Published in final edited form as:

Semin Arthritis Rheum. 2015 February ; 44(4): 399–404. doi:10.1016/j.semarthrit.2014.08.003.

Do Rheumatologists Know Best? An Outcomes Study of Inconsistent Users of Disease-Modifying Anti-Rheumatic Drugs

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Abstract

Objective—Current recommendations advocate treatment with disease-modifying anti-rheumatic drugs (DMARDs) in all patients with active rheumatoid arthritis (RA). We analyzed short-term disease outcome in patients according to the consistency of DMARD use in a clinical rheumatology cohort.

Methods—Patients in an RA registry (N=617) were studied for DMARD use at semi-annual study time points during the first 18 months of follow-up, and were divided into 4 groups according to the number of study time points with any DMARD use (0–1 study time points (n=31), 2 study time points (n=24), 3 study time points (n=77), and 4 study time points (n=485). The primary outcome analyses were performed at 24 months and included Disease Activity Score 28 (DAS28-CRP), modified Health Assessment Questionnaire (MHAQ) change, Short Form Health Survey-12 physical and mental summary scores (SF-12 PCS, SF-12 MCS), EuroQol 5-Dimensional health index (EQ-5D) and radiographic progression. Unadjusted, adjusted and analyses stratified for seropositivity and disease activity were performed. A secondary analysis investigated 36 month-outcomes.

Results—No significant 24-month outcome differences could be found between the DMARD use categories. For seropositive patients there was evidence of a linear trend for SF-12 PCS (p=0.02) and EQ-5D (p=0.01) with worse outcomes for inconsistent DMARD users. At 36 months, there was a linear trend for higher DAS28-CRP scores for inconsistent users (p<0.01)

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Competing interests

MDM declared no competing interests. HR declared no competing interests. MLF declared no competing interests. CKI declared no competing interests. DHS declared no competing interests.

Conclusions—Overall, we found poor correlation between inconsistent DMARD use and short-term disease outcome. However, outcome in the longer term could be negatively influenced by inconsistent DMARD use, as well as short-term outcome in seropositive patients.

Keywords

Rheumatoid arthritis; disease-modifying anti-rheumatic drugs; drug adherence; disease outcomes; longitudinal study

Introduction

Evidence from controlled clinical trials shows that disease-modifying anti-rheumatic drugs (DMARDs) improve outcomes in RA in terms of disease activity, physical function, quality of life and structural damage to the joints. (1–3) Current treatment recommendations and quality indicators state that all patients with active RA should be treated with DMARDs. (4–6) However, recent literature reviews show that a proportion (2–58%) of patients in typical rheumatology practice, when assessed at one point in time, are not treated with DMARDs. (7, 8) The clinical effectiveness of DMARDs has also been proven in observational DMARD registries; these are mainly studies that compared different types of DMARDs and DMARD combinations and none have investigated the use of any DMARD vs. no DMARD. (9, 10)

We recently described characteristics of patients who were inconsistent users of DMARDs in a clinical rheumatology cohort, and found that inconsistent use was associated with higher age, longer disease duration and seronegative RA (manuscript submitted). The aim of the present study was to study short-term disease outcomes assessed by disease activity, physical function, health-related quality of life and joint damage in RA patients in a clinical rheumatology cohort according to the consistency of DMARD use during the first 18 months after cohort inclusion.

Methods

Subjects

The Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS) is a single-center observational cohort of adult patients with a clinical diagnosis of RA. (11) No predefined treatment protocol is employed. Patients are assessed every 6 months; annually with a comprehensive clinical visit and semi-annually with questionnaires. For this analysis, we selected participants in BRASS with at least 24 months of follow-up who had all five semi-annual study time points during the first two study years recorded (n=617). These subjects were included in BRASS from 2003–2010. For an overview of patient selection, see Figure 1. Included patients were older (mean 57.1 vs. 55.0 years, $p=0.02$), more frequently white (94.8% vs. 91.4%, $p=0.045$) and scored higher on patient global disease activity (mean 33.1 vs. 29.6, $p=0.009$) than excluded patients, but the groups did not differ for any other baseline characteristics (Supplementary table 1).

Assessment of DMARD use

We assessed DMARD use as a dichotomous variable (yes/no) at each of the first four study time points of the study (i.e., at 0–6–12–18 months). Information about current DMARD use was obtained at each study time point through patient questionnaires. Information on current DMARD use from the patient questionnaires has previously been shown to correlate well with the medical record in the BRASS study.(12) The following agents were considered as DMARDs in these analyses: methotrexate, leflunomide, cyclosporine, azathioprine, penicillamine, cyclophosphamide, hydroxychloroquine, sulfasalazine, auranofin, injectable gold salts, etanercept, infliximab, golimumab, certolizumab, anakinra, adalimumab, rituximab, abatacept, tocilizumab. We analyzed the consistency of DMARD use as an ordinal variable divided into four categories according to the number of study time points with DMARD use: 0–1 study time points (n=31), 2 study time points (n=24), 3 study time points (n=77), and all 4 study time points (n=485).

Assessment of disease outcome

We performed the primary outcome analyses with data from the 24-month visit. We measured disease activity by the Disease Activity Score 28 calculated with C-reactive protein (DAS28-CRP), and functional status by the change in the modified Health Assessment Questionnaire (MHAQ) from study inclusion (baseline) to 24 months. We evaluated health related quality of life at 24 months with the Short Form Health Survey-12 (SF-12), Physical Component Summary (PCS), Mental Component Summary (MCS), as well as the EuroQol 5-Dimensional health index (EQ-5D). X-rays of hands and wrists from baseline and 24 months were available in 334 patients (54.1%), and were scored according to the van der Heijde modified Sharp scoring method by four trained radiologists blinded to the sequence of the radiographs. We assessed progression in structural joint damage by the change in the van der Heijde modified Sharp score (TSS) from baseline to 24 months. Outcome data from the 36-month visit were studied as a secondary analysis when available; SF-12 and TSS was not recorded at 3 years.

Statistical analysis

Baseline characteristics and unadjusted outcomes were compared between groups with Chi-Square, analysis of variance (ANOVA) and Kruskal-Wallis tests as appropriate. Adjusted outcome analyses were performed with linear regression models (general linear modeling, GLM) adjusting for variables found to significantly differ between groups at baseline, as well as factors identified as potential confounders from a clinical perspective (age, gender, RA duration, seropositivity, baseline DAS28-CRP, pain level, Charlson index, body mass index, and smoking). We present estimated marginal means (predicted mean values of the dependent variable for each category with covariates held at their mean values) and 95% confidence intervals (CI). Unadjusted and adjusted outcomes were also tested for a linear trend across the ordered categories of DMARD use.

Finally, we performed several sensitivity analyses, stratifying for the DAS28-CRP disease activity status at baseline (remission or low disease activity (DAS28-CRP ≤ 3.2) vs. moderate to high disease activity (DAS28-CRP > 3.2)) and seropositivity (rheumatoid factor and/or anti-cyclic citrullinated peptide positivity at baseline). For the stratified analyses, category 1

(DMARD use on 0–1 study time points) and category 2 (DMARD use on 2 study time points) were combined, due to the low numbers of patients in these groups.

Analyses were performed in IBM SPSS Statistics version 21.

Results

Baseline characteristics

In the 617 RA patients included in the analyses, the mean ($\pm$ standard deviation) age was 57.1 ± 12.6 years, 519 (84.1%) were females, and the mean time since RA diagnosis was 13.8 ± 12.3 years. At study inclusion, the mean DAS28-CRP was 3.92 ± 1.60 . Overall, there were several differences in the baseline characteristics between the 4 groups based on consistency of DMARD use (Table 1). There seemed to be an inverse relationship between the proportion of RF- or anti-CCP positive patients and the inconsistency of DMARD use. Also, the groups significantly differed in age and disease duration, as well as disease activity, pain levels and TSS.

Outcomes at 24 months

The adjusted disease outcomes at 24 months are illustrated in Figure 2. There were no significant differences between the groups, and no evidence of a clear linear trend for any of the outcomes studied. Sensitivity analyses adjusted for previous use of DMARDs and prednisone use at baseline did not yield significantly different results for any outcome (data not shown). The adjusted mean DAS28-CRP was in the low to moderate range (2.72–3.52) in all groups at 24 months, and the mean MHAQ improved slightly from baseline in all groups. There was also a slight increase in TSS in all groups, but these results were only available in half of the patients.

Stratified analyses

No statistically significant influence of the consistency of DMARD use could be found for any of the outcomes within the strata based on disease activity status (see Supplementary Figure 1). There was a statistically significant trend towards lower SF-12 PCS ($p=0.02$) and EQ-5D ($p=0.01$) scores as well as more radiographic progression ($p=0.03$) in seropositive patients who were less consistently treated with DMARDs, but this trend was not seen for the other outcomes (Supplementary Figure 2).

Outcomes at 36 months

As a secondary analysis, we analyzed disease outcome at 36 months (Figure 3). There was evidence of a linear trend for higher disease activity in patients less consistently treated with DMARDs in both unadjusted ($p=0.01$) and adjusted analyses ($p=0.004$). There was no statistical evidence of a linear trend for the change in MHAQ from baseline or EQ-5D at 36 months.

Discussion

Multiple prior studies have found that not all patients in typical rheumatology practice use DMARDs.(7, 8) DMARDs are recommended for all patients with RA, but there are no published data from typical rheumatology practice comparing outcomes for patients who do and do not consistently use DMARDs. Short-term disease outcomes were not significantly worse for inconsistent DMARD users in this clinical RA cohort. However, there was a trend towards worse health related quality of life scores at 24 months for seropositive patients who were inconsistently treated. Disease activity was higher at 36 months in patients who were inconsistent DMARD users during the first 18 months of follow-up, but this trend was not apparent for other outcomes.

Compelling evidence from placebo-controlled clinical trials has taught us that using DMARDs leads to better disease outcomes.(13, 14) However, patients enrolled in randomized controlled trials are a highly selected group; they have often failed methotrexate or other DMARDs prior to enrollment, have moderate to high disease activity as well as other prognostic features that make them prone to disease progression if untreated. In fact, the majority of patients in routine care fail to meet such inclusion criteria.(15) This possible lack of generalizability makes it important to investigate and confirm DMARD effectiveness in observational registries of patients in typical clinical practice.(16) However, most studies from DMARD registries compare one DMARD with another or different combinations of DMARDs. Recently, increasing attention has been focused on tapering and discontinuation of DMARDs in patients in remission, but nothing has been published on how patients fare in typical modern practice if they are inconsistently treated with DMARDs or do not receive DMARD treatment at all.(17)

Our findings suggest that a small and selected group of patients do fairly well over the short-term in the absence of consistent DMARD treatment. While this conclusion may seem contrary to the established body of evidence from clinical trials, we believe that most rheumatologists see some patients who do not use DMARDs consistently and who may also have reasonable short-term outcomes. The reason for this study's non-intuitive finding could not be clearly determined from the data. In a previous analysis, we determined the reasons for DMARD non-use in the BRASS cohort through chart review, and found that the most common reason for not using a DMARD was that the rheumatologist felt the patient to be in remission or have inactive disease (manuscript submitted, available for reviewers as supplementary material). If patients not on DMARDs were in a drug-free remission, this could theoretically explain the similar outcomes in patients not using DMARDs compared to those using DMARDs. However, analyses stratified for disease activity status at baseline did not show worse outcomes for inconsistent DMARD users with moderate or high disease activity compared to patients in remission or low disease activity. There seemed to be an inverse dose-response relationship between RF- or anti-CCP positivity and inconsistent DMARD use in this study. Patients with seropositive RA are known to have more severe disease in terms of disease activity, extra-articular features and worse long-term disease outcomes and could therefore be more prone to be prescribed with DMARDs and to accept taking the drugs when recommended.(18–21) For some disease outcomes, there was evidence of a linear trend for worse outcomes in seropositive patients who used DMARDs

inconsistently, supporting the need for continuous DMARD use in this patient group. Concomitant prednisone use could theoretically have influenced disease outcome in inconsistent DMARD users, as this drug is considered disease-modifying by some rheumatologists. However, adjustment for prednisone use did not change our results, nor did use of DMARDs before entering the study seem to have an impact on the disease outcome in our analyses. One theory suggests that the experienced rheumatologist takes all available information into consideration and selects some patients to go without treatment based on an “educated guess”. It is hard to advocate such an approach without more information about the factors predicting good outcomes despite inconsistent treatment. However, our results imply that quality indicators should allow for a small proportion of RA patients not to be treated with DMARDs.

This study has several limitations, the first being that it is a single-center study. However, a number of experienced rheumatologists were involved in the care of the RA patients in this cohort and this could enhance generalizability of the results. Another limitation is the low number of patients in some of the DMARD use categories, which could increase the risk of not finding a difference between the groups. Also, all the outcomes selected are subject to possible measurement limitations, which could have implications for the interpretation of our results. We believe that the investigation of several different aspects of disease outcome, as well as the investigation of both unadjusted, adjusted and stratified analyses improve the validity of our findings. An important limitation is the short time between assessment of exposure (DMARD use) and outcome in the primary analyses. This could limit the opportunity to detect differences in some of the outcomes. Although not available in all patients, we decided to also include 36-month data as a secondary analysis to shed some light on longer-term outcome. Finally, X-ray data were only available in about half of the patients.

Strengths of this study include the longitudinal assessment of DMARD use and that it is an observational study with no predefined treatment protocol, within a typical rheumatology clinic with typical RA patients. We believe that the originality of the study question sets it apart from other studies on disease outcome in RA.

Conclusion

In this clinical cohort of typical RA patients, some patients seemed to have acceptable short-term disease outcomes in the absence of consistent DMARD treatment. The reasons for this finding could not be clearly determined from the data, and it is hard to advocate such an approach without knowing more about the factors predicting good response in the absence of DMARD treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support: DHS is supported by a mentoring award from the NIH (K24 AR055989). The Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study receives support from UCB, Bristol Myers Squibb, Medimmune and Crescendo Bioscience.

Role of the funding source

DHS is supported by a mentoring award from the NIH (K24 AR055989). The Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study receives support from UCB, Bristol Myers Squibb, Medimmune and Crescendo Bioscience. The study sponsors had no involvement in the study design, collection, analysis and interpretation of data; in the writing of the manuscript; nor in the decision to submit the manuscript for publication.

KY received honoraria and served as an instructor at a musculoskeletal ultrasonography workshop sponsored by Abbott Japan. NAS receives research grant funding from Amgen, AbbVie, BMS and Genentech. TKK has received speaker fees, consultancy fees or grants/pending grants from Abbott/AbbVie, BMS, MSD/Schering-Plough, Pfizer/Wyeth, Roche, UCB, Celltrion, Orion Pharma, Hospira, AstraZeneca and Eli Lilly. MEW reports grants and personal fees from Bristol Myers Squibb, UCB and pharma, grants and Crescendo Bioscience during the conduct of the study.

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Figure 1. Overview of patient selection. DMARD, disease-modifying anti-rheumatic drug.

Figure 2.

Adjusted disease outcomes at 24 months in rheumatoid arthritis (RA) patients according to the consistency of use of disease-modifying anti-rheumatic drugs (DMARDs) in the first 18 months of follow-up. A) Disease Activity Score 28 calculated with C-reactive protein (DAS28-CRP) B) Change in modified Health Assessment Questionnaire (MHAQ) scores from study inclusion C) Short Form Health Survey-12 Physical Component Summary (SF-12 PCS) D) Short Form Health Survey-12 Mental Component Summary (SF-12 MCS) E) EuroQol 5-Dimensional health index (EQ-5D) F) Change in total van der Heijde

modified Sharp Score (TSS) from study inclusion. Estimated marginal means (diamonds) and 95 % confidence intervals (whiskers) are shown. Models were adjusted for age, gender, RA duration, seropositivity, baseline DAS28-CRP, pain level, Charlson index, body mass index, and smoking.

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Figure 3.

Adjusted disease outcomes at 36 months in rheumatoid arthritis (RA) patients according to the consistency of use of disease-modifying anti-rheumatic drugs (DMARDs) in the first 18 months of follow-up. A) Disease Activity Score 28 calculated with C-reactive protein (DAS28-CRP) B) Change in modified Health Assessment Questionnaire (MHAQ) scores from study inclusion C) EuroQol 5-Dimensional health index (EQ-5D) Estimated marginal means (diamonds) and 95 % confidence intervals (whiskers) are shown. Models were adjusted for age, gender, RA duration, seropositivity, baseline DAS28-CRP, pain level, Charlson index, body mass index, and smoking. The numbers of patients with available outcome data for the 36-month study visit were as follows: DAS28-CRP (n=436), MHAQ (n=476), and EQ-5D (n=493).

Table 1

Comparison of baseline characteristics in 617 rheumatoid arthritis (RA) patients according to the consistency of use of disease-modifying anti-rheumatic drugs (DMARDs). RF, rheumatoid factor; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS28-CRP, Disease Activity Score 28 calculated with CRP, MHAQ, Modified Health Assessment Questionnaire; MDHAQ, Multi-Dimensional HAQ; TSS, Total van der Heijde modified Sharp Score.

Baseline characteristics	Missing values	Number of study time points on DMARD				p
		0-1 (n=31)	2 (n=24)	3 (n=77)	4 (n=485)	
Age (years), mean (SD)	0	58.9 (13.2)	63.4 (15.6)	54.4 (14.1)	57.1 (2.1)	0.02
Female gender, n (%)	0	26 (83.9)	18 (75.0)	68 (88.3)	407 (83.9)	0.47
RA duration (years), mean (SD)	0	18.2 (14.5)	13.8 (14.2)	8.2 (10.9)	14.4 (12.0)	<0.0001
RF positive, n (%)	17	10 (33.3)	10 (43.5)	41 (56.9)	330 (69.5)	<0.0001
Anti-CCP positive, n (%)	10	8 (27.6)	11 (47.8)	38 (51.4)	334 (69.4)	<0.0001
Employed, n (%)	21	14 (46.7)	12 (50.0)	41 (53.9)	245 (52.6)	0.91
White, n (%)	3	29 (93.5)	4 (100.0)	70 (90.9)	459 (95.2)	0.27
Ever smokers, n (%)	23	12 (38.7)	11 (45.8)	39 (52.0)	235 (50.6)	0.58
Body mass index, mean (SD)	24	26.44 (4.84)	27.33 (4.83)	26.40 (5.19)	26.47 (5.19)	0.88
Charlson index, median (25 th –75 th percentile)	0	1.0 (1.0–3.0)	1.5 (1.0–2.0)	1.0 (1.0–2.0)	2.0 (1.0–2.0)	0.6
Prednisone use, n (%)	0	11 (35.5)	5 (20.8)	26 (33.8)	135 (27.8)	0.46
Previous DMARD use, n (%)	0	27 (87.1)	13 (54.2)	40 (51.9)	351 (72.4)	<0.001
Swollen joints (0–28), mean (SD)	0	5.9 (7.0)	6.2 (5.6)	9.7 (8.0)	7.4 (7.1)	0.02
Painful joints (0–28), mean (SD)	0	8.5 (8.5)	8.5 (7.2)	10.9 (8.1)	7.8 (7.8)	0.02
CRP (mg/L), median (IQR)	5	4.00 (1.30–17.58)	3.68 (1.52–2.35)	3.78 (1.02–2.77)	2.94 (1.07–8.16)	0.34
Patient global disease activity, mean (SD)	22	25.7 (24.5)	36.7 (25.9)	38.2 (27.8)	28.2 (23.3)	0.003
Physician global disease activity, mean (SD)	3	34.5 (29.8)	28.3 (20.4)	43.1 (24.2)	31.5 (20.7)	<0.001
DAS28-CRP, mean (SD)	27	3.92 (1.57)	4.02 (1.37)	4.52 (1.62)	3.82 (1.59)	0.006
DAS28-CRP states, n (%)	27					0.36
-remission (>2.6)		7 (23.3)	5 (21.7)	10 (13.7)	126 (27.2)	
-low disease activity (2.6–3.2)		4 (13.3)	1 (4.3)	6 (8.2)	53 (11.4)	
-moderate disease activity (>3.2–5.1)		12 (40.0)	11 (47.8)	33 (45.2)	172 (37.1)	
-high disease activity (>5.1)		7 (23.3)	6 (26.1)	24 (32.9)	113 (24.4)	

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Baseline characteristics	Missing values	Number of study time points on DMARD				p
		0–1 (n=31)	2 (n=24)	3 (n=77)	4 (n=485)	
MHAQ, median (25 th –75 th percentile)	22	0.30 (0.00–0.80)	0.40 (0.00–0.75)	0.40 (0.10–0.80)	0.30 (0.00–0.60)	0.17
MDHAQ pain, mean (SD)	39	38.7 (30.8)	38.8 (31.8)	42.7 (28.5)	32.8 (26.1)	0.02
MDHAQ fatigue, mean (SD)	22	39.8 (28.7)	28.1 (33.1)	45.9 (27.3)	39.4 (28.2)	0.06
TSS, median (25 th –75 th percentile)	239	9 (2–123)	9 (2–57)	6 (1–19)	39 (7–90)	<0.001