found that SJC was more predictive of DMARD choice than DAS28, implying that rheumatologists are more influenced in routine practice by this clinical finding than by the composite DAS28 index and its other components.

A limitation of our study is an inability to determine whether decisions about DMARD prescription occur after a conscious analysis of factors based on their prognostic value or whether they are made by a subconscious process using ‘experience’, perhaps given the limitations of busy clinical schedules and the complexities of individual cases. Given the pattern that has emerged from our group of 16 geographically distant centres, it would be of interest to determine this in a further study.

In summary, our findings from a large UK inception cohort of patients with newly diagnosed RA suggest that some prognostic factors are influencing the choice of first-line therapy with MTX or SSZ, or the decision not to use a DMARD at all. Our findings support a general impression of MTX being more potent than SSZ and provide evidence that MTX is chosen preferentially over SSZ.
for patients who are perceived to have more aggressive disease.

### Rheumatology key messages
- MTX and SSZ are the most favoured DMARDs in early RA.
- Patients with high SJC are given MTX more frequently.
- Only a small percentage of patients with early RA are started on combination therapy.

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