Patients with Rheumatoid Arthritis in the Australian OPAL Cohort Show Significant Improvement in Disease Activity over 5 Years: A Multicenter Observational Study

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ABSTRACT. ***Objective.*** To evaluate disease activity trends in a large cohort of Australian patients with rheumatoid arthritis (RA) from 2009 to 2014.

Methods. This is a multicenter, cross-sectional, noninterventional study of patients with RA treated in Australia. Patients with RA treated at participating OPAL (Optimising Patient outcome in Australian RheumatoLogy) clinics were included in the study. Data, deidentified by patient, clinic, and clinician, were identified using a purpose-written electronic medical record. Patient demographics, disease onset, medications, and disease measures were analyzed. The Disease Activity Score at 28 joints (DAS28) was used to classify patients into the disease activity states of remission: low disease activity, moderate disease activity (MDA), and high disease activity. Choice of therapy was at the discretion of the treating clinician.

Results. At the time of analysis, the database contained 15,679 patients with RA, 8998 of whom fulfilled the inclusion criteria. Mean age was 63.2 years, mean disease duration was 13.8 years, and the majority were women (72.4%). A total of 37,274 individual DAS28-erythrocyte sedimentation rate scores were recorded for the 8998 patients. The frequency of remission increased significantly from 36.7% in 2009 to 53.5% in 2014 ($p < 0.001$), and that of MDA decreased from 33% (2009) to 22.2% (2014). The use of biologic disease-modifying antirheumatic drugs for the patients in remission increased from 17% in 2009 to 36.9% in 2014.

Conclusion. Contemporary management of RA in Australia shows improvements in disease activity toward the target of remission over a 5-year period. (J Rheumatol First Release July 1 2015; doi:10.3899/ jrheum.141575)

Key Indexing Terms:
RHEUMATOID ARTHRITIS DISEASE ACTIVITY
REMISSION DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

The treatment of rheumatoid arthritis (RA) in Australia has undergone significant change in the last decade. The new treatment paradigm of treating to target, with remission being the goal and supplemented by maintenance of tight control, has become standard of care[1]. These approaches have been facilitated by better use of established disease-modifying antirheumatic drugs (DMARD), as well as the availability of a range of biologic DMARD (bDMARD). RA treatment is initiated early and individualized to the patient's presentation, including comorbidities.

In 2009, we established a network database, OPAL-QUMI (Optimising Patient outcome in Australian Rheumato-Logy-Quality Use of Medicines Initiative), whereby consecutive patient-specific details are identified on a purpose-written electronic medical record (Audit4, Software for Specialists) as part of the routine consultation[2]. No information is added

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after the consultation is completed. Treatment choices are at the discretion of the participating rheumatologist as part of routine clinical practice and are not dictated by any agreed protocol. The only commonality of drug choice in the group is the necessary application of our government authority criteria for subsidy of biological drugs. Identified information, therefore, represents real-life data reflecting everyday care of the Australian patient. The OPAL consortium currently has 64 rheumatologists contributing data derived from their own point-of-care clinical interaction.

Using Disease Activity Score at 28 joints (DAS28)-erythrocyte sedimentation rate (ESR) as a surrogate marker of disease activity, we have previously published results from the Remission study, a cross-sectional analysis of disease activity status within our group[2] that showed that while the majority of patients in the Australian cohort were in remission or had low disease activity (LDA), a significant number were rated as having moderate (MDA) or high disease activity (HDA)[2].

Since the OPAL-QUMI began, there has been increased focus from OPAL members (and rheumatologists in general) on achieving better outcomes for patients with RA; how this translates into improved clinical outcomes has not yet been determined.

As a followup from the previously published Remission study[2], we aimed here to examine the disease activity status of the OPAL cohort over the 5-year period since data collection began. We report serial contemporaneous real-world disease activity of a large number of patients with RA treated in the Australian health system by a large number of rheumatologists with similar guiding principles, although with different individual patient management methods.

MATERIALS AND METHODS

Study design. The design of the Remission study has been reported[2]. Briefly, it was a multicenter, cross-sectional, noninterventional study of patients with RA treated in Australia that aimed to determine the proportion of patients who achieved disease remission and to identify the pharmacological interventions used. The objective of this extended analysis was to examine the 5-year followup of the trends in patients with RA in Australia from 2009 to 2014.

The study was approved by the University of New South Wales Human Research Ethics Committee.

Data collection. Deidentified data were collected during routine visits from 22 private rheumatology practices, participants in the OPAL-QUMI, and representing 4 Australian East Coast States (50 rheumatologists contributed data at the time of analysis). Cross-sectional data collection relied on each physician's own data input; therefore, not all patients had complete datasets. Individual patients would have contributed data at least once per year throughout the study period; some patients might have contributed data more often than others.

Patient population. All patients diagnosed with RA (as defined by their clinician) and being treated at an OPAL-QUMI participating clinic were eligible to be included in the study if they had at least 1 DAS28-ESR documented since 2009 and were over the age of 18 years at the time of data collection. Patients who requested that their data not be collected for research purposes were excluded from the analyses.

Clinical observations. The clinical observations included demographics (sex and age), date first and last seen for RA, RA medications (glucocorticoids, DMARD, and bDMARD), and disease measures [DAS28-ESR and DAS28-C-reactive protein (CRP)], tender joint count (TJC), swollen joint count (SJC), ESR, and CRP levels.

Statistical and analytical assessments. Disease activity was classified based on the DAS28-ESR[3]. Remission was defined as a DAS28-ESR of < 2.6, LDA was defined as DAS28-ESR of 2.6–3.1, MDA was defined as DAS28-ESR of 3.2–5.1, and HDA was defined as DAS28-ESR of > 5.1[4]. The disease activity was analyzed by disease duration, change over the past 5 years, details of current RA treatment, and patterns of joint involvement.

To identify variations in the pattern of treatment for the patients with RA in the Australian OPAL cohort between 2009 and 2014, patients were grouped according to their disease activity category and treatment group, and the percentage of patients receiving treatment within each disease activity category at the time of data analysis (April 2014) were compared with what was previously reported for 2010[2]. Descriptive statistics [mean (SD) and range] were provided for continuous variables and frequency counts for categorical variables. For continuous variables (DAS28-ESR or ESR), the difference between subgroups, such as disease duration, was tested with the nonparametric Kruskal-Wallis test. For categorical variables (disease activity category), the association with subgroups was tested with logistic regression. A statistical test was not applied to the percentage of patients by disease activity level, treatment group, and year because of the repeated measurements across years (which means that these observations were not independent), and because of missing observations. In addition, none of the comparisons were protected by randomization; thus raising the possibility of systematic bias compromising any statistical test.

RESULTS

Demographics. At the time of data analysis, the database contained 15,679 patients. The patient analysis population that met all inclusion criteria included 8998 patients; 72.4% were women, 27.3 were men, and 0.3% were sex unassigned (Table 1). The mean ESR decreased from 20.74 mm/h in 2009 (SD 18.93, 95% CI 20.02–21.46) to 16.28 mm/h in 2014 (SD 16.32, 95% CI 15.46–17.09, $p < 0.001$). The mean CRP decreased from 9.55 mg/l in 2009 (SD 15.15, 95% CI 8.93–10.18) to 7.11 mg/l in 2014 (SD 11.58, 95% CI 6.54–7.69, $p < 0.001$).

Joint involvement. Joint involvement was recorded for 8972 patients. The mean SJC and TJC were similar between male and female patients with RA (Table 1). The mean SJC decreased from 3.32 in 2009 [SD 4.95, interquartile range (IQR) 0–4] to 2.45 in 2013 (SD 4.72, IQR 0–2) and 2.11 in 2014 (SD 4.35, IQR 0–2, $p < 0.001$; Figure 1). The mean TJC decreased from 2.82 in 2009 (SD 4.67, IQR 0–3) to 2.38 in 2013 (SD 4.78, IQR 0–2) and 1.94 in 2014 (SD 4.30, IQR 0–2, $p < 0.001$; Figure 1).

Disease activity. Disease activity was evaluated for 8998 patients who had at least 1 DAS28-ESR and the year in which it was recorded. A total of 37,274 DAS28-ESR scores were recorded; the percentage of DAS28-ESR measurements in the remission category was 46.2%, LDA was 17.1%, MDA was 27.6%, and HDA was 9.0%.

The annual remission rate increased significantly from 36.7% in 2009 to 53.5% in 2014 ($p < 0.001$), and the frequency of MDA and HDA decreased significantly from 33% and 11.1% in 2009 to 22.2% and 6.8% in 2014 (p

Table 1. Demographics and disease activity (on study entry) for the analysis population that met all inclusion criteria.

Characteristics	n	Mean	SD	Minimum	Maximum
Age, yrs					
Female	6514	62.1	14.4	19	102
Male	2459	66.1	12.7	19	99
Disease duration, yrs					
Female	5511	14.3	11.1	1	72
Male	2088	12.5	10.0	1	62
CRP, mg/l					
Female	6341	7.14	12.1	0	262
Male	2382	8.34	15.6	0	275
ESR, mm/h					
Female	6510	17.0	16.2	1	138
Male	2457	14.6	16.7	1	131
TJC					
Female	6514	1.99	4.16	0	27
Male	2458	1.71	4.15	0	28
SJC					
Female	6514	2.07	4.15	0	28
Male	2458	1.91	4.19	0	28
DAS28-ESR					
Female	6514	2.82	1.34	0	8.7
Male	2459	2.56	1.43	0	8.7
DAS28-CRP					
Female	6324	2.64	1.18	1	8.1
Male	2375	2.56	1.23	1	8.4

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; TJC: tender joint count; SJC: swollen joint count; DAS28: Disease Activity Score at 28 joints.

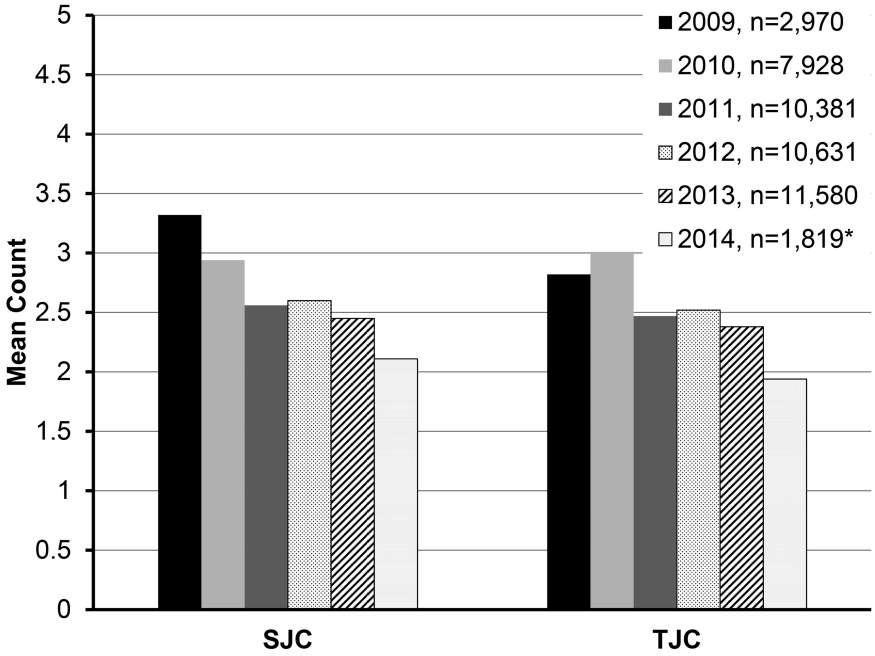

Figure 1. Mean joint count by calendar year. *At the time of analysis, data for 2014 was available only for January–March. SJC: swollen joint count; TJC: tender joint count.

< 0.001). A slight decrease was also observed in the frequency of LDA, 19.1% in 2009 to 16.3% in 2013 (Figure 2).

Disease duration. Disease duration was evaluated for 7620 patients (84.7%) with a recorded disease onset. The 5-year mean disease duration was 13.8 years (SD 10.8, 95% CI 13.6–14.1). The mean disease duration was slightly longer in women (14.3 yrs, SD 11.10) than men (12.5 yrs, SD 10.0).

There were 34,160 individual DAS28-ESR values recorded for the 7620 patients included in the disease activity category by disease duration analysis (Figure 3). Most change in disease status occurred early, within the first 3 years of diagnosis. The rate of DAS28-ESR remission increased from 21% (n = 31/151) at year 0 disease duration (or < 6 mos) to 50% (n = 897/1794) at 3-year disease duration, and appeared to stabilize at around 40–46% for the remaining years. While the rate of HDA decreased from 34.4% (n = 52/151) at year 0 disease duration to 10.6% (n = 191/1794) at 3 years, and stabilized around 6–10% after the 4-year disease duration (Figure 3).

Treatment. The percentage of patients in each disease activity category who were receiving methotrexate (MTX), prednisolone, leflunomide, and bDMARD at data collection in 2014 was compared with that in 2009 (Figure 4).

The percentage of patients treated with bDMARD increased across all disease activity categories. For the remission group, the percentage of patients treated with bDMARD increased from 17% in 2009 to 36.9% in 2014. The percentage of patients treated with prednisolone also increased for the MDA, LDA, and remission groups. The percentage of patients treated with prednisolone in the remission group increased from 27.6% in 2009 to 36.8% in 2014 (Figure 4).

DISCUSSION

RA management focuses on early diagnosis and treatment to defined targets with remission being the goal[5,6,7]. Achieving early remission and maintenance of this state is associated with significantly improved longterm outcomes[5,6]. In clinical practice, there are numerous factors that might modify the goal of remission, such as longterm established disease, availability and/or response to DMARD/bDMARD, adverse events, and comorbid factors, as explored by this group in a previous study[8]. To assess whether current strategies, aiming to achieve better patient outcomes in RA, are effective in everyday clinical practice, we report the changing disease activity over time in Australian patients with RA treated as part of the OPAL-QUMI.

Our results show that over the 5 years of data collection, there has been a gradual increase in the number of patients in remission by DAS28-ESR. In parallel, the number of patients with HDA, MDA, and LDA scores has decreased. The observed remission rates in the Australian population are comparable with the published data from the DANBIO registry (Danish Biologics): 52% for biologic DMARD and 58% for conventional synthetic DMARD[9]. The study demonstrated a shift from the MDA and HDA status to remission and LDA from 2006 to 2013, which is consistent with our results[9].

This report does not provide a reason for the changes in

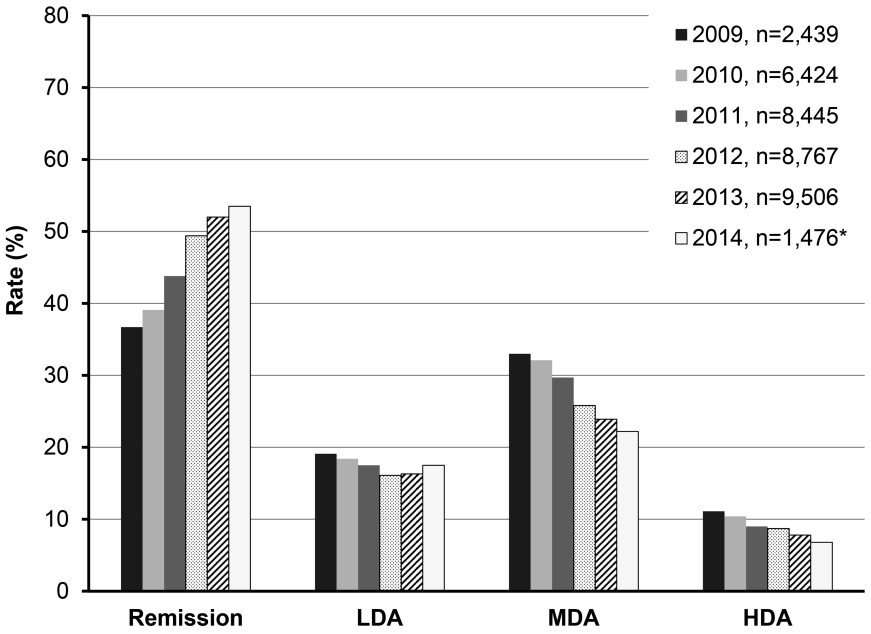

Figure 2. Disease activity by calendar year. *At the time of analysis, data for 2014 was available only for January–March. LDA: low disease activity; MDA: moderate disease activity; HDA: high disease activity.

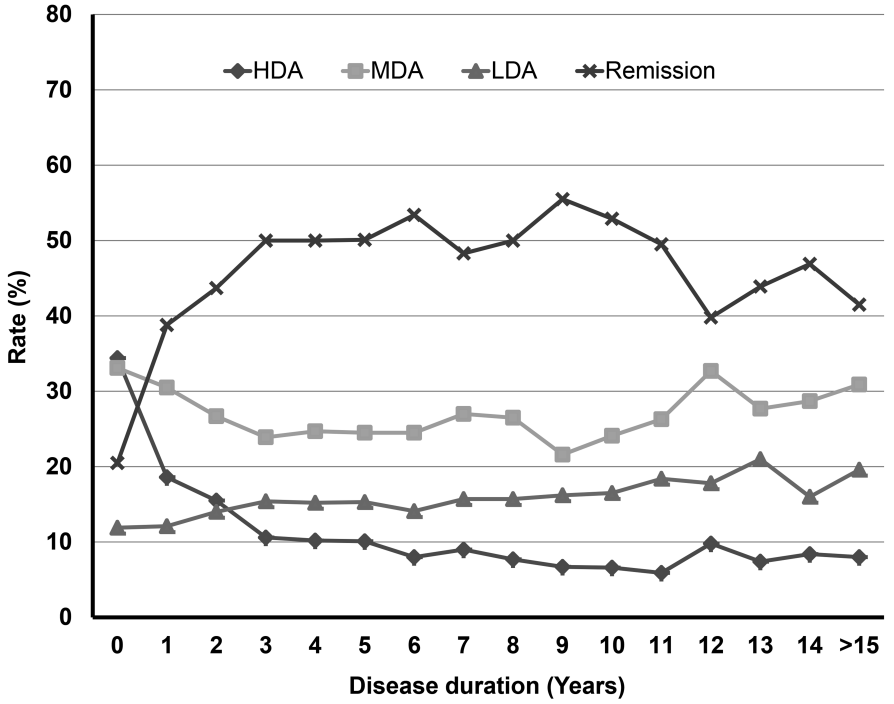

Figure 3. Rate of disease activity category versus disease duration. HDA: high disease activity; MDA: moderate disease activity; LDA: low disease activity.

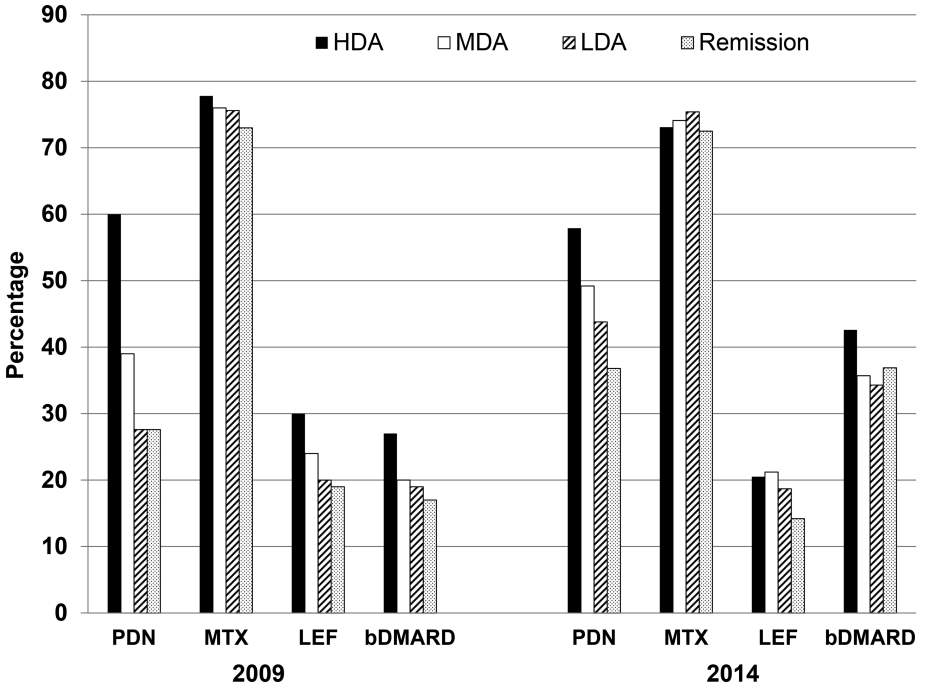

Figure 4. Percentage of patients receiving each treatment. HDA: high disease activity; MDA: moderate disease activity; LDA: low disease activity; PDN: prednisolone; MTX: methotrexate; LEF: leflunomide; bDMARD: biological disease-modifying antirheumatic drugs.

these outcomes. Further studies are planned by OPAL-QUMI to assess the key factors leading to the improved disease activity scores.

Improvements in disease activity in our population are likely to be attributed to the increased focus on a treat-to-target strategy and easy access to DAS28 measures built into the software for discussion with patients at the time of consultation. The number of rheumatologists contributing patients to our group has increased over the 5-year period of our study. It is, therefore, possible that rheumatologists entering the OPAL-QUMI over the last few years are more attuned to the treat-to-target approach than the initial group.

Other potential contributors to the observed improvements in disease activity might be the increased awareness among rheumatologists within our group about the high percentage of patients in MDA in this cohort, and the change in patient management strategy driven by the identification of a number of barriers to treatment by the OPAL group[2,8].

We have previously reported that a limitation of the original analysis of our study in 2010 was incomplete data collection that included a high number of patients who did not have a DAS28-ESR recorded during their clinical visits[2]. The percentage of patients with a DAS28-ESR recorded has increased from 37% in 2009 to 58% in 2013 over the course of our study.

It is difficult to ascertain whether the observed improvements in identifying the DAS28-ESR are because of an increased focus from the clinicians in the OPAL-QUMI on the treat-to-target approach or whether it is because of the need to have components of this measure documented for reimbursement reasons so that patients can have access to bDMARD. The availability of subsidized bDMARD in Australia is subject to government approval, with the requirement for the patient to have persistent significant disease activity (≥ 20 swollen and tender joints, or ≥ 4 swollen and tender large joints, plus an ESR > 25 mm/h or CRP > 15 mg/l) despite a 6-month intensive DMARD treatment trial with a minimum of 2 DMARD agents for a minimum of 3 months each[10]. Patients need to meet certain targets that include a 20% reduction in the baseline ESR or CRP and a 50% reduction in the number of SJC and TJC joints to meet eligibility for treatment subsidy. The patients who qualify for bDMARD treatment in Australia thus have significant persistent disease activity.

When the components of the DAS28 were analyzed, our results showed that the SJC and TJC, as well as the patient global assessment, also decreased steadily over the same time period. It is possible that to maintain access to these expensive medications, some clinical outcomes, such as the SJC and TJC, could be recorded as being lower than that which is actually the case. However, that is not likely to be the situation in this cohort, as demonstrated by the observed decrease in the objective disease measurement of the ESR and CRP levels.

The proportion of patients receiving bDMARD and prednisolone has also risen over the 5-year time period in our cohort. This may suggest that patients with more severe RA are now being managed more aggressively than previously because of the availability of newer medications and careful clinical appraisal of patients who meet government reimbursement criteria for these drugs. The management of RA in Australia is consistent with the European League Against Rheumatism recommendations[7]. The use of bDMARD in Australia is aligned with data presented by the QUEST-RA group; however, Australian rheumatologists appear to be using less prednisolone and MTX than the QUEST-RA group[11].

In this report, we have shown that a large cohort of Australian patients with RA has improved disease activity scores over a 5-year period that coincide with an increased use of bDMARD and prednisolone. This is likely to have a significant effect on the outcome of such patients, with a reduction in longterm comorbidities, less joint damage, and less disability over time. This clearly also has significant economic implications that are also the subject of further exploration by the group.

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