Time to remission in swollen joints is far faster than patient reported outcomes in rheumatoid arthritis: results from the Ontario Best Practices Research Initiative (OBRI)

Janet E. Pope 1, Emmanouil Rampakakis2, Mohammad Movahedi3,4, Angela Cesta3, John S. Sampalis2,5 and Claire Bombardier3,6,7; for OBRI investigators

Abstract

Objectives. RA patients are often not in remission due to patient global assessment of disease activity (PtGA) included in disease activity indices. The aim was to assess the lag of patient-reported outcomes (PROs) after remission measured by clinical disease activity index (CDAI) or swollen joint count (SJC28).

Methods. RA patients enrolled in the Ontario Best Practices Research Initiative registry not in low disease state at baseline with at ≥6 months of follow-up, were included. Low disease state was defined as CDAI ≤10, SJC28 ≤2, PtGA ≤2cm, pain score ≤2cm, or fatigue ≤2cm. Remission included CDAI ≤2.8, SJC28 ≤1, PtGA ≤1cm, pain score ≤1cm, or fatigue ≤1cm. Time to first low disease state/remission based on each definition was calculated overall and stratified by early vs established RA.

Results. A total of 986 patients were included (age 57.4 (12.9), disease duration 8.3 (9.9) years, 80% women). The median (95% CI) time in months to CDAI ≤10 was 12.4 (11.4, 13.6), SJC28 ≤2 was 9 (8.2, 10), PtGA ≤2cm was 18.9 (16.1, 22), pain ≤2cm was 24.5 (19.4, 30.5), and fatigue ≤2cm was 30.4 (24.8, 31.7). For remission, the median (95% CI) time in months to CDAI ≤2.8 was 46.5 (42, 54.1), SJC28 ≤1 was 12.5 (11.4, 13.4), PtGA ≤1cm was 39.6 (34.6, 44.8), pain ≤1cm was 54.7 (43.6, 57.5) and fatigue ≤1cm was 42.6 (36.8, 48). Time to achieving low disease state and remission was generally significantly shorter in early RA compared with established RA with the exception of fatigue.

Conclusion. Time to achieving low disease state or remission based on PROs was considerably longer compared with swollen joint count. Treating to a composite target in RA could lead to inappropriate changes in DMARDs.

Key words: rheumatoid arthritis, outcome measures, patient-reported outcomes, CDAI, remission, LDA, fatigue

Introduction

RA, one of the most common inflammatory diseases, is characterized by chronic inflammation and destruction of synovial joints [1–3]. Initial symptoms include joint pain and stiffness, and if left untreated, can lead to joint damage, reduced function, chronic pain, poor health-related quality of life, and mortality [4]. RA affects ~1% of the population of whom at least 70% are women [5].

RA treatment recommendations have evolved over the years and currently focus on a treating to a target (T2T) approach that was developed by an expert committee involving rheumatologists and patient representatives from multiple countries [6]. The primary goal of RA treatment is clinical remission, as measured by validated composite disease activity scores; however, low disease activity (LDA) is an acceptable alternative target in
Rheumatology key messages

- CDAl and PRO LDA/remission lag significantly behind swollen/tender joint counts and physician global.
- Overall, pain/fatigue lagged behind PtGA; among patients achieving physician-rated LDA/remission only, PtGA was lagging.
- Careful interpretation of PROs should be exercised to prevent overtreatment and unnecessary DMARD switching.

certain scenarios such as established RA [6]. The guidelines also state that drug therapy should be adjusted at least every 3 months when treatment targets have not been reached. Recommendations for first-line treatment of RA suggest the use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) [6–8]. In the event that first-line csDMARD(s) is/are ineffective, it is recommended that patients add or switch to an alternative csDMARD, or to a biologic DMARD (bDMARD) or targeted synthetic DMARD (tsDMARD).

In addition to T2T for clinical outcomes, an important aspect of RA treatment is patient-centered care; using patient-reported outcomes (PROs) [6]. PROs are essential in managing RA disease and have been incorporated into disease activity composite scoring measures. PROs in RA typically include self-reported assessments of global disease activity/general health, pain, physical function, and health-related quality of life [9]. While PROs are useful for providing patient perspectives to help guide treatment, their inclusion in disease activity scores has been criticized for having an excessive impact on the calculated scores, and therefore potentially influencing adversely the achievement of treatment targets such as remission or LDA [10]. In addition, variation in the formulation of PROs often used in real-world may have a considerable impact on treatment targets and, subsequently, management decisions [11].

The goal of this study was to compare the timing of remission and LDA with improvement in PROs in the OBRI, a clinical registry for RA patients from Ontario, Canada followed in routine care. Differences between patients with early and established RA were also explored.

Methods

Study design

The Ontario Best Practices Research Initiative (OBRI) is a multicentre provincial registry in Canada that prospectively collects data on RA patients followed in routine care. Patients eligible for inclusion in the registry must have a diagnosis of RA confirmed by a rheumatologist, disease onset ≥16 years of age, be ≥18 years of age at registry enrolment, and have ≥1 swollen joint. Treating rheumatologists collect data through patient assessment as per routine care, while patients also directly provide data via telephone interviews occurring every six months. The OBRI registry was established in accordance with the Declaration of Helsinki. Ethics approval was obtained for institutional sites [University Health Network Research Ethics Board (REB) #: 07–0729-AR] and approval at each participating site (Supplementary Material, section OBRI Research Ethics Boards, available at Rheumatology online). Written informed consent was provided by all patients prior to enrolment in the registry.

Study population

Patients enrolled in the OBRI registry between January 2008 and January 2019 were selected for inclusion in the study if their first registry visit and first phone interview occurred within 60 days of one another, if they had ≥2 visits and a follow-up of at least 6 months, and were not in remission or considered to have low disease activity (LDA) at baseline based on the definitions provided below (see Study endpoints) in any of the following outcomes: clinical disease activity index (CDAI), swollen joint count based on 28-joints (SJC28), patient global assessment of disease activity (PtGA), fatigue or pain. The study participants eligible from the OBRI registry are presented in Fig. 1.

Study endpoints

Study endpoints of interest were remission based on CDAI (≤2.8), SJC28 (≤1 TJC28 (≤1), PtGA (≤1 cm), pain (≤1 cm), fatigue (≤1 cm), and physician global assessment of disease activity (MDGA) ≤1 cm) and LDA based on the same measures (CDAI ≤10, SJC28 ≤2, TJC28 ≤2, PtGA ≤2 cm, pain ≤2 cm, fatigue ≤2 cm, MDGA ≤2 cm).

Statistical analyses

Baseline characteristics (demographics, disease characteristics, comorbidities and medication use) were summarized using descriptive statistics, which included the mean (±SD) for continuous variables and frequencies and proportions for categorical data. Kaplan–Meier (K–M) survival analysis was used to assess the time to first remission and time to first LDA based on CDAI, SJC28, TJC28, MDGA, PtGA, pain and fatigue. Patients with missing information at routine follow-up assessments, or who did not achieve remission or LDA, were right censored (unknown future target achievement). Cumulative probabilities of achieving each end point at regular intervals were produced; the associated 95% CIs were estimated using a logarithmic
Time to achieving study endpoints was compared between patients with early (\leq 1 year from diagnosis) vs established (>1 year from diagnosis) RA using K–M survival analysis. In addition, sensitivity analyses adjusting for age, gender, presence of comorbidities, and baseline scores, as well as replacing the dichotomous disease duration with continuous variable were also conducted using Cox regression.

**Results**

A total of 989 patients were included in the analysis. Patient demographics and baseline characteristics are summarized in Table 1. The study population was predominantly female (80.0%) with established RA (64.8%) and had a mean (s.o.) age of 57.4 (12.9). Approximately one-third of patients had previously been treated with a bDMARD and 20% were receiving concurrent bDMARD treatment. At baseline, mean (s.o.) levels of CDAI, SJC28, TJC28, MDGA, PtGA, pain and fatigue were 29.8 (11.7), 8.3 (4.6), 9.3 (6.6), 5.7 (2.0), 6.4 (1.9), 6.6 (1.9) and 6.7 (2.0), respectively.

Fig. 2 shows the time to first LDA (Fig. 2A) and time to first remission (Fig. 2B) based on different definitions. The median (95% CI) time to CDAI LDA was 12.4 (11.4, 13.6) months, with cumulative probabilities (95% CI) of endpoint achievement at 6 and 12 months of 24% (21%, 27%) and 49% (46%, 52%), respectfully. For CDAI remission, the median (95% CI) time to endpoint achievement was 46.5 (42, 54.1) months, and 6- and 12-month probabilities were 4% (3%, 6%) and 12% (10%, 15%), respectively.

When evaluating individual disease parameters, the median (95% CI) time in months to SJC28 \leq 2 was 9 (8.2, 10), TJC28 \leq 2cm was 9.1 (8.2, 10), MDGA was 11.4 (10.3, 12.5), PtGA \leq 2cm was 18.9 (16.1, 22), pain \leq 2cm was 24.5 (19.4, 30.5) and fatigue \leq 2cm was 30.4 (24.8, 31.7) (Fig. 2A). For remission, the median (95% CI) time in months to SJ\leq 1 was 12.5 (11.4, 13.4), TJC28 \leq 1cm was 12.2 (10.8, 13.3), MDGA was 20 (18.2, 22.1), PtGA \leq 1cm was 39.6 (34.6, 44.8),
pain/C20 1cm was 54.7 (43.6, 57.5) and fatigue/C20 1cm was 42.6 (36.8, 48.0) (Fig. 2B).

When stratified by early vs established RA, time to achieving LDA based on CDAI [HR (95% CI): 1.23 (1.07, 1.43)], SJC28 [1.32 (1.15, 1.51)], TJC28 [1.18 (1.02, 1.36)], MDGA [1.28 (1.10, 1.49)], PtGA [1.23 (1.05, 1.44)], and pain [1.29 (1.09, 1.52)] was significantly shorter in early RA compared with established RA (Fig. 3A).

Similarly, time to achieving remission based on CDAI [HR (95% CI): 1.50 (1.22, 1.84)], SJC28 [1.35 (1.17, 1.55)], MDGA [1.25 (1.06, 1.47)], PtGA [1.22 (1.02, 1.47)], and pain [1.37 (1.14, 1.65)] was significantly shorter in early RA (Fig. 3B). However, no differences were observed in time to remission based on TJC28 [1.12 (0.96, 1.31)] and either LDA or remission based on fatigue [LDA: 1.10 (0.94, 1.30); remission: 1.09 (0.92, 1.31)] (Fig. 3A and B). Adjustment for age, gender, presence of comorbidities and baseline scores as well as use of disease duration as a continuous variable instead of dichotomous did not alter the results (Supplementary Tables S1 and S2, available at Rheumatology online).

### Table 1: Patient demographics and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (n=986)</th>
<th>Early RA (n=347)</th>
<th>Established RA (n=639)</th>
<th>P-value</th>
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<tr>
<td><strong>Demographic factors</strong></td>
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<tr>
<td>Age, years, mean (s.d.)</td>
<td>57.4 (12.9)</td>
<td>55.8 (13.2)</td>
<td>58.3 (12.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>789 (80.0)</td>
<td>267 (76.9)</td>
<td>522 (81.7)</td>
<td>0.075</td>
</tr>
<tr>
<td>Marital status, married, n (%)</td>
<td>674 (68.4)</td>
<td>234 (67.4)</td>
<td>440 (68.9)</td>
<td>0.646</td>
</tr>
<tr>
<td>Education status, post-secondary, n (%)</td>
<td>537 (54.5)</td>
<td>192 (55.3)</td>
<td>345 (54.0)</td>
<td>0.705</td>
</tr>
<tr>
<td>Household annual income, &gt;$50 000 Canadian, n (%)</td>
<td>428 (54.8)</td>
<td>167 (58.8)</td>
<td>261 (53.2)</td>
<td>0.089</td>
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<tr>
<td>Health insurance coverage, (OHIP + ODB)</td>
<td>831 (84.3)</td>
<td>286 (82.4)</td>
<td>545 (85.3)</td>
<td>0.237</td>
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<td>Smoking history, n (%)</td>
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<tr>
<td>Never smoking</td>
<td>437 (44.3)</td>
<td>135 (38.9)</td>
<td>302 (47.3)</td>
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<tr>
<td>Former smoking</td>
<td>357 (36.2)</td>
<td>143 (41.2)</td>
<td>214 (33.5)</td>
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<tr>
<td>Current smoking</td>
<td>192 (19.5)</td>
<td>69 (19.9)</td>
<td>123 (19.2)</td>
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<tr>
<td><strong>Disease factors</strong></td>
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<tr>
<td>Disease duration, years, mean (s.d.)</td>
<td>8.3 (9.9)</td>
<td>0.3 (0.5)</td>
<td>12.6 (9.9)</td>
<td>N/A</td>
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<tr>
<td>Established RA (-1 year diagnosed), n (%)</td>
<td>639 (64.8)</td>
<td>0 (0.0)</td>
<td>639 (100.0)</td>
<td>N/A</td>
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<td>RF positive, n (%)</td>
<td>468 (71.1)</td>
<td>219 (65.6)</td>
<td>439 (74.2)</td>
<td>0.006</td>
</tr>
<tr>
<td>Presence of erosions, n (%)</td>
<td>400 (50.1)</td>
<td>74 (26.7)</td>
<td>326 (62.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SJC28 (0–28), mean (s.d.)</td>
<td>8.3 (4.6)</td>
<td>8.2 (4.8)</td>
<td>8.3 (4.5)</td>
<td>0.743</td>
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<tr>
<td>TJC28 (0–28), mean (s.d.)</td>
<td>9.3 (6.6)</td>
<td>9.9 (6.6)</td>
<td>9.1 (6.6)</td>
<td>0.055</td>
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<tr>
<td>MDGA (0–10), mean (s.d.)</td>
<td>5.7 (2.0)</td>
<td>5.9 (2.0)</td>
<td>5.7 (2.0)</td>
<td>0.069</td>
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<tr>
<td>PtGA (0–10), mean (s.d.)</td>
<td>6.4 (1.9)</td>
<td>6.5 (2.0)</td>
<td>6.4 (1.9)</td>
<td>0.573</td>
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<td>CDAI (0–76), mean (s.d.)</td>
<td>29.8 (11.7)</td>
<td>30.5 (11.9)</td>
<td>29.5 (11.6)</td>
<td>0.183</td>
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<td>HAQ-DI (0–3), mean (s.d.)</td>
<td>1.6 (0.62)</td>
<td>1.5 (0.6)</td>
<td>1.6 (0.6)</td>
<td>0.030</td>
</tr>
<tr>
<td>Pain (0–10), mean (s.d.)</td>
<td>6.6 (1.9)</td>
<td>6.6 (1.9)</td>
<td>6.6 (1.9)</td>
<td>0.932</td>
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<td>Fatigue, mean (s.d.)</td>
<td>6.7 (2.0)</td>
<td>6.8 (2.0)</td>
<td>6.7 (2.0)</td>
<td>0.850</td>
</tr>
<tr>
<td>ESR, mean (s.d.) (n=867)</td>
<td>26.9 (22.9)</td>
<td>28.5 (22.5)</td>
<td>25.9 (23.2)</td>
<td>0.111</td>
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<tr>
<td>CRP, mean (s.d.) (n=798)</td>
<td>15.4 (22.8)</td>
<td>18.2 (25.3)</td>
<td>13.8 (21.2)</td>
<td>0.009</td>
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<td><strong>Comorbidities</strong></td>
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<td>Number of comorbidities, mean (s.d.)</td>
<td>3.8 (2.6)</td>
<td>3.5 (2.4)</td>
<td>4.0 (2.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>CVD, n (%)</td>
<td>142 (14.4)</td>
<td>37 (10.7)</td>
<td>105 (16.4)</td>
<td>0.014</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>376 (38.1)</td>
<td>122 (35.2)</td>
<td>254 (39.7)</td>
<td>0.156</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>113 (11.5)</td>
<td>35 (10.1)</td>
<td>78 (12.2)</td>
<td>0.318</td>
</tr>
<tr>
<td>Lung diseases, n (%)</td>
<td>154 (15.6)</td>
<td>44 (12.7)</td>
<td>110 (17.2)</td>
<td>0.061</td>
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<tr>
<td><strong>Medication use</strong></td>
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<tr>
<td>Prior use of bDMARDs, n (%)</td>
<td>285 (28.9)</td>
<td>23 (6.6)</td>
<td>262 (41.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior use of csDMARDs, n (%)</td>
<td>789 (80.3)</td>
<td>170 (49.3)</td>
<td>619 (97.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Concurrent bDMARDs use, n (%)</td>
<td>196 (19.9)</td>
<td>26 (7.5)</td>
<td>170 (26.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Concurrent csDMARDs use, n (%)</td>
<td>877 (88.9)</td>
<td>309 (89.0)</td>
<td>568 (88.9)</td>
<td>0.939</td>
</tr>
<tr>
<td>Number of csDMARDs, mean (s.d.)</td>
<td>1.45 (0.85)</td>
<td>1.5 (0.8)</td>
<td>1.4 (0.8)</td>
<td>0.320</td>
</tr>
<tr>
<td>Concurrent steroid use, n (%)</td>
<td>216 (21.9)</td>
<td>83 (23.9)</td>
<td>133 (20.8)</td>
<td>0.260</td>
</tr>
</tbody>
</table>

Fig. 2 Time to first LDA (A) or remission (B) based on physician-rated and patient-reported outcomes

Fig. 2 Continued

- E2. CDAI
- B2. SJC-28
- B3. TJC-28
- B4. MDAI
- B5. PGA
- B5. Pain
- 57. Fatigue
Fig. 3 Time to first LDA (A) or remission (B) based on physician-rated and patient-reported outcomes in early vs established RA.

Fig. 3 Continued

- B1. CDAI
- B2. SJC-28
- B3. TJC-28
- B4. PGA
- B5. MDGA
- B6. Pain
- B7. Fatigue
Time to remission in swollen joints is far faster than patient reported outcomes in rheumatoid arthritis

Table 2 presents the K–M estimated time to PRO LDA (and remission) from the time of achieving CDAI LDA (and remission, respectively) among patients achieving CDAI but not PRO LDA (and remission, respectively). Similar survival analyses for time to PRO LDA (and remission) are shown in the same table for patients.
achieving SJC28, TJC28 and MDGA LDA (and remission), respectively. The median time lag between CDAI/SJC28/TJC28/MDGA LDA/remission and PRO LDA/remission was consistently higher for PtGA compared with fatigue and pain; with the exception of time to PtGA remission and time to fatigue remission after CDAI remission, which were similar. Median time to pain remission following SJC28/TJC28/MDGA remission was also consistently higher compared with time to fatigue remission.

**Discussion**

The aim of this study was to assess the relative timing or potential lag of PRO outcomes after LDA or remission is obtained based on CDAI, SJC28, TJC28 or MDGA.

We have uncovered that LDA and remission based on CDAI and PROs lag significantly behind swollen and tender joint counts, and physician global assessment of disease activity. Previous studies have demonstrated that there is a discordance between physician-rated and patient-reported outcomes [12, 13] and that remission rates based on disease activity indices, including ACR/EULAR Boolean, SDAI, CDAI and DAS28-CRP are sensitive to PtGA variability [11]. Furthermore, PROs have been shown to vary considerably based on age, disease duration, presence of comorbidities and other non-RA factors [14, 15].

The patient perspective is important in RA but when PROs are reported as high and attributed to disease activity, there can be a lack of validity of composite scores if there is no obvious disease activity such as in patients with no swollen joints but high pain scores [16].

To our knowledge, this is the first study to quantify the lag between endpoint achievement for physician-rated and patient-reported outcomes in routine care. The kinetics were very different for SJC achieving ≤2 or ≤1 vs pain and fatigue achieving ≤2 or ≤1 on a 10 cm scale. When assessing the time to first LDA/remission for individual PROs, pain and fatigue lagged behind PtGA; however, when focusing on patients achieving physician-rated but not PRO LDA/remission, PtGA was more resistant to change, potentially suggesting the selection of distinct subgroup(s) of patients rating their disease status high for reasons other than pain and fatigue.

Indeed, previous studies have identified other latent factors underlying the PtGA in RA patients including depression, anxiety, inability to participate and advanced age [17].

When comparing early and established RA, LDA and remission based on all definitions was achieved sooner in patients with early RA. This is in agreement with previous studies showing that early diagnosis and treatment of RA is important for achieving comprehensive disease control and have identified established disease as an independent predictor of worse clinical outcomes [18-20]. However, interestingly, no differences were observed in terms of achieving fatigue endpoints, suggesting that fatigue lags behind other outcomes in early and established RA.

Strengths of the study include the relatively large sample size of patients treated in routine clinical care and the within-patient comparisons of the various endpoints. A potential limitation of our study is that our findings may not be not generalizable to other parts of the world where the relative importance of different symptoms may be weighted differently by patients. However, we would expect that the differences between physician-rated and patient-reported outcomes and their lag are universal. Furthermore, the possible use of concomitant medications may have impacted the relative timing of the improvement of PROs. Treatment was not standardized between sites.

**Conclusion**

Time to achieving low disease state or remission in RA based on PROs is considerably longer compared with swollen joint count, tender joint count and MDGA, which may have a direct impact on the time to achieve CDAI low disease activity and remission. Consideration of patient perspective should be given in patients in low disease state or remission in order to identify disease aspects that may still require attention. However, given that treatment decisions are often based on (non)achievement of CDAI remission/LDA, careful interpretation of PROs among patients that are not at target, such as considering comorbidities and non-RA factors, should be exercised in order to prevent overtreatment and unnecessary switching of DMARDs.

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**Supplementary data**

Supplementary data are available at *Rheumatology* online.
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