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Concise report

Outcome in rheumatoid arthritis patients with continued conventional therapy for moderate disease activity—the early RA network (ERAN)

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Abstract

Objective. To report from early RA network (ERAN) on Years 2 and 3 28-joint DAS (DAS-28) and HAQ outcomes in newly diagnosed RA patients treated with DMARD therapies stratified to DAS-28 status after 1 year.

Methods. ERAN is a prospective observational cohort of newly diagnosed RA patients, monitored and treated according to local practice. Standardized case report forms are completed at first presentation, 3–6 months, 1 year and annually thereafter.

Results. A total of 418 newly diagnosed RA patients with 2 years and 302 with 3 years follow-up were identified in 22 ERAN centres from 2002 to 2008. Within their first year from registration, 67% of patients received monotherapy DMARDs, and 26% combination DMARDs including 2% were on anti-TNF therapies. Between Years 1 and 3, 60% received DMARD monotherapy, 34% combination DMARD therapy including 8% on anti-TNF therapies. Seventy-four per cent of patients with Year 1 DAS-28 <3.2 and 27% with DAS-28 3.2–5.1 achieved a DAS-28 <3.2 outcome at Year 2 [odds ratio (OR) 7.64; 95% CI 4.6, 12.6], and 71 and 35%, respectively, at Year 3 (OR 4.49; 95% CI 2.5, 7.9). Seventy-nine per cent of patients with a Year 1 DAS-28 <3.2 and 52% with DAS-28 3.2–5.1 achieved an HAQ <1.25 at Year 2 (OR 3.47; 95% CI 2.1, 5.6), and 81 and 47%, respectively, at Year 3 (OR 4.92; 95% CI 2.6, 9.0).

Conclusions. In RA patients with a DAS-28 3.2–5.1 at 1 year, the likelihood of achieving a target low DAS-28 <3.2, or a low HAQ, at Years 2 or 3 is poor in a routine care setting using conventional DMARDs according to current practice.

Key words: Early rheumatoid arthritis, DMARD, 28-joint disease activity score, HAQ.

CLINICAL SCIENCE

Introduction

The early RA network (ERAN) is a group of centres in England, Wales and Eire with an interest in treatment and outcome in patients with early RA. A standardized data set including demographic, comorbidity, disease activity and outcome measures is collected prospectively 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. This provides the opportunity to report from a multicentre prospective observational RA cohort on routine care outcomes in differing sub-populations, stratified according to disease activity and type of therapy received. Current guidelines for the management of early RA include the principles of treating to a low disease activity target, such as a 28-joint DAS of <3.2 or a low CRP [1–3], based on consistent evidence of benefits of targeted approaches [2, 4]. Strategies to achieve this include conventional DMARD and biologic drugs, used sequentially or in combinations. In England and Wales, the National Institute for Clinical Excellence (NICE) has restricted funding for anti-TNF-α therapies to RA patients

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who have failed to respond to two DMARDs and have a DAS-28 >5.1 [5]. This means that biologic-naive RA patients in England and Wales with a DAS-28 score between 3.2 and 5.1 can only be treated with non-biologic therapies to reach a target DAS-28 outcome of <3.2. In contrast, other countries of the European Union and the USA allow anti-TNF therapies to be started in RA patients with a DAS-28 score >3.2 with other features of active disease or poor prognostic features [6–9]. Recently, the British Society for Rheumatology (BSR) has updated its guidelines for starting anti TNF therapy in RA, concurring with others, that they should be available for patients with a DAS-28 score >3.2 and specific features of active disease, including at least three swollen and tender joints [10].

There have been few reports of treatment and outcomes in RA patients with moderate disease activity in normal clinical practice, as opposed to participants in clinical trials. We report 2- and 3-year disease activity and functional outcomes in early RA patients from ERAN, treated with conventional, largely non-biologic, DMARD therapies stratified according to their DAS-28 score after 1 year of treatment within the registry.

Patients and methods

Patients diagnosed with new onset RA are prospectively enrolled in the ERAN data set. The diagnosis of RA is left to the discretion of the rheumatologist, and fulfilment of the ACR 1987 criteria is not a prerequisite for recruitment. The study was approved by the Trent Research Ethics Committee (REC) and written consent was obtained.

Standardized case report forms (CRFs) were completed at first presentation, 3–6 months, 1 year and annually thereafter. Source data verification was undertaken by an experienced nurse practitioner at visits to each centre. Completed CRFs were sent to a central site where data entry to an electronic format was initially performed using Optical Scanning (teleforming) into a database designed by the Medical Research Council (MRC) Clinical Trials Unit. Since 2006 data entry has been performed manually.

ERAN centres monitor and treat patients according to local practice, without requirement to follow any particular treatment protocol. Parallel start combination DMARD therapy is defined as two or more drugs started within 3 months of one another. Step-up DMARD therapy is defined as the addition of a second DMARD after 3 months.

Patients with Years 2 and 3 DAS-28 and HAQ outcome data by February 2010 were selected for analysis, stratified according to their DAS-28 score at 1 year after presentation. DAS-28 data were stratified into high, moderate and low disease activity and remission according to The European League Against Rheumatism (EULAR) criteria. HAQ scores were stratified into high ($\geqslant$1.25) or low (<1.25) categories based on the median baseline HAQ score within the ERAN cohort. Statistical analyses were performed using SPSS (version 11.15) computer software (IBM; Chicago, IL, USA).

Results

An inception cohort of 1153 patients with newly diagnosed RA has been recruited within 22 ERAN centres by February 2010, with a maximum of 8 years follow-up. Among these, 418 patients (72% female, median age 57 years) were identified with a minimum 2-year period of follow-up, following initial recruitment between 2002 and 2008, and DAS-28 follow-up both at Years 1 and 2. At baseline assessment, 61% were positive and 39% negative for RF (15% missing), 72% non-erosive and 28% erosive (missing 6%) on plain X-rays of hands and feet, findings similar to other RA inception cohorts. Within this cohort, 302 patients also had a 3-year follow-up. There was a median delay of 6 months from onset of RA symptoms to first outpatient appointment, and a further 1 month to commencement of first DMARD.

Table 1 shows the proportions of patients between baseline and Years 1, 2 and 3 receiving analgesics, NSAIDs or steroids alone, and DMARDs either as monotherapy or combination therapy. The first DMARD used as monotherapy was, most commonly, either MTX (54%) or SSZ (37%). Between baseline and Year 1, oral CSs were co-prescribed to 17% on DMARD monotherapy and 34% on combination DMARD therapies. This proportion remained stable, with 19 and 18% of DMARD monotherapy and 33 and 30% of DMARD combination therapy patients receiving these at Years 2 and 3, respectively. Anti-TNF agents were co-prescribed with DMARDs between baseline and Year 1 in 2% (n = 9), Year 2 in 4.5% (n = 19) and Year 3 in 8% (n = 24). The distribution of patients within

Table 1 Treatment types between baseline and Years 1, 2 and 3

Treatment type	Baseline—Year 1, n = 418; n (%)	Baseline—Year 2, n = 418; n (%)	Baseline—Year 3, n = 302; n (%)
DMARD monotherapy	232 (55.5)	190 (46)	130 (43)
DMARD sequential	48 (11.5)	58 (14)	51 (17)
Combination DMARD step up	57 (14)	89 (21)	75 (25)
Combination DMARD parallel start	52 (12)	52 (12)	28 (9)
Analgesics, NSAID monotherapy	16 (4)	22 (5)	16 (5)
Steroid (IA, i.m., p.o.) monotherapy	13 (3)	7 (2)	2 (1)

DAS-28 subcategories at Year 1 was similar for those with data at 3 years to the full cohort with 2-year data (Table 2).

Year 2 and 3 outcomes

The proportions of patients with Year 2 and 3 DAS-28 $\leqslant$2.6, or >3.2 according to Year 1 DAS-28 status, are shown in Table 2. The proportions of patients with Year 2 and 3 HAQ <1.25 or >1.25, according to Year 1 DAS-28 status, are shown in Table 3.

DAS-28 and HAQ outcomes at Years 2 and 3 were proportionally worse on a continuous scale for incremental increases in Year 1 DAS-28 status. Although 74% of patients with a Year 1 DAS-28 <3.2 also achieved DAS-28 <3.2 at Year 2, only 27% of those with a Year 1 DAS-28 3.2–5.1 achieved a DAS-28 <3.2 outcome at Year 2 [odds ratio (OR) 7.64; 95% CI 4.6, 12.6], and 35% at Year 3 (OR 4.49; 95% CI 2.5, 7.9). Data for the more stringent EULAR remission criteria (DAS-28 <2.6) were similar but even poorer. Furthermore, whereas 79% of patients with a Year 1 DAS-28 <3.2 achieved an HAQ <1.25 at Year 2, only 52% of those with a Year 1 DAS-28 of 3.2–5.1 achieved an HAQ <1.25 at Year 2 (OR 3.47; 95% CI 2.1, 5.6) and 47% (OR 4.92; 95% CI 2.6, 9.0) at Year 3 (Tables 2 and 3).

Patients with a DAS-28 in the 3.2–5.1 range at Year 1 were divided into 3.2–4.1 and 4.2–5.1 sub categories. A DAS-28 <3.2 outcome at Year 2 was achieved in 37% of patients with Year 1 DAS 3.2–4.1 and 16% with Year 1 DAS 4.2–5.2 (OR 3.12; 95% CI 1.5, 6.6), and 48 and 19%, respectively, at Year 3 (OR 4.06; 95% CI 1.7, –9.7). The proportion of patients with a Year 1 DAS-28 4.2–5.1 achieving a DAS-28 <3.2 at Year 2 (16%) and Year 3 (19%) was almost identical to that achieved by patients with a Year 1 DAS-28 >5.1 (13 and 15%, respectively) (See Tables 2 and 3).

Discussion

This inception cohort study allows analysis of RA outcomes in a routine care setting. The data illustrate the low chance of achieving a target DAS-28 <2.6 or <3.2 at Years 2 and 3 with conventional, largely non-biologic therapies, if a low DAS has not already been achieved by Year 1 after a new diagnosis of RA. Although all patient groups with a Year 1 DAS-28 3.2–5.1 did poorly with respect to achieving a Year 2 and 3 DAS-28 <2.6 or <3.2, the outcome was particularly poor if Year 1 DAS-28 was at the higher end of this range, i.e. 4.2–5.1. Outcomes were unchanged if the low proportion on anti-TNF therapies (2% Year 1, 4% Year 2, 8% Year 3) were excluded from the analyses (data not shown). The implication for patients treated in England and Wales, where anti-TNF therapies can only be given to those with a DAS-28 >5.1, is stark. If DAS-28 remains 3.2–5.1 after 1 year of traditional disease-modifying therapy, the likelihood of achieving a target remission DAS-28 <2.6 or a low DAS-28 <3.2 at Years 2 or 3 is poor if treatment continues with largely non-biologic DMARDs, according to current routine practice.

TABLE 2 Year 2 and 3 DAS-28 outcomes according to Year 1 DAS-28 categories

Year 1 DAS-28 category	No. of cohorts with Year 2 data	Year 2 DAS-28 <2.6; *n* (%)	Year 2 DAS-28 <3.2; *n* (%)	Year 2 DAS-28 $\geqslant$3.2; *n* (%)	OR of Year 2 DAS-28 <3.2 (95% CI)	No. of cohorts with Year 3 data	Year 3 DAS-28 <2.6; *n* (%)	Year 3 DAS-28 <3.2; *n* (%)	Year 3 DAS-28 $\geqslant$3.2; *n* (%)	OR of Year 3 DAS-28 <3.2 (95% CI)
All cases	418		176 (42)	242 (58)		274		126 (46)	148 (54)	
<3.2	161	91 (55.1)	119 (74)	42 (26)	7.64 (4.6, 12.6) *vs* Year 1 DAS 3.2–5.1	111	63 (57.7)	79 (71)	32 (29)	4.49 (2.5, 7.9) *vs* Year 1 DAS 3.2–5.1
3.2–5.1	170	22 (13.2)	46 (27)	124 (73)	2.56 (1.2, 5.2) *vs* Year 1 DAS >5.1	110	18 (16.4)	39 (35)	71 (65)	3.09 (1.3, 7.2) *vs* Year 1 DAS >5.1
>5.1	87	6 (6.9)	11 (13)	76 (87)		53	3 (5.7)	8 (15)	45 (85)	
3.2–4.1	93	15 (16.9)	34 (37)	59 (63)	3.12 (1.5, 6.6) *vs* Year 1 DAS 4.2–5.1	62	12 (19.4)	30 (48)	32 (52)	4.06 (1.7, 9.7) *vs* Year 1 DAS 4.2–5.1
4.2–5.1	77	7 (9.1)	12 (16)	65 (84)		48	6 (12.5)	9 (19)	39 (81)	

Table 3 Year 2 and 3 HAQ outcomes according to Year 1 DAS-28 categories

Year 1 DAS-28 category	Year 2 HAQ <1.25; *n* (%)	Year 2 HAQ ⩾1.25; *n* (%)	OR of Year 2 HAQ <1.25 (95% CI)	Year 3 HAQ <1.25; *n* (%)	Year 3 HAQ ⩾1.25; *n* (%)	OR of Year 3 HAQ <1.25 (95% CI)
All cases	227	175		156	119	
<3.2	122 (79)	33 (21)	3.47 (2.1, 5.6) *vs* Year 1 DAS 3.2, 5.1	91 (81)	21 (19)	4.92 (2.6, 9.0) *vs* Year 1 DAS 3.2–5.1
3.2–5.1	84 (52)	79 (48)	3.19 (1.7, 5.7) *vs* Year 1 DAS >5.1	51 (47)	58 (53)	2.5 (1.2, 5.1) *vs* Year 1 DAS >5.1
>5.1	21 (25)	63 (75)		14 (26)	40 (74)	
3.2–4.1	56 (61.5)	35 (38.5)	2.51 (1.3, 4.7) *vs* Year 1 DAS 4.2–5.1	34 (56)	27 (44)	2.29 (1.05, 4.9) *vs* Year 1 DAS 4.2–5.1
4.2–5.1	28 (39)	44 (61)		17 (35)	31 (65)	

The HAQ score is a measure of function. It is not generally measured in routine care settings and is recognized to be less sensitive to changes in disease activity once damage has accrued. HAQ is therefore not proposed as a candidate measure to treat target models of care. Nevertheless, it is used in cost-effectiveness modelling and in early disease is reflective of changes in quality of life related to disease activity. For this reason, we have also studied the HAQ response in these patients with early RA. There is no consensus on an equivalent target HAQ score akin to a low DAS-28, and we have arbitrarily divided patients into low and high groups, <1.25 or ⩾1.25, approximately corresponding to the median baseline score for patients registered with ERAN. Patients with a Year 1 DAS-28 3.2–5.1 were less than one-third as likely to achieve a low HAQ (<1.25) at Year 2 compared with those with a Year 1 DAS-28 <3.2, and even less likely at Year 3. The high proportions of those patients with moderate disease activity 1 year after RA diagnosis with HAQ scores ⩾1.25 at 2 and 3 years (48 and 53%, respectively) are indicative that failure to achieve early tight control of disease activity is associated with substantial and persistent disability. High HAQ scores and poor radiographic outcome in patients with a DAS-28 3.2–5.1 receiving non-biologic therapies have also been reported in another early RA inception cohort, the Early Rheumatoid Arthritis Study (ERAS) [11]. In contrast to the disappointing outcomes observed in the ERAS and present study, anti-TNF therapies have the potential to reduce disability in patients with moderate disease activity. RA patients receiving anti-TNF therapies with a baseline DAS-28 score 3.2–5.1 demonstrated an equivalent drop in HAQ (mean 1.78–1.51 at 12 months) compared with those meeting current NICE criteria with a baseline DAS-28 >5.1 (mean HAQ decrease from 2.05 to 1.71 at 12 months) [12].

Routine care in most ERAN centres during the period of data collection for this study was dominated by initial use of DMARD monotherapy, followed by continued monotherapy or escalation to combination DMARDs as a second-line strategy [13]. The principles of tight control [2, 3] were not in common practice and, irrespective of frequency of follow-up or use of protocol driven treatment to target, it is noteworthy that there was a low use of combination DMARDs (26% Year 1, 33% Year 2, 34% Year 3) and steroids (up to 33% co-prescribed with combination DMARDs, <20% with monotherapy DMARDs at time of data collection) in this cohort. The poor DAS-28 outcome that we observed is similar to controlled trials where only a low percentage of patients are reported to achieve a DAS-28 <3.2 with MTX monotherapy; for example, 30% in the Swedish Pharmacotherapy trial (SWEFOT) at 3–4 months [14]. This contrasts with the benefits of a treatment strategy for early RA commencing with combination DMARDs and steroids, exemplified by the combination therapy for RA (COBRA) protocol [15], and subsequently shown to be superior to a delayed step-up combination regime [16, 17].

Adoption of some or all of the principles of tight control might improve the proportion of patients achieving a low DAS-28 in routine care. This is suggested by Fransen *et al.* [18], who compared outcome in Dutch rheumatology centres where the DAS-28 was or was not recorded at each visit, and a target of 3.2 was advised, without a mandatory dose escalation protocol. Although DMARD changes were made in that study on only 20% of occasions that the DAS-28 was >3.2, the proportion of patients achieving a low DAS-28 after 24 weeks was 31% compared with 16% in the comparator group where DAS-28 was not recorded. While the shift into the DAS-28 <3.2 range came from patients who had had a baseline DAS-28 in the 3.2–5.1 category, a large proportion of patients remained in the DAS-28 3.2–5.1 range, despite DAS-28 being recorded. It remains to be established what impact a more thorough tight control model of care with mandatory treatment escalation and use of biologics at lower DAS-28 thresholds would achieve.

For patients within the ERAN cohort, DAS-28 is recorded by the responsible clinicians or nurse practitioners at least annually, but was not necessarily available at the time of routine clinic visits when treatment decisions were made. Our data concur with the Dutch findings that availability of DAS-28 data alone in normal clinical practice does not always lead to achievement of DAS-28 <3.2.

Factors other than disease activity may contribute to DAS-28 scores (e.g. OA, FM) and treatment choices (e.g. comorbidities and concerns about treatment toxicity). Although attempts to achieve DAS-28 <3.2 may not be desirable or realistic for all patients, the low levels of tight control observed in this study, including restrictions on the use of biologic therapies, were clearly associated with sustained and substantial disability illustrated by the HAQ responses. Further research is required to identify barriers to DMARD escalation and tight control, how to identify and treat patients for whom DMARD escalation is not appropriate, and to define appropriate outcome targets by which to benchmark future clinical care.

In summary, these data have demonstrated in a routine care setting that ongoing DMARD therapy from Year 1 to 2 or 3 results in a very low likelihood of achieving target DAS-28 <2.6 or 3.2 in patients with early RA who have not already achieved this by Year 1. This supports the recent NICE RA treatment guidelines recommending tighter control and early combination DMARD therapy [1] and lends weight to the new BSR guidelines recommending that anti-TNF therapies should be available to patients with active disease and a DAS-28 >3.2 [9].

Rheumatology key messages

- DMARD therapy results in a low likelihood of achieving target DAS-28 <3.2 if Year 1 DAS-28 >3.2.
- DMARD therapy results in a low likelihood of achieving a low HAQ if Year 1 DAS-28 >3.2.

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