Sustained clinical remission in rheumatoid arthritis: prevalence and prognostic factors in an inception cohort of patients treated with conventional DMARDS

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Abstract

Objective. Clinical remission is now a realistic goal in managing RA following the introduction of biologic agents. As there are limited data on sustained remission in conventionally treated RA, this study examines prevalence and predictive factors of sustained remission in a pre-biologic inception cohort of RA.

Methods. Patients with recent onset RA and before use of DMARDs were recruited from nine centres. Standard clinical and radiological assessments were recorded at baseline and yearly. Point remission was defined by DAS of <1.6, and sustained remission if DAS was <1.6 at all 3-, 4- and 5-year follow-ups. Sustained remission was compared with baseline features, with mortality and with radiological and functional progression in 704 patients.

Results. Point remission at 3, 4 and 5 years was 25, 26 and 22%, respectively. Eleven per cent (n = 78) had sustained remission. Male sex, short duration of symptoms and less tender joints at baseline were independent predictors of sustained remission. These patients had fewer DMARD therapies and less radiographic progression by 5 years. Mean HAQ decreased from 0.79 to 0.13 (P < 0.001) in sustained remission, compared with an increase from 0.92 to 1.1 (P < 0.001) in the non-remission group.

Conclusion. Sustained clinical remission by 5 years with conventional DMARDs was 11%, half as likely as point remission. Prognostic factors were similar to comparable studies and simple to measure. Patients in sustained clinical remission showed less structural damage and better functional outcomes.

Key words: rheumatoid arthritis, clinical remission, prognosis, functional outcome, HAQ, X-rays

Introduction

RA has a highly variable course over time. Adverse outcomes include structural damage (X-ray erosions and orthopaedic surgery), functional and work disability and increased morbidity and mortality [1–5]. Disease progression is unpredictable and reported remission rates vary depending on both study design and definition used. The ultimate goal of treatment is to achieve and maintain remission as early as possible, supported by studies reporting better remission rates with early initiation of anti-rheumatic therapy [6]. With the introduction of biological agents, remission has become a realistic goal in clinical practice, and is now a primary outcome of many randomized studies of new therapeutic agents. Prevalence and prognostic factors of remission in normal clinical settings are important aspects of care for rheumatologists, their patients and health-care planners. Only a few studies have examined sustained remission in
Materials and methods

Patients

The early RA study (ERAS) was established in 1986 to recruit all newly diagnosed RA patients and to record standard assessments annually in order to measure outcomes and prognostic markers as previously described in detail [3]. ERAS received ethical approval from the West Hertfordshire Local Research Ethics Committee and subsequently from the Caldicott Guardian. Inclusion criteria were <2 years from symptom onset and no previous DMARD use (n = 1429). For this study, inclusion was based on minimum 5-year follow-up, DAS recorded at each of baseline, third, fourth and fifth year follow-up visits, and outcome data at 5 years (n = 704). Reasons for not completing 5-year follow-up (n = 304) were: deceased (195, 64%), moved (25, 8%), declined for social reasons (28, 9%), remission (10, 3%) and not known (46, 16%).

Clinical assessments

Trained research nurse practitioners assessed patients at baseline, 6 months and annually using standard clinical and laboratory measurements, including early morning stiffness, grip strength, pain visual analogue scale (VAS), swollen joint count (SJC) and tender joint count (TJC), presence of extra-articular features, ESR, RF and modified Stanford HAQ. Also documented were family history of RA, prodromal symptoms or trigger factors, type and speed of onset, socio-economic status and the RA-related shared epitope (SE), as previously described [3, 11, 12]. Five-year outcome measures included Steinbrocker’s functional grade (FG I-IV), RA-related work disability [13], structural damage as measured by X-rays [14] and need for orthopaedic surgery [4] and cause of death [15]. Disease activity was assessed using the original three-variable DAS [9], which uses SJC and TJC, and acute phase (ESR or CRP), as ERAS started before the now more widely used four-variable 28-joint DAS (DAS-28). Both have been validated and widely accepted by the European League Against Rheumatism (EULAR) [16, 17]. Point remission (DAS at one specific time) was defined by DAS <1.6 according to the EULAR response criteria [18]. For this study, sustained remission was defined by DAS <1.6 at all consecutive 3-, 4- and 5-year time points, non-remission if DAS was ≥1.6 at all three follow-ups, and partial remission for other combinations.

Radiological assessment

X-rays of hands and feet were performed at baseline, 1, 2, 3 and 5 years, and coded for the presence of erosions. Films were digitized and scored using Larsen’s method in random order by a trained rheumatologist, who was blinded to clinical details and subject to regular intra-observer variability, as previously described [19].

Treatment profile

All centres followed the UK published framework guidelines for management of RA in the 1990s, which include early use of sequential monotherapy, step-up combination therapy in patients with severe disease and judicious use of steroids. DMARDs were chosen according to the physician’s preference, and reasons for discontinuation ascertained as loss/lack of effect, adverse events, both, remission or other (e.g. patient choice) as previously described [3]. Biological agents were not available during the study period.

Statistical analysis

Summary statistics demonstrate differences in clinical and laboratory features between remission groups. Continuous variables were expressed as either mean (s.d.) or median with interquartile ranges (IQRs). Chi square (χ²) for categorical variables and Mann-Whitney U (MWU) for continuous data were used to compare study groups. Wilcoxon signed-rank test was used to test differences in measures over time. Odds ratio (OR) with 95% CI was used to assess the predictive value of baseline variables for sustained remission by 5 years. Median values were used as cut-off points to dichotomize continuous into categorical variables, except Larsen scores, where 75th percentile was used as most patients had low scores at baseline. Multiple logistic regression using stepwise selection was performed to examine baseline variables for predicting subsequent sustained remission.

Missing baseline data

Data were missing in <1% for all variables except for smoking history (153, 22%), which was only added from 1992 and was unobtainable retrospectively in patients who moved or died before this; HLA typing (140, 20%); Larsen scores (75, 10%) due to inadequate quality of digitized images; and BMI (33, 4%).

Results

Clinical remission

One hundred and seventy-nine (25%) patients achieved DAS remission at 3 years, 183 (26%) at 4 years and 158
Sustained clinical remission in RA

Table 1 Baseline variables in sustained, partial and non-remission groups

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>Total</th>
<th>Sustained</th>
<th>Partial</th>
<th>No remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>704</td>
<td>78 (11)</td>
<td>204 (29)</td>
<td>422 (60)</td>
</tr>
<tr>
<td>RF</td>
<td>242 (34.4)</td>
<td>43 (55.1)</td>
<td>88 (43.1)</td>
<td>111 (26.3)</td>
</tr>
<tr>
<td>X-rays H/F</td>
<td>241 (34.3)</td>
<td>32 (41.0)</td>
<td>64 (31.5)</td>
<td>145 (34.4)</td>
</tr>
<tr>
<td>Smoking history</td>
<td>513 (73.8)</td>
<td>60 (76.9)</td>
<td>157 (78.1)</td>
<td>296 (71.2)</td>
</tr>
<tr>
<td>Social class</td>
<td>312 (56.6)</td>
<td>30 (55.6)</td>
<td>99 (59.6)</td>
<td>183 (55.3)</td>
</tr>
<tr>
<td>HLA-DRB1 SE</td>
<td>146 (20.9)</td>
<td>27 (34.6)</td>
<td>49 (24.3)</td>
<td>70 (16.7)</td>
</tr>
<tr>
<td>Symptom duration</td>
<td>162 (28.7)</td>
<td>20 (32.3)</td>
<td>46 (29.3)</td>
<td>96 (27.8)</td>
</tr>
<tr>
<td>DMARDS by 1 year</td>
<td>347 (49.3)</td>
<td>47 (60.3)</td>
<td>108 (52.9)</td>
<td>192 (45.5)</td>
</tr>
<tr>
<td>Steroids by 1 year</td>
<td>167 (23.7)</td>
<td>27 (34.6)</td>
<td>55 (27.0)</td>
<td>85 (20.1)</td>
</tr>
<tr>
<td>Age of onset, years</td>
<td>601 (85.4)</td>
<td>69 (88.5)</td>
<td>184 (90.2)</td>
<td>348 (82.5)</td>
</tr>
<tr>
<td>RA symptoms</td>
<td>55 (45–64)</td>
<td>57 (3–64)</td>
<td>54.5 (42.3–64)</td>
<td>55 (45–65)</td>
</tr>
<tr>
<td>(months to baseline)</td>
<td>7 (4–12)</td>
<td>5 (3–9)</td>
<td>6 (4–12)</td>
<td>7 (4–12)</td>
</tr>
<tr>
<td>Tender joints</td>
<td>10 (4–19)</td>
<td>6 (2–12)</td>
<td>8 (4–16)</td>
<td>12 (6–22)</td>
</tr>
<tr>
<td>Swollen joints</td>
<td>13 (6–25)</td>
<td>8 (3–20)</td>
<td>10 (5–22)</td>
<td>16 (8–29)</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.0 (0.5–1.5)</td>
<td>0.63 (0.25–1.25)</td>
<td>0.88 (0.38–1.25)</td>
<td>1.13 (0.63–1.63)</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>37 (20–61)</td>
<td>37 (16–51)</td>
<td>36 (20–68)</td>
<td>38 (20–61)</td>
</tr>
<tr>
<td>Steroid start (months from baseline)</td>
<td>1 (0–24)</td>
<td>1 (0–24)</td>
<td>2 (0–24)</td>
<td>1 (0–24)</td>
</tr>
<tr>
<td>DMARD start (months from baseline)</td>
<td>2 (1–4)</td>
<td>2 (1–8)</td>
<td>2 (0–4)</td>
<td>2 (1–3)</td>
</tr>
</tbody>
</table>

Remission = DAS < 1.6. Figures are valid numbers with either percentage of total or remission groups or median with quartile values. Median and IQR for Larsen scores at baseline not included because all were equal to 0. Mean was 4.3 overall and 2.1, 3.4, 5.1 in remission groups.

(22%) at 5 years. DAS remission at 3 years persisted for a further 12 and 24 months in 113 (63%) and 78 (44%), respectively, of these patients. The main baseline disease characteristics of patients with sustained, partial or no DAS remission are shown in Table 1. Since the main endpoint of this study was sustained DAS remission (n = 78, 11%), for statistical analysis this has been compared with the remainder (n = 626, 89%).

Diagnostic certainty

The 1987 revised ARA criteria [20] were not used formally by ERAS clinicians, although all items were recorded as part of yearly assessments. However, when applied, the majority of patients in sustained remission fulfilled the minimum four ARA criteria for the diagnosis of RA at some stage. The minimum four or more ARA criteria were present in 70.5% at baseline and in 96.5% by last visit. ARA criteria were present in 55, 73, 76 and 91.5% at baseline, 6 months, 1 year and ever in sustained remission, compared with 76, 87, 90 and 98% in the remainder. Seven patients in the sustained remission group achieved only three ARA criteria, mean baseline DAS 3.3 (range 1.2–5.5), two seropositive, four with Larsen scores >2, three started DMARDs early. Excluding these seven patients from analysis did not significantly affect the results.

Treatment

Monotherapy was used in 43%, sequential monotherapy in 30% and combination therapy in 18%. Mono or combination DMARD therapy was used more frequently in the non-remission compared with the remission group at all time points (Year 1 = 78 vs 65%; P < 0.01, Year 3 = 85 vs 70%; P < 0.01, Year 5 = 87 vs 70%; P < 0.001). One hundred and three (14.5%) patients were managed with steroidal or non-steroidal drugs alone, because of mild RA or patient preference, 23 (29.5%) in sustained remission, compared with 80 (13%) in the non-remission group. Time in months from baseline (i.e. initial rheumatology presentation) to first DMARD and/or steroid use was similar (median 1 month). However, time from onset of RA to first DMARD was shorter in sustained remission compared with non-remission (median 8 and 10 months), as was steroid use (median 7 and 12 months), but none achieved statistical significance. SSZ was the most common DMARD in all groups (80–83%), followed by MTX. Analysis of individual DMARD effects is limited since this was not a randomized study.

Predictive factors

Baseline variables for sustained DAS remission were examined using univariate and multivariate analyses (Table 2). Family history of RA, speed and type of onset, smoking history and extra-articular features were not predictive and not shown in the table. Multiple logistic regression with forward stepwise selection identified male sex, shorter duration of symptoms and less tender joints at baseline with significant independent predictive value for
sustained clinical remission. Early use of DMARDs was not predictive for sustained DAS remission.

**RA outcomes at 5 years**

Sustained remission was associated with less functional impairment, work disability, X-ray damage and orthopaedic surgery (Table 3). Joint replacement surgery by 5 years was required in 48 (8%) in the non-remission group, but none in the remission group. More patients in the non-remission group died after 5 years follow-up (22.6 vs 15.4%), but the difference was not statistically significant. Comparisons of main cause of death (e.g. cardiovascular) were not possible because of few deaths in sustained remission.

Figures 1 and 2 show rates of progression of RA by Larsen score and HAQ in two groups. In the remission group, HAQ improved from baseline to 5 years ($P < 0.001$). In contrast, HAQ in the non-remission group was higher at baseline, initially improved and then deteriorated. Three extreme outliers for HAQ in the remission group had severe comorbidities (myelopathy secondary to cervical spondylosis, PMR, severe OA of knees), the most likely explanation for HAQ scores higher than expected for inactive RA. This has prompted further detailed study of the effect of comorbidity on function in RA. Larsen scores were similar at baseline in both groups (median 0), but increased more in the non-remission group (median 11, $P < 0.0001$). Figure 1 shows that some X-ray progression still occurred in the sustained remission group, and a more detailed analysis of this cohort is already underway to examine the nature of the progression of radiological damage in apparent clinical remission.

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**Table 2** Predictive factors for sustained remission using univariate and multivariate analysis

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>Univariate, OR (95% CI)</th>
<th>Multivariate, OR (95% CI)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>2.6 (1.6, 4.2)</td>
<td>2.64 (1.54, 4.54)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Symptoms &lt;6 months at entry</td>
<td>1.6 (1.0, 2.7)</td>
<td>3.15 (1.03, 10.00)</td>
<td>0.046</td>
</tr>
<tr>
<td>RF negative</td>
<td>1.4 (0.9, 2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SE negative</td>
<td>1.2 (0.7, 2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No erosions</td>
<td>1.2 (0.7, 2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain score (VAS) &lt;45</td>
<td>2.1 (1.3, 3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMS &lt; 1 h</td>
<td>1.6 (1.0, 2.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grip &gt;140 mm (0–300)</td>
<td>1.6 (1.0, 2.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TJC &lt; 10</td>
<td>3.0 (1.7, 5.0)</td>
<td>3.73 (1.09, 1.28)</td>
<td>0.016</td>
</tr>
<tr>
<td>SJC &lt; 13</td>
<td>1.9 (1.1, 3.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR &lt; 37</td>
<td>1.1 (0.7, 1.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAS &lt; 4.1</td>
<td>2.7 (1.6, 4.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAQ &lt; 1.0</td>
<td>2.1 (1.3, 3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Larsen score &lt; 4</td>
<td>1.6 (0.8, 3.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3** Five-year outcome in remission and non-remission groups

<table>
<thead>
<tr>
<th>Disease activity (DAS)</th>
<th>X-ray Erosions, n (%)</th>
<th>Worse FG (III and IV), n (%)</th>
<th>Stopped work due to RA, n (%)</th>
<th>Orthopaedic interventions, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission (n = 78)</td>
<td>42 (54)</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Non-remission (n = 626)</td>
<td>486 (78)</td>
<td>95 (15)</td>
<td>74 (12)</td>
<td>94 (15)</td>
</tr>
<tr>
<td>$P$-value ($\chi^2$)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.002</td>
</tr>
</tbody>
</table>

**FIG. 1** Radiological (Larsen) progression between baseline and 5 years. Larsen scores are shown as median values (horizontal line) within quartile ranges (boxes) for remission and non-remission groups at baseline, 1, 2, 3 and 5 years. Whiskers (vertical lines) extend to values within 1.5 box lengths, which include outliers.
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sustained remission, which varied from months to epi-

tome with the ARA preliminary criteria for point remission
DAS $<$

defined clinical criteria for remission [26] or DAS, or both.

definitions of both point and sustained remission [7, 8].

clude differences in study design and wide variation in
rates of between 10 and 20% [21].

Sustained DAS remission was 11% by 5 years in this
cohort, around half the prevalence of point remission at
each 3-, 4- and 5-year follow-up assessments. Although
several individual baseline variables showed modest
prognostic value, only male sex, short duration of symp-
toms and few tender joints were predictive of DAS sus-
tained remission in multivariate analysis.

Previous prospective studies on remission in patients
treated with conventional therapy have reported remission
rates of between 10 and 20% [21–25]. Explanations in-
clude differences in study design and wide variation in
definitions of both point and sustained remission [7, 8].
Many have used either the original or modified ARA pre-
liminary clinical criteria for remission [26] or DAS, or both.
DAS $<$ 1.6 and DAS-28 $<$ 2.6 have been shown to corre-
late with the ARA preliminary criteria for point remission
[16–18]. The main difference comparing these studies is
the time of point remission (2–5 years) and the duration of
sustained remission, which varied from months to epi-
sodic events over years. This contrasts with remission
lasting 2 years in the present study, which may explain
the lower rate. The current study design has allowed
examination of sustained remission as a defined outcome
at an important stage of RA in ordinary clinical settings,
and not primarily a measure of treatment response over a
short period, as in other studies.

Clearly, DMARD-free remission is the ultimate goal, and
reliable predictors would greatly assist clinicians in deci-
sions concerning early use of DMARDs and biologics.
An inception cohort in the Netherlands identified several
prognostic factors for DMARD-free remission lasting
1 year. Due to similarities in study design, validation with
the ERAS cohort was possible and five of these predictors
were replicated in our cohort — acute onset, short symp-
tom duration before inclusion, non-smoking, absence of
RF and the HLA SE alleles [10].

Reported baseline predictive factors for remission vary,
but some feature consistently for most definitions of re-
mission. These include men, RF negativity, less swollen
and/or tender joints and absence of radiographic damage,
similar to the findings in this study [10, 21, 23, 25, 27, 28].
An additional and important prognostic factor for sus-
tained DAS remission in the current study was shorter
symptom duration before study inclusion. Sixty per cent
had $<$ 6 months’ symptoms to presentation, compared
with 50% in non-remission. A similar observation has
been reported by the Finnish RA combination therapy
trial (FIN-RACo), where the delay to therapy was the
only significant predictor for remission in patients treated
with a single-DMARD strategy [6]. Similarly patients pre-
senting with a median symptom duration of 4–6 months
had significantly better disease activity, function and
radiographic outcome at 2 years if DMARD monotherapy
was started immediately compared with a historical com-
parator group where treatment was delayed for a further
4 months [29]. This confirms the importance of early re-
ferral and treatment for achieving the best possible out-
come in RA. Interestingly, remission did not necessarily
equate with early use of DMARD or steroid therapy in
our study since 29.5% of patients who achieved sustained
remission did so without DMARDs. Steroid use was simi-
lar at $\sim$15% in all groups. Current recommendations for
the modern management of early RA include more inten-
sive DMARD therapy than in the 1990s, but whether this is
standard practice in the UK is unclear. In fact, in one
recent report on newly diagnosed RA between 2002 and
2007 in 20 centres, DMARD use was higher than the cur-
rent study (97%), but the expected greater use of com-
ination therapy was not seen (9%); most patients started
on monotherapy at outset (91%) [30]. This suggests that
even though the current study reports on a previous
decade, the results remain relevant to management of
RA in this millennium.

ERAS was not designed to examine causal effects, but
we observed that patients in sustained remission also had
better radiographic, orthopaedic and functional outcomes
by 5 years, an important finding since the ultimate thera-
peutic aim of many therapeutic trials is reduced radio-
logical progression. This is not a commonly studied area
in early RA patients treated with traditional DMARDs in routine settings, although correlations have been reported between function (HAQ) and DAS [31]. Radiographic progression despite sustained remission in our patients is an important finding, which supports some other reports [32, 33], and will be the subject of a more detailed study of this cohort.

The strengths of the ERAS inception cohort include large numbers of patients treated conventionally in normal clinical settings, long careful follow-ups and regular assessments of several dimensions of outcome (functional and work disability, structural damage and mortality). Few studies have reported on both sustained DAS remission and different outcome measures by 5 years in RA. Limitations are, first, exclusion of RA patients who did not attend secondary care because of early remission (left censoring), or who stopped attending because of comorbidity or mortality (right censoring). Secondly, DAS was recorded only annually, which would allow disease exacerbations in between visits to escape analysis, but there was little evidence of this from medical records. Missing data at baseline were low except for X-rays, smoking, genetic typing and BMI, and re-analysis of non-missing data only did not materially affect the results.

In conclusion, these data demonstrate the sustained remission rate in the pre-biologic era (11%) and provide a useful benchmark in comparison with the modern pharmacological approach to RA. This includes earlier and more intensive use of DMARDs, with or without steroids, resulting in improved clinical outcomes [6]. Our results would support the use of these therapies in patients with long duration of symptoms of RA and high TJC levels at baseline. Prognostic factors concurred with other comparable studies and were simple to measure. Patients who achieved sustained DAS remission had less structural and functional progression. Maintenance of remission and not only its induction should be the main therapeutic target to achieve better long-term outcome.

### Rheumatology key messages

- Sustained clinical remission is not common in patients treated with conventional DMARDs.
- Predictive markers for clinical remission in RA are simple to measure.
- Sustained clinical remission in RA results in better functional outcome.

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