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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 ($p < 0.01$).
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.

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 [22]. The aim of the present study was to study short-term disease outcomes assessed

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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 5 semi-annual study time points during the first 2 study years recorded ($n = 617$). These subjects were included in BRASS from 2003 to 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 S1).

Assessment of DMARD use

We assessed DMARD use as a dichotomous variable (yes/no) at each of the first 4 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, and tocilizumab. We analyzed the consistency of DMARD use as an ordinal variable divided into 4 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 4 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 were 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

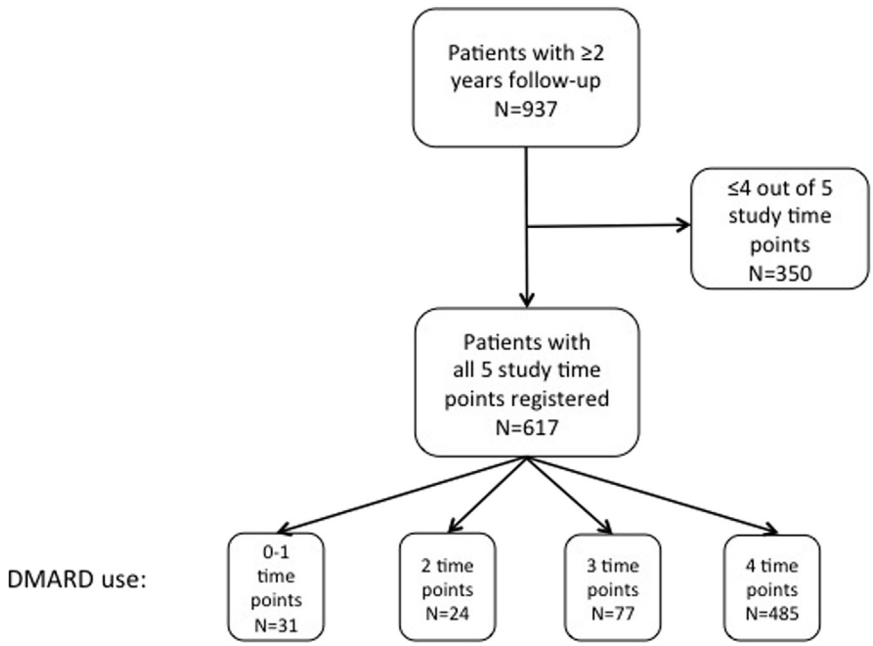

Fig. 1. Overview of patient selection. DMARD, disease-modifying anti-rheumatic drug.