Does disease activity at the start of biologic therapy influence health care costs in patients with RA?

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Abstract

Objective. To investigate whether disease activity at baseline influences health care costs in patients with RA initiating biologic treatment.

Methods. In the Swedish Biologics Register, we identified patients with RA with baseline 28-joint DAS (DAS28) recorded and starting their first biologic in 2007 [n = 1638 with moderate disease activity (DAS28 3.2–5.1) and n = 1870 with high disease activity (DAS28 > 5.1)]. Data on inpatient and outpatient care and prescription drugs were retrieved from nationwide registers. Mean cost differences were estimated adjusted for age, sex and costs the year before treatment start.

Results. Patients with high (vs moderate) disease activity were older (60 vs 56 years; P < 0.001), but did not differ in sex distribution (75 vs 74% women; P = 0.99) or disease duration (10 vs 10 years; P = 0.13). The year after initiation of biologics, patients with high (vs moderate) baseline disease activity accumulated 9% higher health care costs, but the difference was not statistically significant after adjustment [€19,333 vs €17,810; adjusted difference €870 (95% CI −2, 1742)]. In the subgroup of patients with up to 4 years of follow-up data, decreasing costs were observed over the follow-up time, but no difference was found between patients with high compared with moderate baseline disease activity [€13,704 vs €12,349; adjusted difference 878 (95% CI −364, 2120)]. Irrespective of baseline disease activity, health care costs were approximately three times higher the year after initiation of biologics than the year before due to increased drug costs.

Conclusion. Over up to 4 years of follow-up, no difference in health care costs was found after adjustment in patients starting their first biologic treatment with high vs moderate baseline disease activity.

Key words: TNF inhibitors, DMARD, rheumatoid arthritis, disease activity, health care costs.

Introduction

When TNF inhibitors were introduced, their use was typically restricted to RA patients with high disease activity [28-joint DAS (DAS28) >5.1]. Similar restrictions remain in several countries [1]. In many others, and in keeping with the treat-to-target paradigm with remission or low disease activity as treatment goal [2], anti-TNF therapy is increasingly started in patients with moderate disease activity (DAS28 3.2–5.1). For instance, the average DAS28 at the start of biologic therapies decreased from 5.9 to 5.3 in Denmark between 2000 and 2005 [3], and from 4.5 to 3.4 in Germany from 1997 to 2007 [4]. In Sweden, half of all first-time initiators of TNF inhibitors in 2011 had a DAS28 <5.2, the EULAR cut-off for high disease activity [5].
Since most trial data on the efficacy of TNF inhibitors come from patients with high baseline disease activity [6], little is known about TNF inhibitor use in patients with moderate disease activity. In an observational cohort study from the UK, patients starting TNF inhibitor therapy with moderate disease activity had similar 1 year reduction in HAQ to patients starting with high disease activity [7]. The authors concluded that this suggests substantial benefits of TNF inhibitors also in patients with moderate disease activity. They added the caveat that the included patients with moderate disease activity received TNF inhibitors despite guidelines advising against this in the UK, and therefore may differ from patients in countries without such restrictions. In the recent PRESERVE trial [8], 72% of patients starting etanercept with moderate disease activity reached remission during the run-in phase, also suggesting clinical efficacy in this patient segment. However, an economic evaluation of treatment of this patient group requires an understanding of pre- and post-treatment cost distribution and to what extent they are influenced by disease activity. The aim of this study was therefore to investigate real-world health care costs in RA patients with moderate or high disease activity when starting their first TNF inhibitor.

Methods

In 2011, Sweden had a population of 9.5 million (http://www.scb.se). The nationwide prevalence of RA has been estimated as 0.6–0.8% [9]. During the period of our study the Swedish health care system was tax funded and offered universal access, while prescription drugs were provided free of charge above a threshold of SEK1800 annually (~€200/$250). RA patients were typically treated by rheumatologists rather than general practitioners, with the vast majority of rheumatologists working at hospitals rather than private clinics.

Data sources and patients

The Swedish Rheumatology Quality Register contains data primarily on early arthritis and biologic-treated patients, with the latter patients monitored in the module Anti-Rheumatic Treatment in Sweden (ARTIS) [10]. The registers include date of diagnosis, patient characteristics and treatment, and ARTIS covers ~87–95% of all RA patients treated with biologics, depending on the definition of RA [11, 12].

From these data sources we identified two cohorts of adult RA patients starting anti-rheumatic therapies between 1 January 2007 and 31 December 2011: patients starting their first ever biologic (cohort I) or a non-biologic combination DMARD (combo-DMARD; cohort II). The combo-DMARD cohort was included as a reference group rather than for direct comparison. Ethical approval was granted by the regional ethics committee at Karolinska Institutet, Stockholm, Sweden.

By using the unique personal identity number assigned to each Swedish resident, the study population was linked to nationwide health registers to retrieve inpatient care, non-primary outpatient care and drug cost data (supplementary data section on description of register sources available at Rheumatology Online).

Exposure

The main exposure was disease activity at treatment start, with patients categorized into moderate (DAS28 3.2–5.1) or high (DAS28 >5.1) disease activity as registered by the treating rheumatologist. Patients starting biologics with low disease activity (DAS28 <3.2) were excluded.

Outcome and follow-up

The main outcome was annual health care costs (€2012) for hospital days, non-primary outpatient care visits and prescription drugs 1 year from the day of their first biologic (or combo-DMARD) treatment start. The hospital care components were costed using an approximation of SEK10 000 (€1111) per hospital day and SEK3000 (€333) per non-primary outpatient care visit. Total prescription drug costs, cost for non-infusion biologics, DMARDs, glucocorticoids and NSAIDs were collected from the Prescribed Drug Register. The cost for infusion biologics given in the hospital setting was calculated based on treatment data from ARTIS. For comparison, costs were calculated for the 1 year before and annually up to 4 years after the treatment start date.

Statistics

Statistical analyses were performed using SAS version 9.3 (SAS, Cary, NC, USA) and Statata version 11 (StatCorp, College Station, TX, USA). Mean annual cost was used as the main summary measure and the mean cost differences with 95% CI were estimated using non-parametric bootstrapping [13], adjusting for age, sex and costs the previous year.

Results

A total of 3697 patients with RA starting their first biologic were identified. Two hundred and nineteen (6%) had low, 1638 (44%) moderate and 1870 (51%) high disease activity (supplementary Fig. S1, available at Rheumatology Online). The reference cohort of combo-DMARD initiators included 927 patients, of whom 243 (26%) had low, 482 (52%) moderate and 202 (22%) high disease activity.

Patient characteristics

Among biologics initiators, patients with high disease activity were older than those with moderate activity (60 vs 56 years; P = 0.02). Patients starting combo-DMARD therapy did not differ regarding age (59 vs 56 years; P = 0.05) or sex (76% vs 72% women; P = 0.30), but had shorter disease duration (1.8 vs 2.3 years; P = 0.02).

Costs the year before treatment start

Biologics cohort

The year before treatment start there was no statistically significant difference in total health care costs after age
and sex adjustment in patients with high vs moderate disease activity, although patients with high disease activity had greater inpatient care costs (€3370 vs €2250; adjusted difference €821 (95% CI 209, 1433); Fig. 1). No cost differences were observed for non-primary outpatient care or drugs the year before treatment start.

**Combo-DMARD cohort**

Similar to the biologics cohort, there was no difference in either total health care, non-primary outpatient care or drug costs the year before treatment start, but higher inpatient care costs were observed for patients with high compared with moderate disease activity (€2404 vs €1035; adjusted difference €1251 (95% CI 11, 2491)).

**Costs during the year after treatment start**

**Biologics cohort**

The year after biologics initiation, patients with high (vs moderate) baseline disease activity accumulated 9% higher health care costs, but the difference was not statistically significant after adjustment (€19 933 vs €17 810; adjusted difference €870 (95% CI -2, 1742); supplementary Table S1, available at Rheumatology Online).

Comparing the year before with the year after treatment start, non-primary outpatient costs and drug costs increased by ~€500 and €12 000, respectively, for both groups, while the increases in inpatient care did not reach statistical significance (supplementary Table S2, available at Rheumatology Online). Biologic treatment was the largest cost component in both the high and moderate disease activity groups (62% and 67%, respectively).

**Combo-DMARD**

The year after treatment start, no between-group differences were found for any of the cost components (Table 1). Comparing the year before with the year after treatment start, drug and non-primary outpatient costs increased for both disease activity groups (supplementary Table S2, available at Rheumatology Online).

**Costs up to 4 years after treatment start**

Total health care costs decreased over time in both groups, driven by decreasing biologic drug cost (Fig. 1). As in the analysis of the first year after treatment start, no cost differences were observed after adjustment between patients with high vs moderate disease activity at treatment start after 2, 3 or 4 years (supplementary Table S3, available at Rheumatology Online).

**Discussion**

In this study and after adjustment for health care costs the year before treatment start, disease activity at biologic treatment start was not statistically significantly associated with health care costs in subsequent years. Irrespective of baseline disease activity, health care costs were approximately three times, or €12 000, higher the year after biologics initiation than the year before, with the biologic drug cost constituting 62–67% of the total cost.

To the best of our knowledge, and despite the secular trends in initiating biologics in more patients with moderate disease activity [3, 4, 5, 7], no previous study has compared nationwide real-world economic outcomes in patients starting biologic treatment stratified by disease activity.

**Fig. 1** Unadjusted costs during the year before and up to 4 years after biologic treatment start by baseline disease activity

[Graph showing costs over time]
### TABLE 1

Annual costs\(^a\) in Swedish patients with RA by baseline disease activity at biologic or combo-DMARD treatment start (1 year after treatment start)

<table>
<thead>
<tr>
<th>Resource use</th>
<th>Cost</th>
<th>Resource use</th>
<th>Cost</th>
<th>Crude difference, high vs moderate (95% CI)</th>
<th>Adjusted difference(^b), high vs moderate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate (3.2 ≤ DAS28 ≤ 5.1)</strong></td>
<td></td>
<td><strong>High (DAS28 &gt; 5.1)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>((n_{bio} = 1638, n_{combo} = 482))</td>
<td></td>
<td>((n_{bio} = 1870, n_{combo} = 202))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Biologics initiators</strong></td>
<td></td>
<td><strong>Combo-DMARD initiators</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health care use, mean (SD)</td>
<td></td>
<td>Health care use, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-primary outpatient care visits</td>
<td>6.7 (4.8)</td>
<td>€2223 (1606)</td>
<td>7.0 (5.1)</td>
<td>€2332 (1693)</td>
<td>€109 (--7, 225)</td>
</tr>
<tr>
<td>Inpatient care(^c)</td>
<td>2.2 (10.2)</td>
<td>€2486 (11283)</td>
<td>3.3 (10.6)</td>
<td>€3617 (11817)</td>
<td>€1131 (350, 1911)</td>
</tr>
<tr>
<td>Drug use (with any dispensing), n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biologics(^d)</td>
<td>1583 (97)</td>
<td>€11908 (4995)</td>
<td>1801 (97)</td>
<td>€11950 (5600)</td>
<td>€41 (--314, 397)</td>
</tr>
<tr>
<td>DMARDs</td>
<td>1234 (76)</td>
<td>€73 (124)</td>
<td>1377 (75)</td>
<td>€82 (220)</td>
<td>69 (--3, 21)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>961 (53)</td>
<td>€25 (31)</td>
<td>1172 (63)</td>
<td>€28 (34)</td>
<td>63 (0.7, 5)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>936 (53)</td>
<td>€48 (80)</td>
<td>1114 (60)</td>
<td>€50 (82)</td>
<td>62 (--18, 8)</td>
</tr>
<tr>
<td>Total drug costs</td>
<td>€13 100 (7341)</td>
<td>€13 383 (6037)</td>
<td>€283 (--168, 734)</td>
<td>€362 (--12, 739)</td>
<td></td>
</tr>
<tr>
<td>Total health care costs</td>
<td>€17 810 (13268)</td>
<td>€19 333 (13164)</td>
<td>€1523 (623, 2423)</td>
<td>€870 (--2, 1742)</td>
<td></td>
</tr>
<tr>
<td><strong>Drug use, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biologics</td>
<td>49 (10)</td>
<td>€874 (2932)</td>
<td>19 (10)</td>
<td>€759 (2555)</td>
<td>€--114 (--568, 340)</td>
</tr>
<tr>
<td>DMARDs</td>
<td>114 (24)</td>
<td>€52 (167)</td>
<td>48 (24)</td>
<td>€47 (106)</td>
<td>€--4 (--29, 17)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>76 (17)</td>
<td>€6 (17)</td>
<td>41 (21)</td>
<td>€10 (24)</td>
<td>€4 (0.5, 8)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>83 (17)</td>
<td>€15 (50)</td>
<td>27 (14)</td>
<td>€11 (41)</td>
<td>€--4 (--11, 3)</td>
</tr>
<tr>
<td>Total drug costs, mean (SD)</td>
<td>€1971 (18509)</td>
<td>€1038 (2909)</td>
<td>€--333 (--2649, 782)</td>
<td>€--54 (--546, 437)</td>
<td></td>
</tr>
<tr>
<td>Total health care costs, mean (SD)</td>
<td>€5517 (19780)</td>
<td>€6324 (18218)</td>
<td>€807 (--2264, 3879)</td>
<td>€344 (--2291, 2979)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Costs over 365 days from the day of treatment initiation. \(^b\)Adjusted for age, sex, and health care costs during the year prior treatment start; 95% CI estimated by non-parametric bootstrapping. \(^c\)Infusions are generally given in outpatient care, but 6% of inpatient visits were registered as infusion visits in the moderate disease activity group compared with 8% in the high group. \(^d\)Three per cent had a registered biologic treatment start but no drug dispensing in the Prescribed Drug Register. \(n_{bio}\); number of patients on biologic therapy; \(n_{combo}\); number of patients on combination DMARD therapy.

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Health care costs by disease activity in RA

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activity. Previous studies have reported that starting TNF inhibitors with lower DAS28 is associated with a greater likelihood of reaching remission [14–17]. Hyrich et al. [7] highlighted that this is intuitive, as starting from a lower DAS28 increases the chances of reaching a very low score. In terms of health care costs, we found that patients with both high and moderate baseline disease activity accumulated substantially higher costs after biologics initiation. No between-group differences were detected after adjustment for costs during the previous year. As expected, the highest cost was observed during the year of biologic treatment start, and declined thereafter each year of follow-up, but remained considerably higher than before biologic initiation. We did not have data beyond 4 years, but as there was no statistically significant difference between years 3 and 4, one could speculate that the health care costs were stabilizing after 4 years.

Strengths of this study include access to prospectively recorded, routinely collected nationwide registry data on biologic treatment, inpatient and non-primary outpatient care and prescription drugs. We were able to investigate real-world outcomes for a comparatively large number of patients initiating biologic therapy with moderate disease activity, as Sweden has no DAS28-related restrictions for biologics.

The observational design did not permit assessment of whether it is cost effective to treat patients with moderate disease activity with biologics compared with alternative treatment. We could only observe the level of real-world costs before and after treatment initiation and use patients starting non-biologic combo-DMARD therapy for contextualization. Nor did we have access to all health care costs. Costs for primary care, physiotherapy and rehabilitation were not available.

In conclusion, disease activity at biologic treatment start did not influence yearly health care cost development during up to 4 years of follow-up. Irrespective of baseline disease activity, health care costs were approximately three times higher the year after biologics initiation than the year before due to increased drug costs.

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Supplementary data

Supplementary data are available at Rheumatology Online.

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