Research Paper

Rheumatoid Arthritis Patients after Initiation of a New Biologic Agent: Trajectories of Disease Activity in a Large Multinational Cohort Study

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A R T I C L E   I N F O

A B S T R A C T

Background: Response to disease modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis (RA) is often heterogeneous. We aimed to identify types of disease activity trajectories following the initiation of a new biologic DMARD (bDMARD).

Methods: Pooled analysis of nine national registries of patients with diagnosis of RA, who initiated Abatacept and had at least two measures of disease activity (DAS28). We used growth mixture models to identify groups of patients with similar courses of treatment response, and examined these patients' characteristics and effectiveness outcomes.

Findings: We identified three types of treatment response trajectories: 'gradual responders' (GR; 3576 patients, 91·7%) had a baseline mean DAS28 of 4·1 and progressive improvement over time; 'rapid responders' (RR; 219 patients, 5·6%) had higher baseline DAS28 and rapid improvement in disease activity; 'inadequate responders' (IR; 103 patients, 2·6%) had high DAS28 at baseline (5·1) and progressive worsening in disease activity. They were similar in baseline characteristics. Drug discontinuation for ineffectiveness was shorter among inadequate responders ($p = 0.03$), and EULAR good or moderate responses at 1 year was much higher among 'rapid responders' ($p < 0.001$).

Interpretation: Clinical information and baseline clinical characteristics do not allow a reliable prediction of which trajectory the patients will follow after bDMARD initiation.

1. Introduction

The effect of disease modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis (RA) on disease activity is generally presented using population means (Combe et al., 2015; Gabay et al., 2015; Littlejohn et al., 2015). The use of biologic DMARDs (bDMARD) has revolutionized the therapy of severe RA (Sanmarti et al., 2015). However,

the response to treatment is heterogeneous, both to cDMARDs (Aga et al., 2015), and to the various bDMARD agents (Kiely, 2015). As a major aim in the new era of precision medicine is to make anti-rheumatic therapy more personalized, identifying and predicting distinct treatment responses trajectories to DMARDs has major implications for clinical practice. Studies (range n: 568–2752) focused on identifying types of patients with similar evolutions in disease activity (Siemons et al., 2014), physical activity (Demmelmaier et al., 2016), functional limitation (Norton et al., 2013), or psychological distress (Norton et al., 2011) and found subsets of patients with less favorable trajectories. The identification of predictors of response type trajectories could

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enable an early identification of patients needing a distinct treatment strategy.

In RA, disease activity measures are the main clinical outcome used by practitioners to appraise the evolution of RA (Finckh et al., 2007), to modify and adapt treatment, and to determine if patients have reached a state of low disease activity (Inoue et al., 2007) or remission (Mohammed et al., 2015). The Disease Activity Score based on 28 joints (DAS28) is a well-established instrument to assess disease activity (Prevoo et al., 1995).

A study of early RA patients (Siemons et al., 2014) ($n = 568$) found three types of trajectories during the first year after treatment initiation: the most frequent type (82·6% of patients) was a good responder group, the second type (14·1%) comprised patients with a slower response to treatment, and the third one was composed of a very small group (3·3%) of patients who showed no improvement after 1 year. However, the trajectories of disease activity in patients initiating a specific bDMARD or in patients with established disease have not been studied.

The aim of this study was to identify different types of trajectories in RA disease activity following the initiation of a new bDMARD and to examine the determinants of each responder type in a large multi-national observational cohort.

2. Materials and Methods

2.1. Study Design

This is a pooled analysis of data from nine national registries of RA patients: ARTIS (Sweden), ATTRA (Czech Republic), DANBIO (Denmark), GISEA (Italy), NOR-DMARD (Norway), ORA (France), REUMA.PT (Portugal), RHUMADATA (Canada), and SCQM (Switzerland), collected from 2006 to 2015. Each of the registries was approved by the local Ethics Committee and national guidelines for collection of informed consent form before enrolment in the study in accordance with the Declaration of Helsinki were followed. A more detailed description of the registries is available elsewhere (Curtis et al., 2010; Finckh et al., 2015). Inclusion criteria for this analysis were a diagnosis of RA, initiation of ABA treatment and at least two assessments of DAS28. The primary outcome to model response trajectories was the disease activity score based on 28 joints (DAS28) (Prevoo et al., 1995). Most registries used DAS28-ESR; when not available, we used the DAS28-CRP instead. All patients had either complete data for the DAS28-ESR or complete data for the DAS28-CRP. Almost all registries had some patients with missing DAS28-ESR data. The Italian registry, GISEA, was the only registry with only DAS28-CRP data.

In addition to the DAS28, we extracted demographic variables, BMI, smoking status, comorbidities, seropositivity according to rheumatoid factor or anti-citrullinated protein antibodies (ACPAs), disease duration, and disability as measured by the health assessment questionnaire (HAQ). We also extracted information about treatment, including number of past biologics treatment, conventional DMARD (cDMARD) and glucocorticosteroid therapy. We further computed ABA drug retention, which integrates both drug effectiveness and tolerance, ABA drug retention until stopping for ineffectiveness, reason for ABA discontinuation, EULAR good or moderate response rate at 6 months, one year, and two years (van Riel, 2014) corrected for drug discontinuation (Lundex) (Kristensen et al., 2006). ABA drug retention was defined as the time between drug initiation and last administration, plus one dispensation interval. Patients lost to follow-up were censored at the last registered visit.

2.2. Statistical Analysis

We used growth mixture models (GMM) to identify groups of patients with similar courses of treatment response, modeling time since beginning of treatment as polynomials with a linear, quadratic and cubic terms and derived empirically based trajectory subgroups. GMM

are used to model unobserved types of evolution of disease activity over time. GMM estimate groups of patients in which the trajectories of DAS28 are similar within each trajectory type and different from the trajectories in the other types (Reineke and Seddig, 2011). To determine the optimal number of types (also called latent classes in growth mixture models terminology) of disease activity trajectories, we used two information criteria (Akaike's information criteria, and Bayesian information criteria), with lower value indicating a better fit of the model to the data.

We then examined the association of these groups with demographic-, disease-, and treatment-related covariates, as well as treatment effectiveness. We analyzed patients and disease characteristics at treatment initiation using standard descriptive statistics and Fisher exact test for categorical variables or Wilcoxon rank sum test for continuous variables. We ran a sensitivity analysis using probability-weighted regression with weights based on posterior probability of classification in each trajectory group. Data are presented as means (SD) or medians (interquartile ranges) depending on their distribution. ABA drug retention was analyzed by the Kaplan Meier method. Given the inherent differences between registries (Finckh et al., 2015), we tested for effect modification by registry using an interaction term between types of trajectories and national registry using a Cox proportional hazard model. Analyses were performed using R v3.2.4 (R foundation, Vienna, Austria) and the lcmm package (Proust-Lima et al., 2015).

3. Results

A total of 3898 patients initiated ABA with a mean number of 3.94 DAS28 assessments. Follow-up time ranged from 1 month to 11.7 years. Trajectory analysis of the entire sample identified three types of disease activity trajectories with low misclassification (for goodness of fit indices, see Appendix 1). The largest group (3576 patients, 91·7%) can be labeled as the 'gradual responders' (GR) type, with a mean DAS28 at baseline of 4·1 and a progressive improvement over time. Fig. 1 presents the observed means for patients based on assigned types of trajectories. Estimated mean trajectories were quite similar (data not shown). The second group (219 patients, 5·6%) can be described as the 'rapid responders' (RR) type, with higher DAS28 values at baseline, and a rapid improvement in disease activity. The third group (103 patients, 2·6%) can be identified as 'inadequate responders' (IR) type, with higher DAS28 values at baseline, a short improvement during the first 6 months, followed by a return to initial disease activity level (for exact estimates of the DAS28 trajectories for these three types of patients, see Appendix 2).

The three types were similar in age, sex, BMI distributions, disease duration, and comorbidities (Table 1). 'Gradual responders' group had
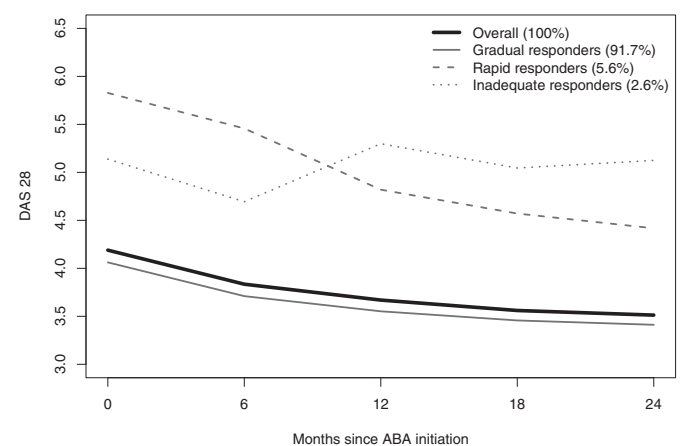

Fig. 1. Class-specific DAS28 trajectories based on observed means. Time horizon was cut at 2 years to focus on the period with most available data.