# Inconsistent Treatment with Disease-modifying Antirheumatic Drugs: A Longitudinal Data Analysis

Maria D. Mjaavatten, Helga Radner, Kazuki Yoshida, Nancy A. Shadick, Michelle L. Frits, Christine K. Iannaccone, Tore K. Kvien, Michael E. Weinblatt, and Daniel H. Solomon

*ABSTRACT.* ***Objective.*** Current recommendations advocate treatment with disease-modifying antirheumatic drugs (DMARD) in all patients with active rheumatoid arthritis (RA). We investigated the frequency of and reasons for inconsistent DMARD use among patients in a clinical rheumatology cohort.

***Methods.*** Patients in the Brigham Rheumatoid Arthritis Sequential Study were studied for DMARD use (any or none) at each semiannual study timepoint during the first 2 study years. Inconsistent use was defined as DMARD use at ≤ 40% of study timepoints. Characteristics were compared between inconsistent and consistent users (> 40%), and factors associated with inconsistent DMARD use were determined through multivariate logistic regression. A medical record review was performed to determine the reasons for inconsistent use.

***Results.*** Of 848 patients with ≥ 4 out of 5 visits recorded, 55 (6.5%) were inconsistent DMARD users. Higher age, longer disease duration, and rheumatoid factor negativity were statistically significant correlates of inconsistent use in the multivariate analyses. The primary reasons for inconsistent use identified through chart review, allowing for up to 2 co-primary reasons, were inactive disease (n = 28, 50.9%), intolerance to DMARD (n = 18, 32.7%), patient preference (n = 7, 12.7%), comorbidity (n = 6, 10.9%), DMARD not being effective (n = 3, 5.5%), and pregnancy (n = 3, 5.5%). During subsequent followup, 14/45 (31.1%) inconsistent users with sufficient data became consistent users of DMARD.

***Conclusion.*** A small proportion of patients with RA in a clinical rheumatology cohort were inconsistent DMARD users during the first 2 years of followup. While various patient factors correlate with inconsistent use, many patients re-start DMARD and become consistent users over time. (J Rheumatol First Release Oct 15 2014; doi:10.3899/jrheum.140306)

*Key Indexing Terms:*
RHEUMATOID ARTHRITIS
DISEASE-MODIFYING ANTIRHEUMATIC DRUGS
LONGITUDINAL STUDIES
DRUG ADHERENCE

Disease-modifying antirheumatic drugs (DMARD) have been shown to effectively reduce the signs and symptoms of rheumatoid arthritis (RA) and to improve longterm outcomes[1,2]. Accordingly, current American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) recommendations support the use of DMARD in all patients with active RA[3,4]. As a result of the focus on timely intervention with DMARD and close monitoring of disease activity with a structured, treat-to-target approach in recent years, patients seen by rheumatologists are more likely to receive DMARD than patients seen by unselected physicians[5]. However, results from contemporary RA cohorts show that even in specialized rheumatology clinics, a proportion of patients are not treated with DMARD[6,7,8,9,10,11,12].

Previous studies investigating DMARD use have mainly

*From the Division of Rheumatology, Immunology and Allergy, and the Division of Pharmacoepidemiology, Brigham and Women's Hospital, Boston, Massachusetts, USA; Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway; Department of Internal Medicine III, Division of Rheumatology, Medical University Vienna, Vienna, Austria; Department of Rheumatology, Kameda Medical Center, Kamogawa, Chiba Prefecture, Japan.*

*Dr. Solomon is supported by a mentoring award from the US National Institutes of Health (K24 AR055989). The Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study receives support from Bristol Myers Squibb, Medimmune, and Crescendo Bioscience.*

*M.D. Mjaavatten, MD, PhD, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, and Department of Rheumatology, Diakonhjemmet Hospital; H. Radner, MD, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, and Department of Internal Medicine III, Division of Rheumatology, Medical University Vienna; K. Yoshida, MD, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, and Department of Rheumatology, Kameda Medical Center; N.A. Shadick, MD, MPH; M.L. Frits, BA; C.K. Iannaccone, MPH, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital; T.K. Kvien, MD, PhD, Department of Rheumatology, Diakonhjemmet Hospital; M.E. Weinblatt, MD, MPH, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital; D.H. Solomon, MD, MPH, Division of Rheumatology, and Immunology and Allergy, and Division of Pharmacoepidemiology, Brigham and Women's Hospital.*

*Address correspondence to Dr. M.D. Mjaavatten, Department of Rheumatology, Diakonhjemmet Hospital, P.O. Box 23, Vinderen, 0319 Oslo, Norway. E-mail: maria_mjaavatten@hotmail.com*

*Accepted for publication August 26, 2014.*

performed cross-sectional analyses, and are thus unable to characterize consistency of use over time and changes in DMARD use patterns. To our knowledge, no detailed reports have been published that analyzed the consistency of DMARD use in longitudinal data. Understanding the extent of inconsistent use and examining the reasons why some patients with RA do not use DMARD over a longer period of time could aid clinical treatment decisions and help tailor quality improvement interventions at the patient level.

The aims of this study were (1) to describe the consistency of DMARD use during the first 2 years after inclusion in an observational RA cohort, (2) to identify factors associated with inconsistent versus consistent DMARD use, and (3) to determine the reasons for inconsistent DMARD use according to the medical record.

## MATERIALS AND METHODS

*Study cohort*. The Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS) is an observational single-center cohort consisting of more than 1300 patients who have been diagnosed with RA by board-certified rheumatologists[13]. Ninety-six percent of BRASS patients fulfilled the 1987 ACR classification criteria for RA at inclusion[14,15]. Patients were assessed annually with a comprehensive investigation including clinical and laboratory measures, and semiannually with patient-reported outcome measures. There was no predefined treatment protocol in BRASS. Thirty-eight rheumatologists participated in the data collection and provided patient care, with 10 (26%) being full-time clinicians. Patients included in the present analyses were recruited between 2003 and 2010 and had at least 4 study timepoints recorded within the first 2 years of followup. Of 848 patients, 670 (79%) were included in 2003 and 2004. The study was approved by The Brigham and Women's Hospital Institutional Review Board and all patients gave written consent.

*Assessment of DMARD use*. The following agents were considered DMARD in these analyses: methotrexate (MTX), leflunomide (LEF), cyclosporine, azathioprine, penicillamine, cyclophosphamide, hydroxychloroquine (HCQ), sulfasalazine (SSZ), auranofin, injectable gold salts, etanercept, infliximab, golimumab, certolizumab, anakinra, adalimumab, rituximab, abatacept, and tocilizumab. Patients were categorized as consistent DMARD users if they reported using any DMARD on 3 or more out of a possible maximum of 5 study timepoints during the first 2 years of followup (> 40% of timepoints). Persistence on the same DMARD was not required because DMARD were treated as a drug class. Patients using DMARD on 2 or fewer timepoints during the first 2 years of followup were categorized as inconsistent users. Patients were assumed to be treated with DMARD on missing study timepoints to prevent underestimation of use. Missing timepoints constituted 5.4% of the total number of study timepoints.

*Medical record review*. The electronic medical records (EMR) of patients identified as inconsistent users from the study data were reviewed in a structured way by one of the authors (MDM), using a data extraction sheet created for this purpose (Appendix 1). The treating rheumatologist's notes were reviewed for data on previous and current DMARD use (number and type), and the reasons for not using DMARD were recorded and categorized as well as graded by relevance as the primary reason, secondary reason, or tertiary reason. Intolerance to treatment was recorded when side effects or adverse events were mentioned as the reason for inconsistent DMARD use. We also determined whether any of the inconsistent users became consistent DMARD users subsequent to the first 2 study years. For this analysis, we used all available data in the EMR for patients with ≥ 24 months of EMR followup subsequent to the first 2 years after enrollment in BRASS. No minimum number of EMR entries within this followup was required. Patients were defined as subsequent consistent DMARD users if they were found to use DMARD continuously for 24 months or more during subsequent followup and were still using DMARD at the last recorded EMR entry.

*Statistical analysis*. Continuous measures were reported as means and SD or medians and 25th to 75th percentiles according to the distribution of the data. Categorical data were reported as numbers and proportions. For the proportions reported from the EMR review, CI were calculated according to the method described by Clopper and Pearson[16]. Comparisons between inconsistent and consistent DMARD users were performed with Student t tests, Mann-Whitney U tests, or chi-square tests as appropriate. The following variables were assessed: age, sex, disease duration, positivity for rheumatoid factor (RF) and anticyclic citrullinated peptide antibody (anti-CCP), current smoking, comorbidity measured by the Charlson index[17] (a modified version of the Charlson index that does not include information on all comorbidities was used), marital status, employment status, level of education, ethnicity (white yes/no), prednisone use at baseline and during followup, C-reactive protein (CRP), number of swollen and tender joints, patient's assessment of global disease activity measured by the Multidimensional Health Assessment Questionnaire (MDHAQ)[18], physician's assessment of global disease activity, 28-joint Disease Activity Score (DAS28) calculated with CRP, pain and fatigue measured by the MDHAQ, and functional status measured by the HAQ[19]. Factors independently associated with inconsistent DMARD use were determined by logistic regression analyses. Variables with p values < 0.25 in univariate analyses were included in multivariate logistic regression analyses, with inconsistent DMARD use as the dependent variable. All models were controlled for age and sex. First, the most parsimonious primary model was determined by backward manual selection. Second, alternative models were explored by introducing clinically meaningful variables into the primary model. The discriminative abilities of the models were assessed by calculating the area under the curve (AUC) of the predicted probabilities of each model. P values < 0.05 were considered significant. Analyses were performed in IBM SPSS Statistics version 21 and R version 3.0.2/pROC package version 1.5.4[20].

## RESULTS

The patient selection and distribution of DMARD use is illustrated in Figure 1. Of the 937 patients who had 2 years of followup, 848 had 4 (n = 231) or 5 (n = 617) study timepoints for the first 2 years recorded. Sixty-two patients were identified as inconsistent DMARD users in the BRASS data file, but 7 of these were reclassified as consistent users after the EMR review, leaving 55 inconsistent users (6.5%) for further study. Of these, 29 (52.7%) did not use a DMARD on any study timepoints during the first 2 years of followup, 10 used a DMARD on 1 timepoint, and 16 patients used a DMARD on 2 timepoints. The majority (94.7%) of the 793 consistent DMARD users reported DMARD use on 4 or 5 timepoints (n = 751). Among the 26 inconsistent users who did use 1 or more DMARD on ≤ 2 study timepoints during the 2-year study period, the most frequently used drug was MTX (n = 12), followed by HCQ (n = 6), LEF (n = 5), and SSZ (n = 3; Appendix 1). Five patients used a biologic DMARD. Other agents taken by inconsistent users were gold, penicillamine, and cyclosporine (n = 3). In these 26 patients, more than 1 drug could be used simultaneously or at different timepoints by the same patient.

*Factors associated with inconsistent DMARD use.*

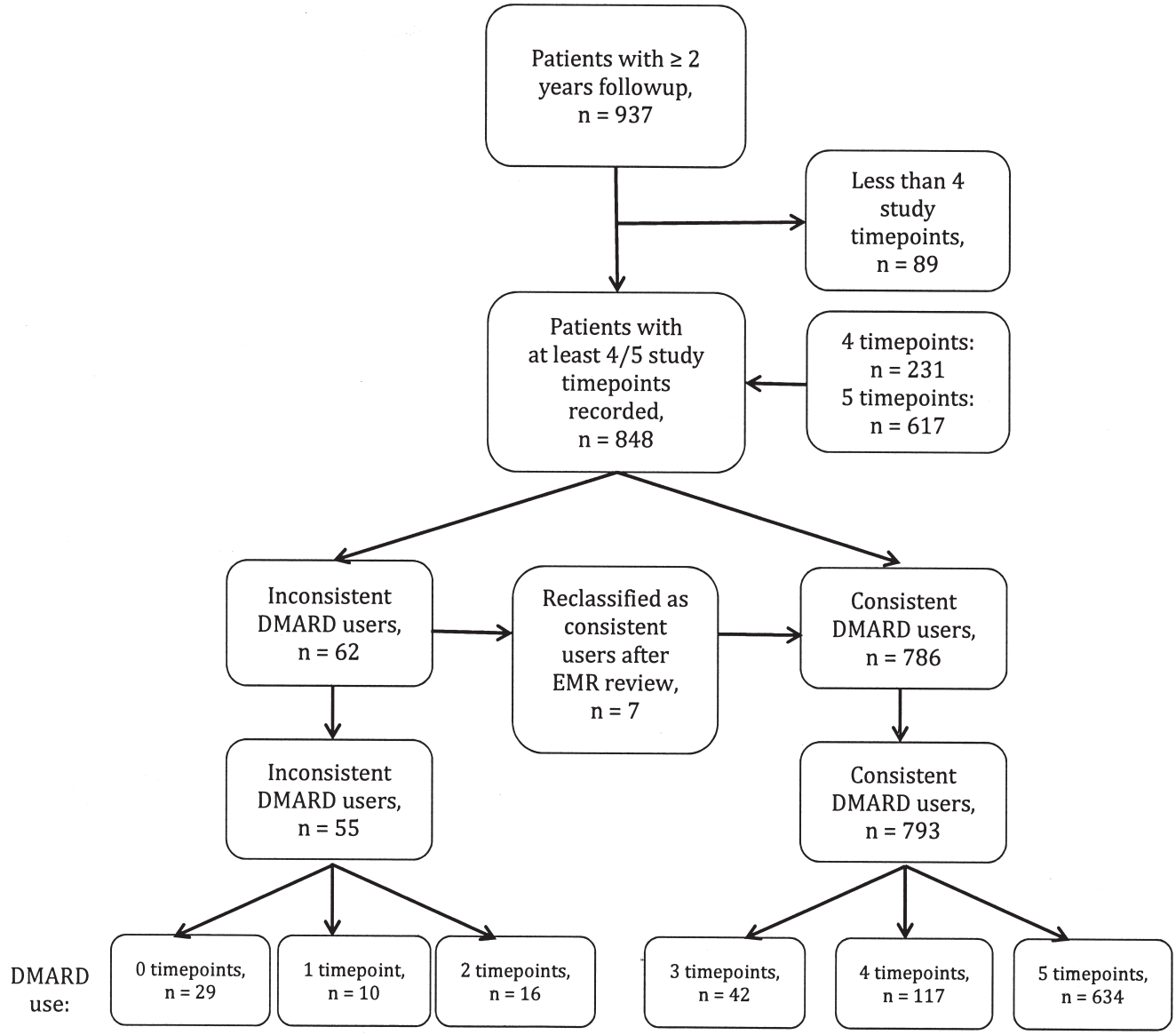


*Figure 1*. Overview of patient selection and DMARD use. DMARD: disease-modifying antirheumatic drug; EMR: electronic medical records.

Inconsistent DMARD users were older (mean age 60.6 yrs vs 56.3 yrs, p = 0.02) and were less frequently RF-positive (33.3 vs 67.1%, p < 0.0001) or anti-CCP-positive (40.0 vs 65.8%, p < 0.001) than consistent users in the univariate analyses (Table 1). Inconsistent users also had a lower rate of employment (37.7 vs 52.6%, p = 0.04). There was a trend toward longer disease duration and higher Charlson index in the inconsistent user group, but the differences were not statistically significant. Pain, fatigue, functional status, and disease activity were similar in the 2 groups.

The results of the multivariate logistic regression analyses are shown in Table 2. The primary model showed that older age, longer disease duration, and RF negativity were associated with inconsistent DMARD use. We explored several alternative models, including models with the individual components of the DAS28: the baseline DAS28, the time-averaged DAS28 (calculated as in Bøyesen, *et al*[21]; method description in Appendix 2) over the first 2 years of followup, and concurrent prednisone use and comorbidity measured by a modified version of the Charlson index[22]. The results of 3 alternative models are shown in Table 2. The AUC did not improve in any of the alternative models, compared to the primary model.

*Reasons for not using DMARD, according to the medical record*. The reasons for inconsistent DMARD use found in the medical records could all be placed into 1 of 5 categories (Table 3). While many patients were found to have several reasons for inconsistent DMARD use, in most patients a single primary reason for not taking a DMARD could be determined from the EMR review (Appendix 1). The most

*Table 1*. Comparison of characteristics in inconsistent and consistent DMARD users in the BRASS cohort. Means (SD) are presented for normally distributed variables, and medians (25th–75th percentiles) are presented for nonnormally distributed variables.

| Variable[$] | Missing Values | Inconsistent Users, n = 55 | Consistent Users, n = 793 | p |
|---|---|---|---|---|
| Age, yrs, mean (SD) | 0 | 60.6 (14.5) | 56.3 (13.0) | 0.02* |
| Females, n (%) | 0 | 45 (81.8) | 663 (83.6) | 0.73 |
| RA duration, yrs, mean (SD) | 0 | 16.5 (13.9) | 13.6 (11.8) | 0.08* |
| RF-positive, n (%) | 19 | 18/54 (33.3) | 520/775 (67.1) | < 0.0001* |
| Anti-CCP–positive, n (%) | 0 | 22 (40.0) | 522 (65.8) | < 0.001* |
| Current smokers, n (%) | 41 | 5/54 (9.3) | 55/753 (7.3) | 0.60 |
| Charlson index, median (25th-75th percentile) | 0 | 2 (1–3) | 2 (1–2) | 0.10* |
| Married, n (%) | 2 | 37 (67.3) | 520/791 (65.7) | 0.82 |
| Employed, n (%) | 38 | 20/53 (37.7) | 398/757(52.6) | 0.04* |
| Highest level of education, n (%) | 5 | | | 0.16* |
| Did not graduate from high school | | 1 (1.8) | 24 (3.0) | |
| Graduated high school but not college | | 30 (54.5) | 327 (41.5) | |
| Graduated college | | 24 (43.6) | 437 (55.5) | |
| White, n (%) | 8 | 49 (89.1) | 740/785 (94.3) | 0.12* |
| Prednisone use at inclusion, n (%) | 0 | 19 (34.5) | 295 (37.2) | 0.69 |
| Prednisone use any time during the 2-yr followup, n (%) | 0 | 295 (37.2) | 19 (34.5) | 0.70 |
| CRP, mg/l, median (25th–75th percentile) | 7 | 4.04 (1.11–12.81) | 2.87 (1.05–7.87) | 0.29 |
| No. swollen joints (0–28), mean (SD) | 0 | 7.1 (8.2) | 7.4 (7.2) | 0.75 |
| No. tender joints (0–28), mean (SD) | 0 | 9.2 (8.9) | 8.1 (7.8) | 0.32 |
| MDHAQ patient global scale[§], mean (SD) | 40 | 25.9 (24.3) | 31.0 (24.7) | 0.15* |
| Physician global disease activity[£], mean (SD) | 12 | 34.4 (27.4) | 32.8 (21.2) | 0.61 |
| DAS28-CRP(4), mean (SD) | 47 | 3.96 (1.65) | 3.89 (1.60) | 0.78 |
| DAS28-CRP(4) AUC, mean (SD) | 1 | 3.67 (1.59) | 3.48 (1.39) | 0.33 |
| MDHAQ pain scale[§], mean (SD) | 65 | 37.1 (31.1) | 34.7 (26.8) | 0.54 |
| MDHAQ fatigue scale[§], mean (SD) | 40 | 38.2 (28.4) | 41.3 (28.7) | 0.43 |
| MHAQ score, median (25th–75th percentile) | 40 | 0.20 (0.00–0.65) | 0.30 (0.00–0.60) | 0.86 |

[$]At study inclusion unless stated otherwise. * $p < 0.25$, variable included in multivariate analyses (Table 2). [§]Recorded from 0-100 in increments of 5, with higher values corresponding to a worse state. [£]Recorded from 0–100 in integers of 10, with higher values corresponding to a worse state. RA: rheumatoid arthritis; RF: rheumatoid factor; DMARD: disease-modifying antirheumatic drug; anti-CCP: anticyclic citrullinated peptide; CRP: C-reactive protein; MDHAQ: Multidimensional Health Assessment Questionnaire; DAS28-CRP(4): 28-joint Disease Activity Score by CRP with 4 variables; AUC: area under the curve over 2 years' followup; MHAQ: Modified Health Assessment Questionnaire.

*Table 2*. Logistic regression models with inconsistent DMARD use as dependent variable. All data are OR (95% CI).

| | Univariate Analysis | Primary Model | Secondary Models | | |
|---|---|---|---|---|---|
| | | | + Baseline DAS28 | + Time-averaged DAS28 | + Charlson Index |
| Age, per yr | 1.03 (1.00–1.05) | 1.03 (1.00–1.05) | 1.03 (1.00–1.05) | 1.02 (1.00–1.05) | 1.02 (1.00–1.05) |
| Female | 0.88 (0.43–1.80) | 1.12 (0.53–2.35) | 0.93 (0.44–1.97) | 1.09 (0.52–2.29) | 1.11 (0.53–2.34) |
| RA duration, per yr | 1.02 (1.00–1.04) | 1.03 (1.01–1.05) | 1.02 (1.00–1.05) | 1.03 (1.00–1.05) | 1.03 (1.00–1.05) |
| RF+ | 0.25 (0.14–0.44) | 0.20 (0.11–0.36) | 0.23 (0.12–0.42) | 0.19 (0.10–0.35) | 0.20 (0.11–0.36) |
| Baseline DAS28 | 1.03 (0.86–1.23) | — | 1.01 (0.83–1.23) | — | — |
| Time-averaged DAS28 | 1.10 (0.91–1.33) | — | — | 1.12 (0.90–1.39) | — |
| Charlson index | 1.20 (0.99–1.44) | — | — | — | 1.16 (0.95–1.41) |
| AUC (95 % CI) | | 0.74 (0.67–0.81) | 0.73 (0.65–0.80) | 0.74 (0.67–0.81) | 0.74 (0.67–0.81) |

DMARD: disease-modifying antirheumatic drug; DAS28: 28-joint Disease Activity Score; time-averaged: area under the curve over 2 years; AUC: area under the curve; RA: rheumatoid arthritis; RF: rheumatoid factor.

frequent reason for not using DMARD was that the patients were felt by their rheumatologist to have inactive disease and thus were without indication for a DMARD to be prescribed. This was supported by the clinical data, which showed that the mean (SD) time-averaged DAS28 was lower in patients whose primary reason for inconsistent DMARD use was inactive disease (n = 28) than it was in the other inconsistent users [3.26 (1.53) vs 4.16 (1.55), p = 0.03]. The majority of the inconsistent DMARD users whose providers determined that they had inactive RA had previously been treated with 1 or more DMARD (Appendix 1), most frequently HCQ, MTX, SSZ, and gold (detailed data not shown).

Intolerance to the treatment was the second most

*Table 3*. Reasons for inconsistent DMARD use in 55 patients in BRASS study as determined from medical record review.

| | Primary Reason | | Any Reason, n (%) | |
|---|---|---|---|---|
| | n | % (95% CI)* | n | % (95% CI)* |
| DMARD not indicated/inactive disease | 28 | 50.9 (37.1–64.6) | 36 | 65.5 (51.4–77.8) |
| Intolerance to DMARD/adverse events | 18 | 32.7 (20.7–46.7) | 30 | 54.5 (40.6–68.0) |
| Patient reluctant to take DMARD | 7 | 12.7 (5.3–24.5) | 15 | 27.3 (16.1–41.0) |
| Comorbidity | 6 | 10.9 (4.1–22.2) | 14 | 25.5 (14.7–39.0) |
| DMARD not effective | 3 | 5.5 (1.1–15.1) | 4 | 7.3 (2.0–17.6) |
| Pregnancy | 3 | 5.5 (1.1–15.1) | 3 | 5.5 (1.1–15.1) |

*Adds up to > 100% because 10 patients were found to have 2 co-primary reasons. BRASS: Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study; DMARD, disease-modifying antirheumatic drug.

common reason, followed by the patient's choice not to take a DMARD even though it was recommended by the rheumatologist. Other reasons were comorbidity, lack of efficiency of previously used DMARD, pregnancy, or trying to conceive. In the 6 patients in whom comorbidities were found to be the primary reason for avoiding DMARD use, the comorbid conditions were chronic leg ulcers (n = 3), lung cancer (n = 1), history of near-fatal meningitis while taking combination MTX and LEF (n = 1), and myelodysplasia/pancytopenia (n = 1). Ten patients were found to have multiple reasons that played equal roles in influencing inconsistent use. For example, 1 patient was found to be in remission for the first year of the study, and when a flare occurred during the second year, the patient decided not to take the recommended drug. Insurance issues or financial problems were not mentioned as a reason for DMARD nonuse in any of the 55 subjects' medical records. Detailed results from the EMR review for each patient are given in Appendix 1.

*Subsequent DMARD treatment*. In 45 of the inconsistent users, information about DMARD treatment for at least 2 additional years was available in the EMR. The mean followup time in these patients was 81 months. Fourteen of these 45 inconsistent DMARD users (31.1%) started DMARD treatment during followup and continued taking the treatment for at least 24 months (i.e., became consistent DMARD users).

## DISCUSSION

Consistent use of DMARD over time is recommended for improved longterm outcomes in RA. Treatment should be tightly controlled, aimed at remission or low disease activity, and based on a shared decision between the patient and the rheumatologist regarding the appropriate treatment target[3,4]. However, little is known about the consistency of DMARD use over time in clinical rheumatology practice. Our study is the first longitudinal study, to our knowledge, to analyze the pattern of DMARD treatment in individual patients. We found very few inconsistent users in this rheumatology-based RA cohort. Patient characteristics associated with inconsistent use included older age, seronegative RA, and longer RA duration. A number of clinically sensible factors could be found in the EMR as reasons for inconsistent use. Also, almost one-third of inconsistent users became consistent users over the subsequent 2 years.

A systematic literature review found that 2–23% of patients with RA followed by a rheumatologist did not receive DMARD[5]. Another review of selected clinical databases and cohorts found that 5–58% of the patients in studies reporting data from the 2000s were not treated with DMARD[23]. It is interesting that the rate of DMARD use over time in BRASS was fairly high compared to the findings in the cross-sectional studies presented in these reviews. This could reflect that some patients in cross-sectional analyses are misclassified as nonusers when DMARD use is studied at only 1 timepoint. The different rates of DMARD use could also be explained by differences in study demographics, availability of DMARD, and cultural factors.

Inconsistent use was associated with older age, even after controlling for comorbidity and disease activity. DeWitt, *et al* studied predictors of initiation of biologics in 1545 patients with RA in the ARAMIS databank, and found that higher age was significantly associated with decreased use of biologics[10]. They also found that higher income, higher disability, and previous steroid use were associated with starting biologics. Relative underuse of DMARD in older patients has also been found in claims-based and observational studies[24,25]. A mail survey performed among 204 US rheumatologists asked for their treatment recommendations for 2 case scenarios that only differed with regard to age[26]. The respondents were more likely to prefer less aggressive treatment for the older patient with RA.

In addition to older age, RF-negative RA was associated with being an inconsistent DMARD user. Seronegative patients have a better prognosis in terms of joint destruction, extraarticular disease, and disease activity over time, and knowledge about the antibody status is therefore likely to have influenced treatment decisions[27,28,29]. Further, it was

apparent from the EMR review that the rheumatologist questioned the validity of the RA diagnosis in at least some seronegative patients, and thus would be less likely to recommend DMARD treatment for those patients. Anti-CCP results were not commonly available to the rheumatologists in this clinic until 2005, and that could explain why RF was more strongly associated with consistent use than was anti-CCP.

Inconsistent use was also associated with longer disease duration. Patients with longstanding disease could have been more likely to have experienced side effects or failure of DMARD in the past, making introduction of a new DMARD more difficult. This assumption was supported by the finding of intolerance as one of the major reasons for inconsistent DMARD use in the EMR review.

Our study has some limitations. The first is that it is a single-center study, which potentially could decrease the generalizability of the results. However, several experienced board-certified rheumatologists provided care for the BRASS patients, unlike some other cohorts in which only a few selected doctors participated. Also, patients who enroll in BRASS may be a selective group who are more likely to use DMARD consistently. Nevertheless, we thought it worthwhile to study inconsistent use in this patient population, because it is made up of patients who were all perceived by their caretaker to have RA at the time of inclusion, and for whom DMARD treatment is recommended. The cohort of inconsistent DMARD users is not very large. However, this allowed us to perform a detailed chart review to uncover the reasons for inconsistent use. Moreover, the threshold to define inconsistent use was chosen somewhat arbitrarily, and may have affected our results. Another potential issue is that treatment data were partially provided by patient self-report. However, patient-reported DMARD use was previously found to correlate well with the medical record for current use in BRASS[30]. We assumed patients to be using DMARD on missing timepoints and this assumption could have overestimated use. If we had instead assumed patients to not be using DMARD on missing timepoints, the proportion of inconsistent users would have remained low (7.8%). We were unable to specifically report on the role of "rheumatologist choice" in determining inconsistent DMARD use. The rheumatologist could choose not to recommend DMARD use in patients with seemingly active disease because of the impression that pain was noninflammatory or related to irreversible joint damage. The specific reasons why rheumatologists may choose not to prescribe DMARD could only be inferred from the available data. Lastly, we did not include data on the availability of medical insurance in the analyses. However, insurance problems were not mentioned in the EMR as a reason for inconsistent use in any of the 55 patients.

Strengths of our study include the longitudinal assessment of DMARD use, and that we had access to actual treatment data in a contemporary rheumatology practice. Inconsistent DMARD use was verified through EMR review, ensuring homogeneity of the study sample, and this allowed for a synthesis of quantitative and "semiqualitative" data that offers a new perspective on DMARD treatment.

We found that 6.5% of the patients with RA in a clinical cohort were inconsistently treated with DMARD. Patients with older age, longer disease duration, and those who were RF-negative were less likely to be consistent users. The most common reasons for inconsistent use were inactive disease and intolerance to treatment. Our finding that a substantial minority of inconsistent users become consistent users suggests a need for continued efforts to characterize such patients, to identify them and work with them to find DMARD that they can tolerate and find effective. Future analyses will explore to what degree inconsistent DMARD use has implications for disease outcomes.

## REFERENCES


1. Gaujoux-Viala C, Smolen JS, Landewe R, Dougados M, Kvien TK, Mola EM, et al. Current evidence for the management of rheumatoid arthritis with synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69:1004-9.
2. Nam JL, Winthrop KL, van Vollenhoven RF, Pavelka K, Valesini G, Hensor EM, et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis 2010;69:976-86.
3. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 2012;64:625-39.
4. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492-509.
5. Schmajuk G, Solomon DH, Yazdany J. Patterns of disease-modifying antirheumatic drug use in rheumatoid arthritis patients after 2002: a systematic review. Arthritis Care Res 2013;65:1927-35.
6. Söderlin MK, Lindroth Y, Jacobsson LT. Trends in medication and health-related quality of life in a population-based rheumatoid arthritis register in Malmo, Sweden. Rheumatology 2007; 46:1355-8.
7. Sokka T, Pincus T. Ascendancy of weekly low-dose methotrexate in usual care of rheumatoid arthritis from 1980 to 2004 at two sites in Finland and the United States. Rheumatology 2008;47:1543-7.
8. Gonzalez-Alvaro I, Descalzo MA, Carmona L. Trends towards an improved disease state in rheumatoid arthritis over time: influence of new therapies and changes in management approach: analysis of the EMECAR cohort. Arthritis Res Ther 2008;10:R138.
9. Yamanaka H, Inoue E, Singh G, Tanaka E, Nakajima A, Taniguchi A, et al. Improvement of disease activity of rheumatoid arthritis patients from 2000 to 2006 in a large observational cohort study IORRA in Japan. Mod Rheumatol 2007;17:283-9.

10. DeWitt EM, Lin L, Glick HA, Anstrom KJ, Schulman KA, Reed SD. Pattern and predictors of the initiation of biologic agents for the treatment of rheumatoid arthritis in the United States: an analysis using a large observational data bank. Clin Ther 2009;31:1871-80; discussion 58.
11. Ziegler S, Huscher D, Karberg K, Krause A, Wassenberg S, Zink A. Trends in treatment and outcomes of rheumatoid arthritis in Germany 1997-2007: results from the National Database of the German Collaborative Arthritis Centres. Ann Rheum Dis 2010;69:1803-8.
12. Sung YK, Cho SK, Choi CB, Park SY, Shim J, Ahn JK, et al. Korean Observational Study Network for Arthritis (KORONA): establishment of a prospective multicenter cohort for rheumatoid arthritis in South Korea. Semin Arthritis Rheum 2012;41:745-51.
13. Iannaccone CK, Lee YC, Cui J, Frits ML, Glass RJ, Plenge RM, et al. Using genetic and clinical data to understand response to disease-modifying anti-rheumatic drug therapy: data from the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study. Rheumatology 2011;50:40-6.
14. Lillegraven S, Paynter N, Prince FH, Shadick NA, Haavardsholm EA, Frits ML, et al. Performance of matrix-based risk models for rapid radiographic progression in a cohort of patients with established rheumatoid arthritis. Arthritis Care Res 2013;65:526-33.
15. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
16. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404-13.
17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
18. Pincus T, Swearingen C, Wolfe F. Toward a multidimensional Health Assessment Questionnaire (MDHAQ): assessment of advanced activities of daily living and psychological status in the patient-friendly health assessment questionnaire format. Arthritis Rheum 1999;42:2220-30.
19. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-45.
20. Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez JC, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinformatics 2011;12:77.
21. Bøyesen P, Haavardsholm EA, Ostergaard M, van der Heijde D, Sesseng S, Kvien TK. MRI in early rheumatoid arthritis: synovitis and bone marrow oedema are independent predictors of subsequent radiographic progression. Ann Rheum Dis 2011;70:428-33.
22. Sung YK, Yoshida K, Prince F, Frits ML, Choe JY, Chung WT, et al. Quality of life in rheumatoid arthritis: cross-national comparison study between US and South Korea [abstract]. Arthritis Rheum 2013;65 Suppl 10:S438.
23. Sokka T. Increases in use of methotrexate since the 1980s. Clin Exp Rheumatol 2010;28:S13-20.
24. Schmajuk G, Schneeweiss S, Katz JN, Weinblatt ME, Setoguchi S, Avorn J, et al. Treatment of older adult patients diagnosed with rheumatoid arthritis: improved but not optimal. Arthritis Rheum 2007;57:928-34.
25. Tutuncu Z, Reed G, Kremer J, Kavanaugh A. Do patients with older-onset rheumatoid arthritis receive less aggressive treatment? Ann Rheum Dis 2006;65:1226-9.
26. Fraenkel L, Rabidou N, Dhar R. Are rheumatologists' treatment decisions influenced by patients' age? Rheumatology 2006;45:1555-7.
27. Kastbom A, Strandberg G, Lindroos A, Skogh T. Anti-CCP antibody test predicts the disease course during 3 years in early rheumatoid arthritis (the Swedish TIRA project). Ann Rheum Dis 2004;63:1085-9.
28. Syversen SW, Gaarder PI, Goll GL, Ødegard S, Haavardsholm EA, Mowinckel P, et al. High anti-cyclic citrullinated peptide levels and an algorithm of four variables predict radiographic progression in patients with rheumatoid arthritis: results from a 10-year longitudinal study. Ann Rheum Dis 2008;67:212-7.
29. Lopez-Longo FJ, Sanchez-Ramon S, Carreno L. The value of anti-cyclic citrullinated peptide antibodies in rheumatoid arthritis: do they imply new risk factors? Drug News Perspect 2009; 22:543-8.
30. Solomon DH, Stedman M, Licari A, Weinblatt ME, Maher N, Shadick N. Agreement between patient report and medical record review for medications used for rheumatoid arthritis: the accuracy of self-reported medication information in patient registries. Arthritis Rheum 2007;57:234-9.

**APPENDIX 1.** Individual results of the EMR review for the 55 inconsistent DMARD users.

| Pt No. | Sex | Age, yrs | RA Duration, yrs | No. Previous DMARD | Visits While Taking DMARD | Type of DMARD (during 2-yr study period) | Reasons for Inconsistent DMARD Use | | | | | Subsequent Consistent DMARD Use |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Inactive Disease | Adverse Events | Comorbidity | Pt's Choice | Pregnancy | Not Effective | |
| 1 | F | 45 | 34 | 1 | 1 | LEF | 1 | | | | | | N |
| 2 | M | 70 | 0 | 0 | 2 | SSZ, MTX | | 1 | | | | | N |
| 3 | M | 88 | 10 | 1 | 0 | Short course SSZ | 1 | 2 | | | | | N |
| 4 | F | 67 | 15 | 2 | 2 | PEN, LEF | | 1 | 2 | | | | Y |
| 5 | F | 75 | 52 | 2 | 0 | - | 1 | 2 | 3 | 2 | | | N |
| 6 | F | 82 | 4 | 3 | 0 | - | 1 | 2 | | | | | N |
| 7 | F | 53 | 10 | 1 | 2 | HCQ | 2 | 1 | | | | | N |
| 8 | F | 57 | 32 | 1 | 0 | - | 1 | | | | | | N |
| 9 | F | 69 | 29 | 2 | 2 | MTX | | | | 1 | | | Y |
| 10 | F | 75 | 46 | 6 | 0 | - | | 1 | 2 | 2 | | | - |
| 11 | F | 69 | 16 | 1 | 2 | MTX | 1 | | 2 | | | | N |
| 12 | F | 75 | 12 | 3 | 0 | - | 1 | | | | | 2 | N |
| 13 | F | 62 | 31 | 3 | 0 | - | 1 | 2 | | 2 | | | Y |
| 14 | F | 79 | 27 | 0 | 2 | MTX | | | 1 | | | | - |
| 15 | F | 37 | 7 | 3 | 0 | - | 1 | | | | | | N |
| 16 | F | 62 | 6 | 1 | 1 | HCQ | 1 | 3 | 2 | | | | Y |
| 17 | F | 56 | 5 | 0 | 0 | Short course SSZ | 3 | 2 | | 1 | | | N |
| 18 | F | 63 | 40 | 3 | 0 | - | | 2 | 1 | | | | N |
| 19 | M | 65 | 10 | 0 | 0 | Short course i.m. gold | 1 | 1 | | | | | Y |
| 20 | M | 83 | 5 | 1 | 0 | - | 1 | 2 | | | | | N |
| 21 | F | 36 | 33 | 1 | 0 | Short course HCQ | 1 | 1 | | | | | Y |
| 22 | F | 68 | 30 | 2 | 1 | LEF | | | 1 | | | | N |
| 23 | F | 59 | 46 | 2 | 1 | LEF | | 1 | | | | | - |
| 24 | M | 61 | 2 | 1 | 1 | ADA | 2 | 1 | | | | | N |
| 25 | M | 31 | 5 | 1 | 2 | MTX, ETN | | 1 | 2 | | | | Y |
| 26 | F | 61 | 19 | 1 | 0 | - | 1 | | | | | | N |
| 27 | F | 71 | 16 | 2 | 0 | - | | | | 2 | | 1 | N |
| 28 | F | 43 | 1 | 0 | 1 | SSZ | | 1 | | 2 | | | N |
| 29 | F | 59 | 24 | 3 | 0 | - | 1 | 2 | | 3 | | | N |
| 30 | F | 46 | 3 | 1 | 2 | MTX | 1 | | | | | | Y |
| 31 | F | 64 | 8 | 1 | 1 | HCQ, MTX | 1 | | | 1 | | | N |
| 32 | F | 71 | 11 | 3 | 0 | - | 1 | | | 1 | | | N |
| 33 | F | 59 | 1 | 0 | 2 | HCQ | 1 | | | | | | Y |
| 34 | M | 60 | 42 | 2 | 0 | - | 1 | | | | | | N |
| 35 | F | 67 | 21 | 1 | 2 | MTX | 1 | | | | | | - |
| 36 | F | 54 | 2 | 1 | 0 | - | 1 | | | 2 | | | N |
| 37 | M | 71 | 13 | 5 | 2 | CYC, ABA | | 2 | 1 | 2 | | | N |
| 38 | M | 42 | 7 | TNFi | 0 | - | 1 | 1 | | | | | Y |
| 39 | F | 52 | 12 | 2 | 0 | - | 1 | | | | | | N |
| 40 | F | 27 | 8 | 3 | 1 | MTX | | | | | 1 | | N |
| 41 | F | 81 | 42 | 1 | 2 | ETN | 2 | | 1 | 1 | | | - |
| 42 | F | 56 | 27 | "All trad." | 0 | - | 2 | | | 1 | | 1 | N |
| 43 | F | 60 | 4 | 1 | 0 | - | 1 | | | | | 1 | N |
| 44 | F | 31 | 3 | 0 | 2 | HCQ | | | | | 1 | | - |
| 45 | F | 80 | 1 | 0 | 2 | HCQ, SSZ | | 1 | | | | | Y |
| 46 | F | 36 | 7 | 3 | 0 | - | | | | | 1 | | Y |
| 47 | F | 45 | 17 | 3 | 0 | - | 1 | | | | | | N |
| 48 | F | 72 | 20 | 4 | 0 | Short course LEF | | 2 | | 1 | | | Y |
| 49 | F | 77 | 13 | 0 | 0 | Short course MTX | 1 | 1 | | | | | - |
| 50 | F | 44 | 8 | 5 | 0 | - | 2 | 1 | | | | | N |
| 51 | F | 65 | 1 | 0 | 1 | MTX | 2 | 1 | 2 | | | | - |
| 52 | F | 74 | 7 | 1 | 2 | MTX, gold | 2 | 1 | | | | | - |
| 53 | F | 55 | 31 | 2 | 1 | ABA | 1 | 1 | | | | | Y |
| 54 | F | 57 | 9 | 6 | 0 | - | | 1 | 2 | | | | - |
| 55 | F | 67 | 21 | 2 | 2 | LEF, MTX | | 2 | 1 | | | | N |

Pt: Patient; EMR: electronic medical record; DMARD: disease-modifying antirheumatic drug; RA: rheumatoid arthritis; LEF: leflunomide; SSZ: sulfasalazine; MTX: methotrexate; PEN: penicillamine; HCQ: hydroxychloroquine; i.m.: intramuscular; ADA: adalimumab; ETN: etanercept; CYC: cyclosporine; TNFi: tumor necrosis factor inhibitor; All trad.: all traditional DMARD; ABA: abatacept.

**APPENDIX 2.**

Imputation of missing 28-joint Disease Activity Score (DAS28) values for calculation of time-integrated DAS28 (DAS28 AUC).

Values were carried backward when there were no earlier data [e.g., if no data were available for study timepoint 1 (T1), then the T2 value was imputed for T1]. Values were carried forward when there were no later data (e.g., if no data were available for T5, then the T4 value was imputed for T5). For missing values at visits with both previous and later data, weighted average values were imputed (e.g., T1 and T4 had data, T2 and T3 missing: T2 = T1/3*2+T4/3*1, T3 = T1/3*1+T4/3*2). The time-integrated DAS28 was then calculated from the imputed values according to the following formula:

DAS 28 AUC = ((T1+T2)/2+(T2+T3)/2+(T3+T4)/2+(T4+T5)/2)/4