# Effect of Adherence to Protocolized Targeted Intensifications of Disease-modifying Antirheumatic Drugs on Treatment Outcomes in Rheumatoid Arthritis: Results from an Australian Early Arthritis Cohort

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*ABSTRACT.* ***Objective.*** To investigate the association between adherence to treat-to-target (T2T) protocol and disease activity, functional outcomes, and radiographic outcomes in early rheumatoid arthritis (RA).
***Methods.*** Data from a longitudinal cohort of patients with early RA were used. Adherence was determined at each followup visit over 3 years according to predefined criteria. The primary endpoint was remission according to Disease Activity Score in 28 joints (DAS28) and Simplified Disease Activity Index (SDAI) criteria. Functional and radiographic outcomes measured by modified Health Assessment Questionnaire and modified total Sharp score, respectively, were secondary endpoints.
***Results.*** A total of 198 patients with 3078 clinic visits over 3 years were included in this analysis. After adjusting for relevant variables, although there was no significant association between adherence to T2T and remission rate after 1 year, the associations reached significance after 3 years for both DAS28 (OR 1.71, 95% CI 1.16–2.50; p = 0.006) and SDAI criteria (OR 1.94, 95% CI 1.06–3.56; p = 0.033). After 3 years, adherence was also associated with improvement in physical function ($\beta$ = 0.12, 95% CI 0.06–0.18; p < 0.0001). None of the radiographic outcomes were associated with adherence after either 1 or 3 years, although there was a trend for higher adherence to be associated with less radiographic progression at the end of the study (p = 0.061).
***Conclusion.*** Increased adherence to T2T was associated with better longterm disease activity and functional outcomes, which suggests that the benefit of a T2T protocol may be enhanced by ensuring adequate adherence. (J Rheumatol First Release July 15 2016; doi:10.3899/jrheum.151392)

*Key Indexing Terms:*
TREAT TO TARGET
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Contemporary rheumatoid arthritis (RA) management involves a tight control strategy called treat to target (T2T), with the aim of maintaining normal physical, psychological, and socioeconomic function through timely control of symptoms and prevention of structural damage[1,2]. It is a target-driven process whereby treatment is intensified until target is reached[2]. With the advent of the T2T, patients with RA are now more likely to attain remission and have improved health-related quality of life with less joint damage[3,4,5,6,7].

Successful implementation of a T2T in routine clinical practice depends on several factors, starting with early referral and timely commencement of disease-modifying antirheumatic drugs (DMARD), followed by close

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monitoring of disease activity and drug toxicities, all of which require frequent clinic visits[8,9,10]. A metaanalysis demonstrated that protocolized targeted intensification of treatment is more advantageous than nonprotocolized therapy adjustment[11]. Adherence to T2T protocol may play an important role in determining the outcome of treatment, but the relationship between the extent of adherence to protocolized escalation of therapy and outcomes of treatment has not yet been established, to our knowledge.

We have described the deviations from a T2T protocol and shown that nonadherence occurred in about one-quarter of followup visits[12]. The most common reasons for nonadherence were patient factors, physician's own decisions, drug toxicities, and comorbidities. The objective of this study was to determine the effect of physician adherence to T2T protocol on disease activity, radiographic outcomes, and functional outcomes among recent-onset patients with RA treated with protocolized escalation of DMARD.

## MATERIALS AND METHODS

*Design and patient population*. Patients who were followed for at least 1 year in a longitudinal observational cohort of early RA at the Royal Adelaide Hospital (Adelaide, Australia) were included. Since 2001, consecutive treatment-naive patients aged 18 years or older with currently active RA according to the 1987 revised American College of Rheumatology (ACR)[13] or 2010 ACR/European League Against Rheumatism criteria[14] for < 2 years have been enrolled in the cohort.

The following data were obtained at baseline and/or followup visits: sociodemographics, clinical variables, 28-joint Disease Activity Score (DAS28) based on the erythrocyte sedimentation rate, physician's global assessment [PGA; 100 mm visual analog scale (VAS), 100 = worst rating], patient-reported measures [patient global assessment (PtGA), pain and fatigue all measured using 100 mm VAS], physical function [modified Health Assessment Questionnaire (mHAQ) rated on 0 to 3 scale, lower score representing better functioning[15]], and helplessness [assessed by Rheumatology Attitudes Index helplessness subscale ranked from 5 to 25, lower score representing lowest degree of helplessness[16]] and modified total Sharp score (mTSS).

Ethical approval was obtained from the Royal Adelaide Hospital Research and Ethics Committee, and participants' informed consent was obtained.

*Treatment strategy*. Patients were managed according to a T2T strategy as described[4,12,17]. Briefly, participants were initially treated with 3 DMARD [10 mg/week methotrexate (MTX), 500 mg/day sulfasalazine (SSZ) and 400 mg/day hydroxychloroquine (HCQ)]. Further intensification occurred until the target disease activity was achieved according to a structured algorithm (Supplementary Figure 1, available from the authors on request). Injectable corticosteroids were used temporarily if needed to reduce disease activity, while oral corticosteroids were actively discouraged.

*Adherence to T2T*. At each followup visit, there was an assessment of whether target disease activity was achieved, whether DMARD-related toxicities occurred, and whether therapy modification was needed[12]. Assessment of adherence was made against local clinic guidelines, which state that a decision regarding treatment intensification is to occur every 3-6 weeks initially and then every 3 months unless treatment target was achieved or significant toxicity occurred (Table 1). First, the adherence rate was expressed as the proportion of visits with correct adherence to the protocol (i.e., dividing the no. visits that were adherent by the total no. visits over the specified time period). To explore whether better outcomes were due to better adherence, or whether those with more responsive disease had better outcomes because they had less opportunity to be nonadherent, a modified version of adherence was also calculated whereby the denominator included only clinic visits during which drug (or drug dose) change was indicated.

*Outcome measures*. The primary endpoint was the rate of remission according to DAS28 and the Simplified Disease Activity Index (SDAI) criteria at Year 1 and Year 3. Accordingly, remission was defined as DAS28 < 2.6 and SDAI ≤ 3.3[18,19,20]. Secondary outcomes were physical function[15] and radiographic outcomes [absolute change and progression (i.e., increase of ≥ 1)] of mTSS[21] at Year 1 and Year 3.

*Statistical analysis*. For the purposes of analysis, the adherence level was converted into a decile (i.e., as a 10% increment) to aid with interpretation. Adherence levels at Year 1 and Year 3 were used in analysis of outcomes after 1 and 3 years, respectively. Logistic regression was used to determine the effect of adherence after adjustment for conventional predictors of outcome. Any variable having a p value of < 0.25 in univariate analysis at 1 or 3 years was selected as a candidate for the multivariate analysis[22]. The association was reported using OR with 95% CI. In the case of continuous outcomes, univariate and then multivariate linear regression was performed as above, and a β coefficient with a 95% CI was used as the measure of association. Analysis was performed using Statistical Package for Social Sciences (SPSS) for Windows version 21.0 (SPSS Inc.).

## RESULTS

*Baseline patient characteristics*. Out of 231 patients, 33 were excluded because they were lost to followup (n = 21), had short followup (10), or had other medical conditions (n = 2; Supplementary Figure 2, available from the authors on request). With 1931 clinic visits, 198 patients completed 1 year of treatment. With a total of 3078 clinic visits, 149 patients completed 3 years of treatment. The majority of patients were female (71.7%), rheumatoid-factor positive (62.6%), and shared epitope–positive (61.0%), and the mean (SD) DAS28 was 5.5 (± 1.3; Table 2).

*DMARD usage patterns and adherence to T2T*. About 90% (n = 175) of patients were initiated on triple DMARD therapy. Over the 3-year followup, 82.6% of individuals required a dose escalation and/or addition of new DMARD. Treatment intensification was rapid with a median time to first intensification of 6 weeks and on average each patient received 3.6 DMARD during the treatment period.

Table 3 presents treatment characteristics during the followup period. The median dose of MTX was 20 mg/week at Year 1 and 15 mg/week at Year 3, while that of SSZ and HCQ was 2 g/day and 400 mg/day, respectively, at both years 1 and 3. Leflunomide (LEF) was added in slightly over half of the patients, and < 10% of the cohort received a biological DMARD by Year 3. Injectable corticosteroids were received by around two-thirds of patients (Table 3).

From the total of 3078 clinic visits over 3 years, the mean proportion of visits that were adherent to T2T protocol was 81.5% after 1 year and 77.5% after 3 years.

*Correlates of disease activity outcome*. Remission rate according to DAS28 and SDAI was attained by 28.3% and 18.3% at 6 months, respectively. After 1 year, 42.3% and 24.2% patients achieved DAS28 and SDAI remission, respectively, and these increased to 46.4% (DAS28) and 31.5% (SDAI) by the end of Year 3.

Baseline variables associated with either DAS28 or SDAI

*Table 1*. Assessment of adherence to a T2T protocol.

| Target Achieved | Significant Toxicity Occurred[1] | Adherent | Nonadherent |
|---|---|---|---|
| No | No | Intensified | Continued/tapered/discontinued |
| No | Yes | Intensified[2] | Continued/tapered/discontinued[3] |
| Yes | No | Continued | Intensified/tapered/discontinued |
| Yes | Yes | Continued/tapered/discontinued | Intensified |
| Yes/No | Yes/No | | Discontinuation of all DMARD[4] |

[1]Severe toxicities, according to physician's assessment, deemed to be unfavorable to the health of the patient. [2]By definition it could be considered adherent, but when significant toxicity occurred, physicians rarely intensified therapy at the same visit. [3]If significant toxicity occurred, therapy escalation is not expected. However, it is still considered nonadherent because the target has not been achieved. [4]Stopping all DMARD regardless of patient's disease activity or toxicity status was considered nonadherent. T2T: treat to target; DMARD: disease-modifying antirheumatic drug.

*Table 2*. Baseline patient characteristics (n = 198). Data are n (%) or median (interquartile range).

| Characteristics | Values |
|---|---|
| Female | 142 (71.7) |
| Age, yrs | 56.2 (44.6–66.5) |
| Body mass index, kg/m$^2$ | 27.2 (24.0–30.8) |
| Current and former smoker | 107 (54.0) |
| Weeks of polyarthritis at baseline | 16 (12–27) |
| RF positive | 124 (62.6) |
| Anti-CCP positive | 109 (56.2) |
| Shared epitope positive | 119 (61.0) |
| DAS28 | 5.5 (4.7–6.4) |
| PGA, VAS, 0–100 mm | 54.0 (34.0–70.0) |
| Erosive disease | 36 (23.5) |
| Modified total Sharp score | 2.0 (0.0–7.0) |
| Physical function, mHAQ, 0–3 | 0.63 (0.25–1.13) |
| Pain, VAS, 0–100 mm | 57.0 (30.5–75.0) |
| Fatigue, VAS, 0–100 mm | 50.5 (23.0–69.0) |
| PtGA, VAS, 0–100 mm | 49.0 (26.0–64.8) |
| Helplessness, RAI, 5–25 | 14.0 (10.0–18.3) |

VAS: visual analog scale; mHAQ: modified Health Assessment Questionnaire; RAI: Rheumatology Attitudes Index; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide antibodies; DAS28: Disease Activity Score in 28 joints; PGA: physician's global assessment; PtGA: patient's global assessment.

*Table 3*. Treatment characteristics during the followup visits.

| Characteristics | Year 1, n = 198 | Year 3, n = 149 |
|---|---|---|
| MTX dose, mg/week, median (IQR) | 20.0 (10.0–25.0) | 15.0 (8.75–25.0) |
| MTX dose ≥ 20 mg/week, n (%) | 108 (54.5) | 61 (40.9) |
| SSZ dose, g/day, median (IQR) | 2.0 (0.0–3.0) | 2.0 (0.0–3.0) |
| SSZ dose ≥ 2 g/day, n (%) | 114 (57.8) | 79 (53.0) |
| HCQ dose, mg/day, median (IQR) | 400.0 (0) | 400.0 (0) |
| Concomitant DMARD, n (%) | | |
| Leflunomide | 65 (32.8) | 75 (50.3) |
| Gold injection | 8 (4.0) | 23 (15.4) |
| Biologics | 3 (1.5) | 14 (9.4) |
| Cyclosporine | 1 (0.5) | 4 (2.7) |
| Azathioprine | 1 (0.5) | 2 (1.3) |
| Injectable corticosteroids, n (%) | 120 (60.6) | 108 (72.3) |

MTX: methotrexate; SSZ: sulfasalazine; HCQ: hydroxychloroquine; DMARD: disease-modifying antirheumatic drug.

remission after 1 year were body mass index (BMI), DAS28, PGA, mHAQ, pain, helplessness, and fatigue. After 3 years, baseline smoking status, pain, and fatigue were associated with both DAS28 and SDAI remission. Concomitant use of new DMARD, more frequent clinic visits, or occurrence of a significant toxicity were inversely associated with remission after both 1 and 3 years, whereas individuals with longer time to first DMARD dose escalation were more likely to achieve remission after 1 but not 3 years (Table 4).

After correcting for these variables, there was no significant association between adherence and remission rate after 1 year (DAS28: OR 1.61, p = 0.124; SDAI: OR 1.34, p = 0.390), but the associations reached significance after 3 years for both DAS28 (OR 1.71, p = 0.006) and SDAI criteria (OR 1.94, p = 0.033). Nonsmokers were more likely to achieve remission as measured by both DAS28 (OR 7.14, p = 0.014) and SDAI (OR 14.51, p = 0.027) after 3 years. On the other hand, the rate of remission was lower among patients who required additional DMARD after 1 year, although there was no association after 3 years (Table 5).

*Sensitivity analysis*. In the following analyses, results are presented after adjustment for baseline DAS28, BMI, smoking status, PGA, mHAQ, helplessness, pain, fatigue, weeks to dose escalation, frequency of clinic visits, existence of significant toxicity, and the need for new DMARD.

*Categorizing adherence using 80% cutoff*. There were no major differences between adherence > 80% and ≤ 80% with regard to doses of MTX, SSZ, and HCQ at 1 and 3 years. However, usage of concomitant DMARD and injectable corticosteroids were more common among patients with adherence < 80% (Supplementary Table 1, available from the authors on request).

At Year 1, there were no significant differences in remission rate between adherence groups in multivariate analysis. However, patients with adherence ≥ 80% were more likely to achieve remission according to both DAS28 (OR 5.08, p = 0.004) and SDAI (OR 10.37, p = 0.006) criteria compared to participants with adherence < 80% after 3 years (Table 6).

*Modified definition of adherence*. Of the visits that required dose/drug modifications, therapy adjustments were indicated

*Table 4*. Univariate analysis of the factors associated with remission after 1 and 3 years. Data are OR (95% CI).

| Variables | Year 1, n = 198 | | Year 3, n = 149 | |
|---|---|---|---|---|
| | DAS28 | SDAI | DAS28 | SDAI |
| Adherence level (10% increment) | 2.01 (1.45–2.69) | 2.00 (1.40–2.88) | 2.11 (1.58–2.80) | 2.14 (1.48–3.09) |
| Weeks to dose escalation | 1.01 (1.00–1.02) | 1.01 (1.00–1.01) | 1.01 (0.99–1.02) | 1.01 (1.00–1.02) |
| Addition of new DMARD (yes vs *no*) | 0.17 (0.08–0.32) | 0.16 (0.07–0.35) | 0.16 (0.08–0.33) | 0.17 (0.07–0.40) |
| Frequency of clinic visits | 0.76 (0.64–0.91) | 0.79 (0.65–0.96) | 0.81 (0.74–0.89) | 0.81 (0.74–0.89) |
| Significant toxicity (yes vs *no*) | 0.49 (0.26–0.94) | 0.42 (0.19–0.95) | 0.20 (0.10–0.41) | 0.27 (0.12–0.62) |
| Baseline BMI, kg/m$^2$ | 0.94 (0.89–0.99) | 0.99 (0.94–0.06) | 0.96 (0.90–1.02) | 0.97 (0.90–1.04) |
| Baseline nonsmoker vs *current smoker* | 1.78 (0.76–4.16) | 1.27 (0.48–3.35) | 3.52 (1.22–10.16) | 5.31 (1.17–24.04) |
| Baseline DAS28 | 0.73 (0.57–0.93) | 0.96 (0.93–0.98) | 0.88 (0.67–1.15) | 0.98 (0.95–1.01) |
| Baseline PGA | 0.98 (0.97–0.99) | 0.98 (0.97–0.99) | 0.97 (0.98–1.01) | 0.99 (0.97–1.01) |
| Baseline physical function | 0.56 (0.32–0.99) | 0.34 (0.17–0.75) | 0.71 (0.38–1.32) | 0.47 (0.22–1.01) |
| Baseline pain | 0.98 (0.97–0.99) | 0.98 (0.97–0.99) | 0.98 (0.97–0.96) | 0.97 (0.96–0.99) |
| Baseline helplessness | 0.92 (0.86–0.98) | 0.93 (0.86–0.99) | 0.95 (0.88–1.01) | 0.89 (0.82–0.96) |
| Baseline fatigue | 0.98 (0.97–0.99) | 0.98 (0.97–0.99) | 0.98 (0.97–0.99) | 0.98 (0.97–0.99) |

These factors did not show significant association with outcome: sex, age, disease duration, RF status, anti-CCP status, SE status, erosion score, and mTSS. For dichotomous outcomes, the reference category is indicated with italics. All variables included here were significantly associated with remission at 1 and/or 3 years. DAS28: Disease Activity Score in 28 joints; SDAI: Simplified Disease Activity Index; BMI: body mass index; PGA: physician's global assessment; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide antibodies; SE: shared epitope; mTSS: modified total Sharp score; DMARD: disease-modifying antirheumatic drug.

*Table 5*. Multivariate predictors of remission after 1 and 3 years. Data are OR (95% CI) except for Nagelkerke $R^2$.

| Variables | Year 1, n = 198 | | Year 3, n = 149 | |
|---|---|---|---|---|
| | DAS28 | SDAI | DAS28 | SDAI |
| Adherence level (10% increment) | 1.61 (0.88–2.96) | 1.34 (0.68–2.62) | 1.71 (1.16–2.50)* | 1.94 (1.06–3.56)* |
| Addition of new drug (yes vs *no*) | 0.14 (0.04–0.49)* | 0.08 (0.01–0.4)* | 0.77 (0.21–2.79) | 0.84 (0.17–4.03) |
| Frequency of clinic visits | 0.80 (0.56–1.14) | 0.89 (0.62–1.27) | 0.90 (0.77–1.05) | 0.81 (0.65–0.99)* |
| Baseline nonsmoker vs *current smoker* | 3.28 (0.76–14.19) | 1.58 (0.36–6.95) | 7.14 (1.50–33.0)* | 14.51 (1.34–156.3)* |
| *Nagelkerke $R^2$* | *0.516* | *0.398* | *0.484* | *0.510* |

*p < 0.05. Variables with a p value of < 0.25 in univariate analysis were included in this multivariate analysis. A backward elimination technique was used to identify independent predictors of remission. For dichotomous outcomes, the reference category was indicated using italics. DAS28: Disease Activity Score in 28 joints; SDAI: Simplified Disease Activity Index.

*Table 6*. Univariate and multivariate predictors of remission after 1 and 3 years. Data are OR (95% CI) except for Nagelkerke $R^2$.

| Variables | Year 1, n = 198 | | Year 3, n = 149 | |
|---|---|---|---|---|
| | DAS28 | SDAI | DAS28 | SDAI |
| Univariate | | | | |
| Adherence level (≥ 80% vs < 80%) | 3.70 (1.96–6.97)* | 4.85 (2.10–11.23)* | 6.87 (3.21–14.66)* | 7.31 (2.78–19.19)* |
| Modified adherence (10% increment) | 1.26 (1.03–1.54)* | 1.22 (0.97–1.54) | 1.57 (1.26–1.95)* | 1.75 (1.35–2.27)* |
| Multivariate | | | | |
| Adherence level (≥ 80% vs < 80%) | 1.81 (0.57–5.70) | 3.06 (0.76–12.41) | 5.08 (1.67–15.45)* | 10.37 (1.94–55.49)* |
| Modified adherence (10% increment) | 1.14 (0.83–1.56) | 1.00 (0.67–1.36) | 1.45 (1.06–1.98)* | 1.49 (0.99–2.25) |
| *Nagelkerke $R^2$* | *0.446* | *0.384* | *0.447* | *0.514* |

* p < 0.05. Multivariate analysis was controlled for baseline DAS28, BMI, smoking status, PGA, physical function, helplessness, pain, fatigue, weeks to dose escalation, frequency of clinic visits, addition of further DMARD, and existence of significant toxicity (yes/no). DAS28: Disease Activity Score in 28 joints; SDAI: Simplified Disease Activity Index; BMI: body mass index; PGA: physician's global assessment; DMARD: disease-modifying antirheumatic drug.

in 1594 of 3078 (51.8%) total clinic visits over 3 years. Adherence with the treatment protocol was observed in 956 (60%) of these visits with mean proportion of 68.0% per patient at the end of the followup period; lower than the adherence rate observed when total number of visits was included.

After correcting for other predictors, there was no association between the modified level of adherence and remission

after 1 year of followup, but after 3 years there was a significant association with DAS28 remission (OR 1.45, p = 0.019) and a trend for an association with SDAI remission (OR 1.49, p = 0.056; Table 6).

*Effect on physical function and radiographic outcome*. The mean (SD) reduction in mHAQ from baseline to Year 1 and Year 3 was 0.42 (0.58) and 0.46 (0.58), respectively. At Year 1, there was no association between adherence and change from baseline in mHAQ score (univariate analysis), but there was a significant association after 3 years. After controlling for baseline DAS28, PGA, pain, PtGA, fatigue, and helplessness, adherence level was significantly associated with improvement in mHAQ [β = 0.12 (95% CI 0.06-0.18); p < 0.0001], i.e., a 10% increment in adherence level was associated with a 0.12-unit improvement in mHAQ score.

The median (IQR) mTSS at baseline was 2.0 (0.0–7.0). The median (IQR) increase in mTSS from baseline to years 1 and 3 was 0.0 (0.0–2.0) and 2.0 (0.0–5.0), respectively, and radiographic progression occurred in 43.2% of patients at Year 1 and 63.3% of patients at Year 3. Generally, none of the radiographic outcomes were statistically significantly associated with adherence level, but there was a trend for higher adherence to be associated with a lower increase in mTSS at Year 3 [β = –0.74 (95% CI –0.04 to 1.51); p = 0.061].

## DISCUSSION

In our cohort, a strong association between adherence to T2T and longterm treatment outcomes was observed. Specifically, higher adherence was associated with higher remission rates and greater improvement in physical function, and this relationship was maintained even after correcting for the indicators of hard-to-treat disease such as the more frequent clinic visits, the need for additional DMARD, and higher baseline disease activity. Given that easier-to-control RA is likely associated with both better outcomes and higher adherence, we confirmed that when adherence was calculated based only on the clinic visits during which a change in treatment was indicated, an association between adherence and remission was still apparent.

The results from the current study highlight that implementing a T2T protocol is not enough to guarantee better treatment outcomes; appropriate adherence to the treatment protocol substantially increases the likelihood of attaining better outcomes. Although we found superior longterm disease activity outcomes for patients with better adherence, full adherence to the T2T protocol is not always possible because toxicity, comorbidities, patient/physician reasons, and other related factors have previously been shown to contribute to nonadherence[9,10,12,23]. The effects of modifiable factors causing nonadherence such as patient resistance and some physicians' reasons should be minimized where possible.

This study has some important clinical implications. First, to the extent that adherence is a negotiation between physician and patient, in which the physician's beliefs and actions play a leading role, the findings should fortify the physician's conviction to follow the rules and to transfer her/his belief in the rules to the patient, a practice that is likely to improve adherence. Second, baseline disease activity appears important in achieving early outcomes, but adherence increases in importance as time with a treatment progresses, suggesting, similar to the "window of opportunity" hypothesis[24], that good short-term adherence promotes lower longterm disease activity. Finally, because drug toxicity is a reason for nonadherence with the dose escalation rules[12], and nonadherence is associated with poorer outcomes, patients could be encouraged to test their tolerance by explaining that the toxicities are rarely dangerous with appropriate surveillance, and if treatment is tolerated, a favorable outcome is likely.

In our present study, about half of the patients reached DAS28 remission and one-third of them achieved SDAI remission after 3 years of intensive treatment. This was comparable to other cohorts[25,26], although lower than that achieved when anti–tumor necrosis factor agents are used as initial therapy[7]. There are 2 points that are worth mentioning here. First, members of our cohort were early adopters of T2T, such that all individuals in the cohort were treated according to this approach, whereas in many other practices the rate of T2T increased markedly over the past 10–15 years, which may explain why some large cohorts have demonstrated substantially improved outcomes during this period[25]. Second, biological agents are not available under the Australian subsidy schemes until a patient has relatively high active disease despite 6 months of synthetic agents. Such a system creates problems for individuals who have low to moderate disease activity, because they do not qualify for biological agents, but have not achieved optimal outcomes according to contemporary standards. The clinicians' dilemma is a potential incentive to artificially increase disease activity, although this is not our practice[27]. Therefore, remission rates may be lower than expected if biological agents are used more liberally.

Similar to our findings, smoking status has previously been shown to be negatively associated with remission[28], and the finding that addition of DMARD was associated with a lower remission rate was not surprising, because addition of new drugs indicates individuals who have disease that is more difficult to treat. After adding a new drug, adherence to T2T protocol declined and remission was less common, further indicating the influence of adherence on treatment outcome. It may also be that both patients and physicians are more willing to tolerate higher disease activity if they have never experienced a good outcome — for example, once LEF is added, addition of the next DMARD may be perceived as more toxic, and hence more active disease may be acceptable.

The effect of adherence to the T2T on radiographic

outcomes was less remarkable than on disease activity and functional outcomes. The reason for lack of difference in radiographic outcome may be the low overall rate of radiographic progression in the entire population, relatively short followup, or simply the overall effectiveness of the T2T with conventional DMARD, and may have less to do with adherence level. In this regard, it is notable that intensive use of conventional DMARD appears to provide little additional benefit in preventing radiographic progression compared to standard therapy[3,29].

To the best of our knowledge, this is the first study to explore the relationship between adherence to T2T and the outcomes of therapy. Earlier studies have been limited mostly to identifying reasons for nonadherence[10,30], exploring barriers to achieving the desired treatment goal[9], exploring reasons for resistance to therapy modification[31], examining how patients and physicians approach the decision to escalate treatment, or identifying factors that affect the decision to intensify therapy[32,33]. Our present study is advantageous in that it highlights the importance of adhering to treatment guidelines to achieve optimal clinical outcomes when following a T2T protocol.

It is worth mentioning that some of our patients received high or low doses of omega-3 fatty acids, and others in the cohort were encouraged to take high-dose omega-3 fatty acids, but this was not mandated. Analysis of these patients (those randomized to high-dose vs low-dose omega-3 fatty acids) did not show any significant difference in adherence to T2T between them and the rest of the patients. Further, patients seen in our clinic have already been triaged as having RA and they almost all agree to enroll in the cohort. The number of participants included in the study is a relatively accurate reflection of the number of individuals who presented to the clinic in our rheumatology department between 2001 and 2014. This makes recruitment bias unlikely to be apparent in the study.

There are some limitations to consider when interpreting the findings of our current study. We conducted our study at a single hospital and used only 1 form of T2T approach. Thus, the findings may not be representative of all other treatment approaches within a T2T framework. Studies should be conducted to determine whether simpler treatment regimens improve adherence to T2T. Given the observational nature of our study, it is difficult to tease apart the effects of better adherence, good treatment outcomes, and disease that is inherently easier to control, and therefore conclusions regarding the causal relationships should be viewed with a degree of caution. However, because better treatment outcome was associated with increased adherence even after adjusting for several confounding variables and considering just the visits during which a change in treatment was indicated, the results of our present study are highly suggestive that physician adherence to protocol may be one of the main factors determining the outcome of treatment in RA following T2T. The first participants in this study began treatment in 2001 when the benefits of T2T had not yet been fully realized or biological DMARD were not commonly available. Although there has since been increased awareness of T2T, and further evidence of its effectiveness and increased uptake in clinical practice, subgroup analysis did not show any differences in treatment outcome and adherence to T2T, according to the date treatment was initiated (data not shown). This could be due to stable personnel and consistent rheumatologist practice patterns over the years in our study. We assumed that adherence to T2T was equally distributed among treating physicians because patients were not assigned to a single rheumatologist throughout followup. However, it cannot be discounted that differences in the pattern of adherence to T2T protocol among physicians may affect patients' behavior and the outcome of treatment.

Higher adherence to a T2T strategy was associated with better longterm disease activity and functional outcomes, and it is therefore possible to increase the benefits of T2T in day-to-day clinical practice by maximizing adherence to the protocol.

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