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Abstract
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Reference

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


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Abstract

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Keywords: Abatacept Rheumatoid arthritis Disease activity DAS28 Longitudinal data Drug retention Response rate

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.

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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 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
by practitioners to tailor the treatment to the patient's needs. This is
particularly important in the management of RA, where disease
activity measures are the main clinical outcome used to
evaluate treatment effectiveness. We analyzed patients and disease
characteristics using standard descriptive statistics and Fish-
ner's 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 to account for the inherent differences between registries.

2.2. Statistical Analysis
We used growth mixture models (GMM) to identify groups of pa-
tients with similar courses of treatment response, modeling time since
ABA initiation and death, and determined trajectories using growth
centric and growth-variant based trajectories. GMM was used to
identify trajectory subgroups within the data. We then examined the
association of these groups with demographic, treatment-related
covariates, and ABA drug retention. We used multivariate logistic
regression models to determine the independent factors associated with
different response types. We used survival analysis to estimate the
influence of different trajectories on treatment effectiveness. We also
analyzed patients and disease characteristics using Fisher's 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 to
correct for the inherent differences between registries.

2.3. Results
A total of 3,988 patients initiated ABA with a mean number of
3.4 DAS28 assessments per patient. Follow-up was available from 1 month
to 11.7 years. Trajectory analysis of the entire sample identified three
types of disease activity trajectories with low misclassification rates.

1. Gradual responders (91.7%) with similar values at baseline, a gradual
improvement during the first 6 months, followed by a return to initial
disease activity levels. These patients showed a mean DAS28 at baseline of
3.4.

2. Inadequate responders (2.6%) with the worst disease activity trajec-
tories. These patients showed a mean DAS28 at baseline of 5.0.

3. Rapid responders (5.6%) with the best disease activity trajectories. These
patients showed a mean DAS28 at baseline of 3.5.

In addition, we calculated ABA drug retention, defined as the time
between ABA initiation and treatment discontinuation, and characterized
the inherent differences between registries.

3. Discussion
The aim of this study was to identify different types of trajectories in
patients with RA and to determine the factors associated with
different response types. We used a pooled analysis of data from nine
national registries to analyze patients and disease characteristics.
We found three distinct types of response trajectories: gradual,
inadequate, and rapid responders. These trajectories were associated
with different demographic, treatment-related, and ABA drug reten-
tion characteristics. We used multivariate logistic regression models
to determine the independent factors associated with different
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of group membership since the variability of DAS28 at baseline was large, and there was a large overlap of DAS28 values between groups (Fig. 2). Groups also differed in the components of the DAS28 score (i.e., tender joints, swollen joints, ESR or CRP, and patient global assessment). The sensitivity analysis using probability-weighted regression accounting for uncertainty in classification of patients into three groups found similar results. In particular, significant and non-significant results remained the same.

ABA overall drug retention time was similar across all groups (p = 0·11). However, as could be expected, ABA drug retention until discontinuation for inefficacy was much shorter among ‘inadequate responders’ (median time in years: GR: 4·7, RR: 5·3, IR: 2·0, p = 0·03). The proportion of patients with EULAR good or moderate response rate (Lundex corrected) at 1 year was higher among ‘rapid responders’ (GR: 22·1%, RR: 39·2%, IR: 6·4%).

4. Discussion

Safety and efficacy of ABA in early and established RA has been demonstrated in several studies, using population means or – one could say – a single trajectory (Westhovens et al., 2009, 2014; Kremer et al., 2014; Schiif et al., 2011, 2014). The present study focused on trajectory analyses of disease activity following the initiation of ABA, using growth mixture modeling to identify subgroups with similar response patterns. This study, which is a collaboration of nine national registries, is the first to analyze trajectories of disease activity in patients with established RA. Analysis of the entire sample identified three types of disease activity trajectories: a larger group of ‘gradual responders’ (91·7%), who improved gradually over time; a group of ‘rapid responders’ (5·6%), who started with a high DAS28 at baseline and improved quickly; and a smaller group of ‘inadequate responders’ (2·6%), who had a stable and relatively high disease activity over the first two years. Overall, socio-demographic and clinical characteristics at baseline were not strongly associated with future trajectory of disease activity after ABA treatment initiation. The importance of identifying these trajectories is reflected in the close association between clinical effectiveness and type of disease activity trajectory: The ‘inadequate responders’ discontinued ABA due to inefficacy much earlier compared to gradual and rapid responders. Furthermore, EULAR moderate or good response at 1 year was reached by almost none of the “inadequate responders”, compared to more than a third of the ‘rapid responders’.

Similarly to studies that examined disease activity trajectories in early RA (Barnabe et al., 2015; Siemons et al., 2014), we identified a
large group of gradual responders and a small group of rapid re-
sponders. However, the present analysis also detected one group that
displayed no improvement of their disease activity over time. The differ-
ences in findings could be due to study population or to the smaller
sample size of previous studies. Whereas other studies focused on
early RA patients on their first DMARD treatment, our analysis included
more treatment resistant patients, often initiating a second or third line
treatment, who often had long disease duration. In this difficult to treat
patient group, it is not surprising to find inadequate responders, a sub-
group probably composed of both primary non-responders and patients
with secondary failures to this biologic agent. It is also possible that the
smaller sample size and limited follow-up of other studies did not allow
the detection of small trajectory subgroups.

In general, the patients in the three trajectory types could not be
separated by baseline characteristics, except for higher disease activity
and functional disability at baseline among rapid responders. This find-
ing is in line with previous studies of patients with established RA show-
ing that high DAS28 (Narvaez et al., 2016) and high HAQ score at
baseline are associated with good response to biDMARD at 3 months
(Kristensen et al., 2008). In contrast, studies of patients with early RA
(i.e., with less chronicity) described a group of rapid responders with
a lower DAS28 at baseline, and found that patients’ trajectory types dif-
ered in socio-demographic characteristics (e.g., sex, race, education)
(Barnabe et al., 2015). The discrepancies in findings may be explained by
differences in study population.

Much research is currently directed at identifying biomarkers to pre-
dict response and move towards personalized medicine; however no
biomarkers have currently reached a level of discrimination to allow
their use in clinical practice. Seropositivity for rheumatoid factor or
anti-CCP antibodies has been consistently associated with a better effec-
tiveness of ABA (Gottenberg et al., 2016), but were not associated with a
specific disease activity trajectory in this analysis. Clinical effectiveness
outcomes strongly differed between trajectories’ types, in line with pre-
vious studies of disease activity or disability trajectories over time, in
which type of trajectories was associated with mortality (Norton et al.,
2013), remission (Siemons et al., 2014), or radiographic progression
(Barnabe et al., 2015).

A limitation of this study is the observational nature of the data with
the potential bias generated from attrition. In addition, unmeasured
baseline characteristics, such as socioeconomic factors, may be associat-
ed with disease trajectories (Finckh et al., 2015). Another limitation is
that DAS28 is a composite score, and the trajectories found in this
study may not correspond to trajectories of the underlying scores. The
strengths of this study include the large number of patients treated in
a real-life setting, resulting from an international collaboration that
allowed a pooled analysis of nine RA registries.

In conclusion, after ABA treatment initiation, different types of re-
sponders to treatment were identified: gradual, rapid and inadequate
response groups, with differing drug discontinuation and response rates.
However, clinical information such as seropositivity or disease du-
ratio, and baseline characteristics, do not allow to predict reliably the
trajectory a patient will follow after ABA initiation. Other predictors of
responder types should be explored to support clinical decision making.

Funding

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research grant from Bristol Myers-Squibb. Funders had no role in study
design, data collection, data analysis, interpretation and writing.

Author Contribution

DSC did the data analysis, all authors contributed to data interpreta-
tion, provided comments on the manuscript writing, and approved the
final manuscript.

Appendix 1. Goodness-of-fit statistics for growth mixture modeling

<table>
<thead>
<tr>
<th>Model</th>
<th>AIC</th>
<th>BIC</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
<th>Type 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1. 1 class, random intercept</td>
<td>46,624.4</td>
<td>46,664.1</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M2. 1 class, random slope</td>
<td>46,424.0</td>
<td>46,467.8</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M3. 2 classes, random slope</td>
<td>46,269.5</td>
<td>46,344.7</td>
<td>80.2</td>
<td>19.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M4. 3 classes, random slope</td>
<td>46,163.0</td>
<td>46,269.6</td>
<td>91.7</td>
<td>5.6</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>M5. 4 classes, random slope</td>
<td>52,549.8</td>
<td>52,713.0</td>
<td>82.8</td>
<td>11.1</td>
<td>4.5</td>
<td>1.6</td>
</tr>
</tbody>
</table>

For M4, Type 1 (Gradual responders), Type 2 (rapid responders), Type 3 (inadequate responders).
Posterior classification was 0.77% in Type 1, 0.81% in Type 2, and 0.94% in Type 3.

Appendix 2. Estimates of best-fitting growth mixture model

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>4.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time</td>
<td>−0.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time²</td>
<td>0.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time³</td>
<td>−0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intercept</td>
<td>5.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time</td>
<td>−2.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time²</td>
<td>0.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time³</td>
<td>−0.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intercept</td>
<td>5.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time</td>
<td>3.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time²</td>
<td>−1.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time³</td>
<td>0.17</td>
<td>&lt;0.001</td>
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</tbody>
</table>

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