Cost of illness in rheumatoid arthritis in Germany in 1997–98 and 2002: cost drivers and cost savings

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Abstract

Objective. Comparison of overall RA-related costs and of relative contribution of single-cost domains before and after the introduction of TNF-blocking agents in Germany.

Methods. Two cohorts of RA outpatients (ACR ’87 criteria) with long-standing disease are assessed in terms of disease-related costs and cost composition (n = 106 patients in 1997–98 and n = 180 patients in 2002 with similar patient characteristics). Full-cost analyses are performed including direct disease-related costs (medical and non-medical) and productivity costs as collected by patient questionnaires. Absolute costs (€/patient/year) are compared and the impact of single-cost domains on overall costing in RA is estimated (relative proportions of cost components within samples).

Results. Overall costs are comparable (1997–98: €4280; 2002: €3830; not significant). Differences can be observed in medication (1997–98: €550; 2002: €1580; P < 0.001) and hospitalization costs (1997–98: €1240; 2002: €500; P < 0.001). Productivity costs are significantly lower (€1480 vs €850; P < 0.05) in 2002. The impact of medication costs is outstanding in the 2002 sample (42 vs 12%), the proportion of hospitalization costs is substantially lower (29 vs 13%). Costs for DMARDs in 2002 are mostly driven by TNF blockers (37%). The number of DMARDs per patient is higher in 2002 as are costs for osteoporosis medication and gastroprotective treatment.

Conclusion. Although overall costs before and after the introduction of TNF blockers are comparable, the decrease in hospitalization and productivity costs is promising in terms of future long-term cost savings. The development of these aspects and of the increasing medication costs will have to be evaluated with longer time frames.

Key words: Cost-of-illness, Rheumatoid arthritis, Disease-modifying drugs, Tumour necrosis factor inhibitors, Cost savings.
In a nationwide sample of households, Yelin et al. [3] recently reported details on an increase in overall medical care expenditure attributable to arthritis and other rheumatic conditions in the USA. However, data on cost development specified for different cost domains are still sparse. This topic is of interest as it might be the case that higher costs in the drug sector are offset at least partially by savings in other sectors of health care. Hence, the present investigation aims at a comparison of overall disease-related costs and of cost composition before and after the introduction of TNF blockers in Germany, in order to evaluate the potential economic influence on cost development.

Patients and methods

Patients and study design

Two cohorts of RA outpatients (ACR ‘87 criteria) with longstanding disease were assessed in terms of disease-related costs and cost composition. The first sample was recruited in 1997–98 as part of a multi-centre clinical trial on RA, and its predictors also, comprising a piggy-back economic evaluation [4, 5]. The data from the second sample were collected in 2002 during a full-cost analysis linked to a clinical trial assessing quality management in RA [6, 7]. Mean disease duration was 8 years at assessment in both samples. Only patients of working age, who were gainfully employed at the outset of the respective studies, are included in this analysis. Accordingly, a sample of \( n = 106 \) patients (55 years, 61% female) with costing data captured in 1997–98 are compared with a second sample of \( n = 180 \) patients (53 years, 69% female) with costing data assessed in 2002 (Table 1).

Economic evaluation

Full-cost analyses are carried out from the societal perspective including direct disease-related costs (medical and non-medical) and productivity costs. The clinical and economic data are captured by patient questionnaires. For the economic data, the health economic questionnaire for RA patients (HEQ-RA) is employed covering all cost domains according to the current recommendations (OMERACT) [8, 9].

Costs in absolute terms of all components assessed as well as relative proportions of cost components within the samples are compared employing a discount rate of 5% following current German health economic guidelines [10]. A special focus is given on differences of medication costs and the composition of RA-related medications comparing the pre- and post-era after introduction of TNF-blocking agents.

Direct cost components

The major direct cost components that were found to be reported adequately by patient questionnaires in a previous validation study are considered [11]: costs due to RA-related (i) medication; (ii) inpatient treatment; (iii) outpatient physician visits (including diagnostic and therapeutic outpatient measures); and (iv) non-physician service utilization. Minor cost components are displayed summarized as other direct costs. For the monetary valuation, the following data sources are employed: average market prices for all drugs, German physician fee schedules [the Einheitlicher Bewertungsmaßstab (EBM) as a uniform value scale comprising all for remuneration-approved medical services] and official price tariffs for the Statutory Health Insurance [12].

Productivity cost components

Indirect costs are estimated according to the human capital approach taking a friction period into account. Accordingly, productivity losses are counted only within a limited period of time owing to the fact that the patient’s productivity will be replaced assuming that no economy achieves full employment [13, 14]. Productivity losses due to RA-related sick leave, work disability and other loss of work are included. The monetary valuation of productivity losses is based on the German guidelines for health economic evaluation [10] employing population data [15].

Ethical approval and data protection

Prior to enrolment, the patients were informed about the aims and the content of the investigations by specific patient information. Informed consent was given by all patients for their participation and the anonymized data storage and processing by computer data bases. Both studies were approved by the local ethics committee (ethics committee of Hannover Medical School).

Table 1 Comparison of patient characteristics of the samples evaluated in 1997–98 (\( n = 106 \)) and 2002 (\( n = 180 \))

<table>
<thead>
<tr>
<th>Variable</th>
<th>( n = 106 ) (1997)</th>
<th>( n = 180 ) (2002)</th>
<th>( P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (s.d.), years</td>
<td>55 (9)</td>
<td>53 (9)</td>
<td>0.7</td>
</tr>
<tr>
<td>Gender, female, %</td>
<td>61</td>
<td>69</td>
<td>0.3</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>7.4 (1)</td>
<td>8.5 (3)</td>
<td>0.5</td>
</tr>
<tr>
<td>Function (HFAQ), %</td>
<td>27 (21)</td>
<td>25 (20)</td>
<td>0.4</td>
</tr>
<tr>
<td>Pain (VAS)</td>
<td>35 (25)</td>
<td>42 (25)</td>
<td>0.2</td>
</tr>
<tr>
<td>Erosive changes, %</td>
<td>38</td>
<td>43</td>
<td>0.3</td>
</tr>
<tr>
<td>RF positive, %</td>
<td>61</td>
<td>63</td>
<td>0.6</td>
</tr>
<tr>
<td>Disease activity (VAS)</td>
<td>39 (25)</td>
<td>30 (21)</td>
<td>0.2</td>
</tr>
<tr>
<td>On DMARD therapy, %</td>
<td>80</td>
<td>97</td>
<td>0.3</td>
</tr>
<tr>
<td>On one DMARD, %</td>
<td>59</td>
<td>69</td>
<td></td>
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<tr>
<td>On two DMARDs, %</td>
<td>20</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>On three DMARDs, %</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>SF-12 (bodily sum scale)</td>
<td>40 (10)</td>
<td>34 (12)</td>
<td>0.4</td>
</tr>
<tr>
<td>SF-12 (psychological sum scale)</td>
<td>48 (11)</td>
<td>47 (11)</td>
<td>0.6</td>
</tr>
<tr>
<td>Employment, %</td>
<td>51</td>
<td>46</td>
<td>0.3</td>
</tr>
<tr>
<td>Work disability, %</td>
<td>29</td>
<td>34</td>
<td>0.3</td>
</tr>
<tr>
<td>Regional unemployment rate, %</td>
<td>10.9</td>
<td>9.8</td>
<td>0.7</td>
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</tbody>
</table>

HFAQ: Hannover Functional Ability Questionnaire (correlation with HAQ has been shown by Lautenschläger et al. [16]; VAS: visual analogue scale; SF-12: health survey Short Form 12.
Statistics

Data management and data analysis were performed with the current versions of Microsoft ACCESS (Microsoft, Redmond, WA, USA) and SPSS software (SPSS, Armonk, NY, USA). The patient characteristics of the two samples are displayed as frequencies and mean (s.d.) values and compared via t-test (since these parameters are normally distributed) and chi-square test. Frequencies of cost components [n (%), mean (s.e.)] are given and compared by Wilcoxon and Mann-Whitney tests for statistically significant differences.

Results

Comparison of patient characteristics

Patient characteristics proved to be comparable in terms of socio-demographic and clinical variables in the two samples (Table 1). While bodily pain and loss of function are scored a little higher in the sample collected in 2002, disease activity is rated lower (differences not statistically significant).

Disease-related costs

Overall costs are lower in the sample from 2002 (1997–98: €4280; 2002: €3830; Table 2). This overall difference of 11% is not statistically significant. Direct costs outweigh productivity costs in both samples. In 1997–98, productivity costs accounted for only 35% of overall costs (€1480) and in 2002 for even less (23%; €850). The overall productivity costs are significantly lower (reduction by 43%) in the sample from 2002 and also across all productivity sub-domains (sick leave: 24%; work disability: 92%; other work loss: 81%).

Direct costs sum up to €2800 (1997–98) and €2980 (2002), respectively (Table 2). Regarding the main direct cost components, significant differences are seen in the domains medication and hospitalization costs. Medication costs are €550 (1997–98) and €1580 (2002), respectively, showing almost three-fold higher costs in the sample from 2002. In contrast, the hospitalization costs are significantly lower in 2002 (1997–98: €1240 vs 2002: €500), almost compensating for the higher medication costs.

Outpatient physician visits, including diagnostic and therapeutic measures and outpatient non-physician service utilization, render comparable costs in both samples (physician visits: €530 vs €540 and non-physician services: €200 vs €180).

Changes in relative weight of different cost domains

The comparison of relative cost composition reveals a lower proportion of indirect costs in 2002 (1997–98: 35% vs 2002: 23%) (Table 2). Although absolute productivity costs decreased by 43% (€630), their proportion decreased less due to lower overall costs in this group. The impact of medication costs is significant in 2002 with 42% of overall costs compared with only 12% in 1997–98, rendering a 3.5-fold increase. The proportion of hospitalization costs is substantially lower in 2002 (29 vs 13%). Costs due to outpatient physician visits and non-physician service utilization had no impact on relative differences (12 vs 14%; 5 vs 4%).

Medication cost components

Detailed analysis of RA-related medication reveals that not only the costs for DMARDs are higher in 2002, but also all other classes such as steroids, NSAIDs, analgesics, osteoporosis prophylaxis and treatment, and gastroprotective medication. The proportion of these other substance classes increases by 8% (Table 3).

DMARD costs in 1997–98 are mostly driven by CSA (6% on CSA treatment) accounting for almost half of overall medication costs. Other relevant contributors are MTX with 18% (employed in 44%), SSZ with 8% (given to 9% of the cohort) and i.m. gold preparations with 8% (given to 11%). In 2002, the main cost drivers are the TNF blockers infliximab (given to 2%) and etanercept (given to 1%) incurring 37% of overall medication costs. Furthermore, CSA (given to 4%), LEF (given to 13%) and MTX (given to

### Table 2: Comparison of main direct costs and productivity losses of the two samples (1997–98: n = 106; 2002: n = 180) per patient year

<table>
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<tr>
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<tbody>
<tr>
<td>Direct costs, €</td>
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<tr>
<td>Medication</td>
<td>550 (22) (12)</td>
<td>1580 (115) (42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inpatient treatment</td>
<td>1240 (92) (29)</td>
<td>500 (31) (13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Outpatient physician visits (inclusive of diagnostic and therapeutic measures)</td>
<td>530 (41) (12)</td>
<td>540 (45) (14)</td>
<td>0.8</td>
</tr>
<tr>
<td>Outpatient non-physician service utilization</td>
<td>200 (17) (5)</td>
<td>180 (18) (4)</td>
<td>0.6</td>
</tr>
<tr>
<td>Other direct costs</td>
<td>280 (23) (7)</td>
<td>180 (16) (4)</td>
<td>0.2</td>
</tr>
<tr>
<td>Productivity costs, €</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Sick leave</td>
<td>1050 (120) (25)</td>
<td>800 (99) (21)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Work disability</td>
<td>300 (31) (7)</td>
<td>25 (5) (1)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Other RA-related work loss</td>
<td>130 (29) (3)</td>
<td>25 (5) (1)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Overall costs, €</td>
<td>4280 (622)</td>
<td>3830 (435)</td>
<td>0.3</td>
</tr>
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</table>

Values are represented as absolute costs in euros (€) (S.E.M.), with percentage of overall costs within parentheses.
A comparison of the number of DMARDs per patient demonstrates a higher rate of DMARDs and DMARD combinations employed in 2002. The most striking fact is the proportional reduction of patients without DMARD treatment from 20% (1997/98) to 3% (2002).

Regarding other RA-related medications, six-fold higher costs for steroids can be observed in 2002 (Table 3). The frequency of steroid treatment and the mean dosage in regular steroid intake have risen (1997/98: 35% steroid treatment, 20% regularly, mean dosage 2.8 mg/day; 2002: 74% steroid treatment, 65% regularly, mean dosage 4.1 mg/day). Accordingly, costs for NSAIDs are two-fold higher in 2002, 21% of the patients were given NSAIDs on a regular basis and 20% took NSAIDs as needed in 1997-98, compared with 32 and 37%, respectively, in 2002. Furthermore, the costs for analgesics, osteoporosis medication and gastroprotective treatment are substantially higher in 2002 as well.

### Discussion

#### Comparison of overall costs

Comparing both patient samples investigated in 1997-98 and in 2002, a small but not significant decrease is detected in overall costs related to RA per case. Employing comparable standardized measures for the definition of cost components and their valuation, the extent of overall costs is comparable with that of other economic evaluations [1]. Regarding overall costs as well as only direct costs a range of different cost estimates has been described [2]. The most outstanding drivers of the higher estimates are indirect costs, hospitalization costs and medication costs with their extent being dependent on valuation methods chosen, data sources, settings and the respective health-care system [2]. In the present analysis, the cost estimates are to be interpreted in the light of the German health-care system prior to the introduction of the diagnosis-related group (DRG) system for the reimbursement of hospitalization costs. Thus, overall costs range in the lower quartile compared with all other costing studies carried out up to then [2]. For the purpose of the present analysis, it is important that similar methods, data sources and settings have been employed.

There are no cost-of-illness studies available from other countries that render comparable data on RA cost development after the TNF agents were introduced into the treatment. Current research focuses primarily on patient groups in need of biological therapy comparing costs before and under treatment with biologicals in order to explore the cost-effectiveness of these agents. The present analysis aims to show the global impact of these drugs on overall costs in RA as a disease entity. Cost-effectiveness analyses, as recently performed by Sany et al. [17] with original data reveal that the economic changes incurred by biological treatment in a cohort of biological users have to be evaluated regarding long time frames. In the short run, the high medication costs counterbalance most of the economic benefits.

#### Comparison of cost composition

Overall cost estimates remain virtually unchanged and there is a shift in cost composition. The most outstanding change is a more than two-fold increase in medication (prescription) costs, while costs related to inpatient treatment and indirect costs decrease substantially.
A randomized controlled trial has shown that adalimumab combined with MTX in comparison with MTX alone is more effective in preventing work loss [18]. Hence, this finding might underline the importance of indirect cost components as contributors to cost savings due to innovative treatment. The increase in medication costs within the present observation period has been reported for other rheumatic disease entities as well [3].

The role of biological drugs in medication cost increase

Since the most outstanding result is the increase in medication costs, their composition has been investigated in detail. A major concern of health-care payers is the high costs related to biological response modifiers that have become evident since the year 2000. Our data show that these biological drugs are responsible for a large part of cost increases in this cost domain. However, these agents might also have the potential to positively influence cost savings in other areas of the health-care system aside from the clinical benefits they provide. According to our findings, the incidence of biological treatment was 3% in 2002 following the German guidelines at that time (requiring at least two prior DMARD treatment failures including MTX in active RA at that time, which is still the case today) [19], presenting a moderate rate of diffusion into daily practice compared with current data in Germany.

Interestingly, other relevant components of cost increase covering the remaining half of the overall medication cost could be observed. The most important factors are: (i) the introduction of LEF, which is more costly than MTX or other established medications; (ii) the more frequent use of traditional DMARDs as mono- and combination medication; and (iii) the tendency to use more expensive co-medication in terms of NSAID treatment and osteoporosis prophylaxis. The increase in DMARD use might be reflecting efforts to adhere more strictly to current recommendations of early and aggressive treatment [20].

Comparing the prescription frequencies of TNF blockers (3% in 2002 as seen in the present investigation) this number was relatively stable over time in Germany till 2006. However, the actual medical need for the initiation of a biological therapy might be three to five times as high as the numbers in the presented cohort. Undoubtedly this will lead to an increasing relative contribution of these new compounds to the overall direct costs. Newer data suggest that the rate of biological treatment among patients with RA who are under continuous care by a rheumatologist is closer to 10% in Germany [21, 22]. However, as not all patients with RA have access to a rheumatologist, this also might give a biased picture for the overall group of RA patients in Germany. As the trend seen in this analysis might be biased by the slow diffusion of the biologicals in Germany, this comparison cannot be repeated with more recent cohorts. This is due to the fact that the composition of the overall patient population in RA in terms of clinical characteristics has dramatically changed as especially the high efficacy of biologicals has had its impact on the positive side from the perspective of affected patients.

Limitations

Although patient characteristics and disease duration of the two samples match well, there might be confounders influencing costing variables that cannot be ruled out. In the present analysis, we have been able to further minimize the risk of confounding by employing identical methods and instruments for the economic assessment and evaluation.

The comparison of our economic data with other studies is impaired by the fact that our data reflect the situation in secondary care and also as delivered by specialized rheumatologists. Cost composition and overall costs might differ in some aspects from primary care where services are provided by general practitioners. Secondary care in RA may be more expensive at first sight compared with primary care; however, there are data available neither on extent or composition, nor on the development of this difference over time.

Conclusions

The present investigation reports on the potential economic impact of introducing costly TNF agents for RA treatment in Germany. More than half of the notable increase in medication cost is attributed to biological compounds. However, despite these rising medication costs, overall RA-related costs remain virtually unchanged comparing the 1997–98 and 2002 costing data. The incline in medication costs is counterbalanced by decreased hospitalization and productivity costs. Since in a setting of a comparison of two different cohorts confounding cannot be ruled out conclusions have to be drawn carefully. If these economic effects prove to be mainly related to the introduction of the highly effective TNF-blockers, the influence of the achieved cost savings can be expected to further increase over time. Therefore, it appears to be economically highly relevant to validate this assumption in further economic analyses over longer time frames.

Rheumatology key messages

- Substantial parts of the notably increased medication costs are attributable to biological compounds in RA.
- The medication cost incline is counterbalanced by savings related to hospitalization and productivity losses.
- The present data encourage the further recommendation-based employment of innovative drugs in RA.

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