Contemporary patterns of care and disease activity outcome in early rheumatoid arthritis: the ERAN cohort

P. Kiely1, R. Williams2, D. Walsh3 and A. Young4 for the Early Rheumatoid Arthritis Network (ERAN)

Introduction
Clinical trials demonstrate that optimum short- and long-term outcome in early RA is influenced by several factors. The time between symptom onset and start of first DMARD appears to be critical, as does the choice of DMARD, be it as a single drug used alone (monotherapy), or more than one drug used simultaneously (combination therapy) with or without corticosteroids.

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 data set 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. This provides the opportunity to report from a multicentre prospective RA cohort, on patterns and standards of care in routine specialist practice across the UK and Eire, and to compare this with optimum models of care demonstrated in clinical trials.

Patients and methods
Patients diagnosed in routine care 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 diagnostic criteria is not a prerequisite for recruitment. The study was approved by the Trent Research

Objective. To report from the Early Rheumatoid Arthritis Network (ERAN), time from symptom onset to start of therapy, treatment choices and disease outcome in early RA.

Methods. Patients with newly diagnosed RA were prospectively enrolled from 19 centres in the UK and Eire. Standardized information was collected on case report forms at first presentation, 3–6 months, 1 yr and annually thereafter. The choice and intensity of drug treatment was left to the discretion of individual centres.

Results. A total of 808 patients were recruited between 2002 and 2007, with a mean follow-up of 16 (0–60) months. Of them, 62% fulfilled four or more ACR criteria for RA at first visit. The median time from onset of symptoms to referral to secondary care was 4 months [interquartile range (IQR) 2–9, n = 655] and to start of first DMARD 8 months (IQR 4–13, n = 638). DMARDs were prescribed in 97% of the patients, initially as monotherapy in 91%, and as combination therapy in 9%. The second DMARD (n = 220) was a switch to another as monotherapy in 52% and step-up to combination therapy in 48%. The proportions with a 28-joint disease activity score > 5.1 at baseline and 3 yrs were 46 and 19%, > 3.2 were 84 and 54% and < 2.6 were 6 and 33%, respectively.

Conclusions. Patients presenting with RA in ERAN do not receive DMARDs promptly, largely due to delays in referral to secondary care. Contemporary treatment practice is to start with DMARD monotherapy, and to use combination DMARDs as second-line therapy in approximately half of them. Over 3 yrs the proportion of patients continuing to have active disease remains high.

Key words: Early rheumatoid arthritis, Disease-modifying anti-rheumatic drug, Combination therapy, 28-Joint disease activity score.

A total of 808 newly diagnosed RA patients have been recruited from 19 centres between 2002 and 2007. Not all centres recruited patients to ERAN throughout this 5-yr period, some joining part way through and others stopping towards the end. All newly diagnosed RA patients seen by the consultant-led team participating in ERAN were invited to participate during the time that each centre was recruiting. The mean age at baseline was 55 yrs, 67% females, 58% RF positive and 28% erosive on hand or foot radiographs. Mean follow-up to date is 16 months (range 0–60 months). Of the total patients, 484 patients (62%) fulfilled four or more ACR criteria for RA at the first visit. By the last visit this increased to 544 (67%) using traditional ACR criteria, and 564 (70%) using the ACR tree criteria, which allows for missing items.

Time to referral to secondary care. The median time from the onset of first symptoms of RA to the date of GP referral to secondary care was 4 months [interquartile range (IQR) 2–9 months, n = 655]. There was a further median delay of 1 month (IQR 1–2 months, n = 677) for the time from GP referral to first secondary care appointment (Fig. 1).
the choice was MTX in 29% (n = 655), median 4 months, IQR 2–9 months; Onset→OPD: onset of first symptoms to first outpatient appointment (n = 689), median 5 months, IQR 3–12 months; Onset→First DMARD: onset of first symptoms to first DMARD (n = 638), median 8 months, IQR 4–13 months; OPD→First DMARD: first outpatient appointment to first DMARD (n = 578), median 1 month, IQR 0–2 months; Onset→steroids: onset of first symptoms to first corticosteroid (n = 554), median 7 months, IQR 3–14 months.

**DMARD analysis cohort**

DMARD use is reported from the subgroup with a minimum 3-month follow-up (n = 691, 85.5%), in order to allow for the early use of combination DMARD therapy as defined above. This has allowed us to examine DMARD use in the majority of patients recruited, 668 of whom received DMARDs.

**Time to first DMARD.** The median time from the onset of first symptoms of RA to start of first DMARD was 8 months (IQR 4–13 months, n = 638). This interval was the same for patients recruited each year between 2002 and 2006, but in patients recruited in 2007 (n = 78) the median time was 5 months. The delay from the first secondary care appointment to the start of the first DMARD was 1 month (IQR 0–2 months, n = 578) (Fig. 1).

**Choice of first-line DMARD therapy.** A DMARD was prescribed to 668 (97%) patients. The first DMARD used was one drug in monotherapy in 91% of the cases (n = 605) and as two or more drugs in combination therapy in 9% of the cases (n = 63).

When the first DMARD was used as monotherapy (n = 605), the choice was MTX in 51% (n = 309), SSZ in 41% (n = 246), HCQ in 6% (n = 34) and LEF in 2% (n = 12).

When the first DMARD was used in a combination (n = 63), the choice was MTX + SSZ in 37% (n = 23), MTX + SSZ + HCQ in 29% (n = 18), MTX + HCQ in 21% (n = 13), SSZ + HCQ in 6% (n = 4) and MTX + LEF in 6% (n = 4).

**Choice of second-line DMARD therapy.** A second DMARD was prescribed to 220 of those who had first received a DMARD as monotherapy. The choice was a switch to another single DMARD (i.e. sequential monotherapy) in 52% (n = 114) and the addition of a second DMARD (i.e. step-up combination therapy) in 48% (n = 106). The proportion changing to sequential monotherapy and to step-up combination therapy did not change per year from 2004 to 2007.

**Corticosteroid use.** Corticosteroids were given to 489 patients (71%); either intramuscularly or intravenously to 54% (n = 262), orally to 30% (n = 149) and intra-articularly to 16% (n = 78) of the patients. The proportion of new RA patients per year receiving oral steroid between 2002 and 2007 remained ~20%.

**Disease activity outcome variables.** Baseline and 12 months median clinical function and serological variables are shown in Table 1 for patients where paired data at both time-points were available. Each outcome measure improved significantly, with the exception of haemoglobin, over this period.

A 28-joint disease activity score (DAS28) outcome divided into EULAR response categories from paired data in individual patients is illustrated in Table 2 and Fig. 2 for three cohorts where annual data were available for 1, 2 and 3 yrs of follow-up. In the cohort with 1-yr paired data (n = 338) the DAS28 score at 1 yr was >3.2 in 61% of the patients, with 25% achieving a remission score of <2.6. In the cohort with 3-yr paired data (n = 89), the proportion at 3 yrs with a DAS28 >3.2 was 54% and a remission score of <2.6 was 33%.

The chance of achieving a particular DAS28 response at 12 months according to the baseline DAS28 score is shown in Table 3. A 1-yr DAS28 score <3.2 was achieved in 74% of the patients with a baseline DAS28 score <3.2, and in 23% with a baseline DAS28 score of >5.1.

**Discussion**

These data demonstrate contemporary patterns of care and outcome in early RA over the last 5 yrs in 19 centres across the UK and Eire.

In this large prospective cohort (with a minimum of 3-month follow-up data) DMARDs were prescribed to 97% of patients (n = 668), with a median time to commencement of 8 months from the first onset of symptoms. This compares with a median of 23 weeks from symptom onset to assessment by a rheumatologist in a cohort of 169 patients in Birmingham, UK [1] and a median of 8.4 months from symptom onset to start of DMARD treatment in a cohort of 339 patients in Canada [2]. Similarly, in a review of over 4000 patients with RA, a median delay in starting DMARDs was reported to range from 4 to 15 months in 15 different countries [3]. Half of this delay in the ERAN cohort was in the time from the first onset of symptoms to the date of GP referral to secondary care. Similarly, a major delay in the smaller Birmingham and Canadian cohorts was in the phase between symptom onset and referral to a rheumatologist [1, 2]. The ERAN data set did not enable a dissection of this into the time from first onset of symptoms to first GP consultation and from this to GP referral to secondary care. Nevertheless, this interval spanned a median of 4 months with a wide IQR of 2–9 months.
TABLE 2. Percentage of patients achieving DAS28 scores, divided into EULAR response criteria, at defined follow-up times in three cohorts where paired patient follow-up data was available over 1, 2 and 3 yrs.

<table>
<thead>
<tr>
<th>Score</th>
<th>DAS28 &lt;3.2</th>
<th>DAS28 3.2–5.1</th>
<th>DAS28 &gt;5.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline 1 yr</td>
<td>n = 338</td>
<td>n = 338</td>
<td>n = 192</td>
</tr>
<tr>
<td>&lt;3.2</td>
<td>66</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>3.2–5.1</td>
<td>74</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>&gt;5.1</td>
<td>74</td>
<td>45</td>
<td>45</td>
</tr>
</tbody>
</table>

Further 4 months [5]. Further support for the benefits of starting DMARD therapy promptly come from a subgroup analysis of the FIN-RACo study in which patients started on DMARD monotherapy within 4 months of symptom onset were significantly more likely to be in remission after 2 yrs compared with those where monotherapy was started after 4 months of symptom onset [6]. Interestingly, in the same study this effect was not apparent in a group treated with combination therapy.

The implications for contemporary practice from the ERAN cohort, where the majority of patients were treated with DMARD monotherapy, is that we should strive to start treatment sooner. This will require a considerable shortening of the time from symptom onset to referral to secondary care, and/or the commencement of DMARD therapy much earlier in the patient pathway, possibly within primary care. Strategies to achieve this may include public education to encourage early presentation to primary care, and closer working relationships and guidelines between individual primary and secondary care centres to reduce the time to onset of first DMARD therapy.

In the ERAN cohort, the first DMARD was used as a single drug in 91% of the cases, and where a second DMARD was used this was as a switch to another monotherapy drug in over half of them. This contrasts with mounting evidence that combination DMARD therapy is superior to monotherapy in both early and established RA. A meta-analysis of combination therapy trials shows a relative risk of stopping combination therapy due to inefficacy to be 0.35 compared with monotherapy [7]. Long-term benefits of combination therapy are suggested by the COBRA study where 5-yr follow-up showed radiological benefit in the COBRA arm, despite the restriction of combination therapy to the first 40 weeks, compared with patients receiving DMARD monotherapy from the outset [8]. Furthermore, 5-yr follow-up of the FIN-RACo study also shows continued radiological benefit in the combination DMARD arm compared with those initially treated with monotherapy, even though 62% of this group switched to combination therapy at year 2 [9]. Although one would naturally expect a delay between a body of evidence and a change in practice, there was no suggestion of a trend away from sequential DMARD monotherapy to combination therapy in each newly recruited annual ERAN cohort from 2004 to 2007.

Disease outcome within the first 3 yrs of diagnosis in the ERAN cohort was heterogenous. Whilst the proportion of patients achieving a good response or remission by EULAR criteria, i.e. DAS28 <3.2, rose at each year of follow-up (Table 2) the total remains relatively low with only 46% achieving this at 3 yrs and 36% at 2 yrs (Table 2). Interestingly, the chance of achieving a good outcome at 1 yr diminishes with rising baseline DAS28 score (Table 3). To what extent these DAS28 outcomes reflect a delay to the start of first DMARD therapy, or the use of DMARD as monotherapy (and little corticosteroid use), rather than combination therapy is undetermined. However, if more intense combination therapy were to be used the ERAN data suggest that this might be best targeted to those patients with a baseline DAS28 >5.1, as 35% of these still had a 1-yr DAS28 >5.1 after DMARDs were used initially as monotherapy. In contrast, only 6% of the patients with a baseline DAS28 <3.2 had a 1-yr DAS28 of >5.1, and therefore initial DMARD monotherapy may be appropriate for these, given that 74% continued to have a 1-yr DAS28 of <3.2.

In conclusion, the ERAN data set of over 800 newly diagnosed RA patients from 2002 to 2007 has demonstrated that in routine clinical trial data suggest that a delay of >4 months between symptom onset and start of DMARD therapy leads to a significantly worse outcome. In one study, early RA patients started on DMARD monotherapy within 3 months of symptom onset had a significant improvement in composite disease activity (DAS28, ACR20 and -70 response) first detected at 3 months and sustained along with radiographic scores for 3 yrs compared with a comparator group starting DMARD monotherapy after 9 months of symptoms [4]. Similarly, patients presenting with a median symptom duration of 4–6 months had significantly better disease activity, function and radiographic outcome at 2 yrs if DMARD monotherapy was started immediately compared with a historical comparator group where treatment was delayed for a median symptom duration of 4–6 months between symptom onset and start of DMARD therapy.
Rheumatology key messages

- In ERAN, the median time from symptom onset to start of first DMARD is 8 months, with half the delay occurring before referral to secondary care.
- The majority of patients with early RA are treated with DMARD monotherapy, with <10% receiving combination DMARDs within 3 months of first outpatient appointment.
- Disease activity and function scores all improve significantly at 1 yr, but <50% have a DAS28 score <3.2 after 3 yrs.

Acknowledgements

Project management and source data verification: Ms W. Garwood; Data handling and entry: Ms C. Mayes, ERAN Co-ordinating center, Rheumatology Research & Audit Office, St Albans City Hospital, Herts, UK.

ERAN recruiting centers: Dr M. Webley, Dr S. Edmonds, Ms J. Hall (Aylesbury); Dr H. Averns, Ms N. Seaman & J. Brown (Barnstaple); Dr P. Prouse, Ms S. Andrews (Basingstoke); Dr K. Adams, Ms R Hunter (Bolton); Dr P. Creamer, Ms J. Taylor (Bristol); Dr C. Dunne, Ms L. Hawley (Christchurch); Dr J. Griffin, Ms P. Goodman (Enfield); Dr A. Coulson, Dr S. Nagasayi, Ms S. Morris (Haverfordwest); Dr S. Bhalara, Ms E. Jones (Hemel Hempstead); Dr R. Williams, Ms K. Blunn (Hereford); Dr M. Bukhari, Dr J. Halsey, Ms B. Evans & J. Kaye (Lancaster); Dr P. Kiely, Ms F. Leone (St George’s, London); Dr D. Walsh, Dr N. Carter, Ms D. Wilson (Mansfield); Dr J. David, Ms M. Cox (Oxford); Dr A. Young, Ms A. Seymour (St Albans); Dr A. Hassell, Ms M. Roxas (Stoke-on-Trent); Dr J. Devlin, Ms S. Goff (Waterford, Eire); Dr S. Clarke, Ms B. Williams (Weston-super-Mare); Dr T. Pulleran, Ms C. Buckley (Yeovil).

Disclosure statement: The authors have declared no conflicts of interest. ERAN has received funding from Wyeth Pharmaceuticals and the Healthcare Commission.

Supplementary data

Supplementary data are available at Rheumatology Online.

References