Modelling the effect of function and disease activity on costs and quality of life in rheumatoid arthritis

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Objective. When treatments with the potential to change the natural history of a disease are introduced, their longer-term effect on costs and quality of life (utility) has to be estimated using economic models. However, to remain useful tools, models must be updated when new information becomes available. Our earlier models in rheumatoid arthritis (RA) have been based on functional status, but it has recently been shown that disease activity might have an independent effect on utility. The objective of this study was to improve the model by incorporating the effect of a subjective measure of disease severity and activity (global VAS).

Methods. A Markov model was constructed with five states according to functional status (HAQ), and each state was subdivided according to the VAS (<40 and ≥40). Disease development (transition probabilities between the states) was taken from a longitudinal cohort study of patients with early RA in Sweden. A recent population-based survey of 616 patients with RA provided data on costs and utilities. The model incorporates the full distribution of costs and utilities from the survey, and long-term projections are made using Monte Carlo simulation.

Results. The global VAS had a highly significant effect on utilities independently of HAQ. For resource consumption, only HAQ was a significant predictor, with the exception of sick leave, which was correlated with the VAS but not with HAQ. Using the cohort distribution from the longitudinal study, expected mean costs per patient over 10 yr were 106 034 euros (s.d. 5091 euros) (1 euro = SEK 9.20) and the expected number of quality-adjusted life years (QALYs) was 5.08 (s.d. 0.09). Patients starting at HAQ <0.6 but with consistently high VAS scores would have expected costs of 102 830 euros and 4.96 QALYs, while patients with low VAS scores would have costs of 81 603 euros and 6.01 QALYs.

Conclusion. Our new model incorporates for the first time the effect of a subjective measure of disease severity and activity on both costs and utility, making it a sensitive tool to estimate the cost-effectiveness of disease-modifying treatments. New data on resource consumption indicate a shift to higher direct costs, particularly in early disease, and lower indirect costs in more advanced disease. The large size of the data sets used in this model reduces the uncertainty and makes estimates very stable.

Key words: Rheumatoid arthritis, Costs, Utilities, Disease activity, Modelling.
patients will not progress to the next level(s) of functional impairment and therefore higher costs, or will take longer to progress, thereby preventing or delaying increments in costs.

Like costs, QoL (measured as utility) has been shown to be strongly correlated with HAQ [14, 15, 18], and preserving function for a longer time will lead to QoL gains. However, research surrounding new treatments often provides new insights and new information. In a recent analysis of the first year of follow-up in a cohort of patients treated with TNF inhibitors, we found that disease activity, in addition to affecting functional status and thereby utility, has a significant independent impact on utility, most likely through pain and fatigue [19]. We hypothesized that, at a given level of functional status, much of the variability of utility could be explained by disease activity.

Models must change when new data become available or when modelling techniques evolve, and they must be updated and/or adapted if they are to remain useful tools. We therefore present a new disease model that incorporates both functional capacity and a subjective measure of disease severity, as well as updated and more complete costs.

Patients and methods

The model

Disease progression in chronic diseases is generally modelled using Markov models [20], where patients are classified into a finite number of distinct and mutually exclusive disease states. In RA, Markov states have most often been defined by functional status (HAQ), and costs and utilities have been associated with each state [14, 15, 21]. The development of the disease, both progression and improvements, is represented by transitions between the Markov states at defined intervals (cycles). Expected costs and outcome in terms of quality-adjusted life years (QALYs) for defined cohorts of patients are then estimated over different time-frames.

The quality of disease models depends entirely on the quality of the underlying data, both epidemiological and economic. But while data on resource consumption are country-specific and require constant updating, epidemiological data are less subject to changes in the short term and can more easily be generalized. This was illustrated, for instance, by the very similar disease progression in the two inception cohorts in Sweden and the UK used in our earlier model [15], despite considerable differences in patient management. The new model therefore remains based on the first 10 yr of the cohort study in Lund (southern Sweden), which enrolled patients with definite RA and symptoms for less than 2 yr and followed them for up to 19 yr [22-24].

The model was developed in DATA Pro (TreeAge Software, Williamstown, MA, USA) and uses five distinct disease states based on HAQ scores with cut-offs at 0.6, 1.1, 1.6 and 2.1. To estimate the uncertainty around the expected values, we used second-order Monte Carlo simulation. This means that a number of simulations are performed where, in each simulation, each parameter in the model is drawn from its underlying distribution. Means and standard deviations are then calculated across all simulations. To estimate the underlying distribution, we used bootstrapping [25]. One thousand bootstrap replicates were created for each parameter in the model, and during each simulation one of these was drawn at random and used in the calculations. Costs and effects are discounted at 3%.

Epidemiological data

Between 1985 and 1989, the Lund study enrolled 183 patients; this number constituted about half of all new cases in the area. Ethical approval for the study had been obtained from the Lund University Hospital. The mean age at inclusion was 52.4 yr and 63.4% were women. With the exception of one, patients were in functional class I and II and 75% were positive for rheumatoid factor. At the start of the study about half of the group (49%) had erosive disease, defined as a Larson score of 2 in at least one joint in the hands and/or feet. The patients were assessed annually with standardized measures at a team care unit at the Lund University Hospital. They were treated according routine clinical practice. The mean HAQ score at baseline was 0.93 (s.d. 0.6) and increased to 1.10 (s.d. 0.7) after 10 yr.

Disease activity

In clinical trials, disease activity is measured with the disease activity score (DAS or DAS28) and low disease activity has been defined as a DAS28 score of <3.2 [26]. However, DAS is a recent score and has not been included in cohort studies in the past. Also, it is difficult to assess DAS28 in observational studies in which data are collected directly from patients, as clinical and laboratory measurements are required. As an alternative, Kvien has used patients’ assessment of their disease on the global visual analogue scale (VAS) to assess disease activity in the Oslo patient registry, high activity being defined as a global VAS of 40 or above [5]. We verified the correlation between the VAS and disease activity using data from the TEMPO trial [27]. The global VAS, HAQ and DAS28 were available for 682 patients, and we found that the VAS and disease activity were significantly correlated, when controlling for HAQ (P<0.001). In addition, a cut-off at a DAS28 score of 3.2 corresponded to a cut-off of 41 on the VAS [28]. Similar results were found in a second data set from Hungary in which VAS, HAQ and DAS28 were available for 250 patients (personal communication, M. Pentek and L. Gula). A cut-off at a DAS28 score of 3.2 in this data set corresponded to a VAS of 37.5. In both data sets, DAS28 and global VAS were both significantly correlated with utility (P<0.001).

Consequently, we used patients’ assessment of disease severity as a proxy for disease activity, and separated each of the five Markov states in the model into two substates (<40 and ≥40 on the global VAS). The proportion of patients in each substate was estimated from a survey (described below) in patients from a population-based registry in Malmö (Sweden) [29].

Disease progression (transition probabilities)

Disease progression was modelled as transitions between states over time and transition probabilities were based on HAQ only, as in the earlier models [14, 15]. There is evidence that the development of functional disability is influenced by disease activity [30]. However, currently available data make it difficult to calculate a risk function for adjusting the annual HAQ progression at each level of functional disability according to the intensity of disease activity and the duration of inflammatory episodes.

As in our previous model, transition probabilities were estimated using ordered probit regression, whereby the probability of moving to a certain state is determined by age, sex, disease duration and the present disease state [15].

Mortality

The evidence regarding the effect of RA on life expectancy has been conflicting. A number of studies have shown increased mortality in patients with RA, as well as links between functional status and disease activity and mortality [31–34]. In North America and the UK, standardized mortality ratios have been estimated to range between 1.32 and 3.08 [31, 33, 35, 36], whereas studies in Norway and Sweden reported 1.57 and 2.0, respectively [37, 38]. Studies in early RA, on the other hand, including the Lund cohort
study, have not evidenced any increased mortality during the first 10 yr of follow-up [39, 40].

The model therefore included normal age- and gender-adjusted mortality in the two early HAQ states (<1.1), while in the three more advanced HAQ state, we adjusted normal mortality with a relative risk of 1.3 and of 2.0 in the states with low and high VAS scores, respectively. In sensitivity analyses, we tested the impact of changing these assumptions.

Resource utilization

Table 1 shows the details of the samples used for the calculation of resource utilization in the model.

In 1997, a survey of 1009 patients with confirmed RA, representing an estimated 90–95% of patients in the Malmö area, was carried out by the department of rheumatology of the Malmö University Hospital. In 2002, the follow-up survey, answered by 616 patients, included a questionnaire on resource consumption and work capacity, as well as the EQ-5D, a generic utility instrument [41–43]. Ethical approval for both surveys was obtained from the Malmö University Hospital.

The mean age was 64.5 yr and 74% were female, with a mean disease duration of 16.7 yr. Thus, the sample is very similar to the current Lund cohort, in which mean age at enrolment in the late eighties was 52.4 yr and disease duration was slightly less than 1 yr. Although resource consumption data are available throughout the first 10 yr of the Lund study, this represents earlier treatment patterns. In particular, work capacity is expected to be substantially different today, as the job structure has changed to less physically demanding work and invalidity pensions are handled in a less generous fashion. We therefore preferred to use the recent resource utilization data from Malmö in the model, particularly as the two cities are only about 10 miles from each other.

Direct resource utilization included hospitalization, surgical procedures, out-patient and office visits, drug use, community services, modifications to home or car, devices, transport and informal help. Indirect costs included early retirement due to RA, long- and short-term sick leave, loss of leisure time (vacation days due to illness). The amount of missing or unclear answers in the questionnaires was very limited. Patients had been instructed to only include RA-related resources and only a small number of resources had to be excluded as not relevant to RA (e.g. contraception). Missing information related primarily to the hospital department or the specialty of the physician seen; in these cases, we assumed admission to the rheumatology department and a visit to a general practitioner. When information on the number of in-patient days was missing, we imputed the mean value of the sample.

The proportion of patients in the sample on invalidity pension was 36%, which is partly explained by the long disease duration (up to 35 yr). It is possible that early retirement was given more frequently in the late 1980s and early 1990s, particularly in semirural environments such as Malmö, where a higher proportion of jobs involved physical activity. We therefore also obtained data on early retirement for 1810 patients from the Stockholm area, about half of whom are currently also followed in the National Swedish RA registry [44]. Patients in this sample were younger and 93% were aged 65 or less, and the proportion of patients on invalidity pensions was lower (24%). Thus, to adjust early retirement more to the national level, we merged the two data sets to calculate the cost of early retirement due to RA.

Cost valuation

The costs of in-patient and out-patient care and community services costs were obtained from the electronically available information for 2004 of the County Councils of Southern Sweden, who are responsible for the entire health-care expenditures of the region [44]. In-patient admissions for surgery were valued using diagnostic related groups (DRG) costs, while unspecified admissions were valued using the per diem cost. Drug costs were calculated based on the average daily dose and duration of each preparation at public prices [45] plus specific drug-monitoring guidelines in place at the Malmö and Lund hospitals.

Mean annual labour cost by gender (mean salary plus employers’ costs) for 2001 was available from the statistical yearbook (Statistics Sweden) for 2003 [46] and inflated to 2004 costs. As the figure for women includes shorter mean working times, we ignored the indications regarding part-time work in the questionnaires. The annual labour cost was established at 36 100 euros for men and 24 800 euros for women (1 euro = SEK 9.20).

Informal help and care were valued as leisure time, using the estimated net income after tax in Sweden (35% of full labour cost). Other methods of valuing informal care exist, e.g. the replacement method, where the hourly cost of professional paid help is used. However, informal help in this sample concerned mostly housework or transport, and the value of leisure time appears therefore more adequate.

Outcome

Outcome in the model is expressed as QALYs, i.e. life years adjusted with a quality weight (utility). Utility is defined as the preference of patients and/or the general population for given states of health. It is expressed as a value between 0 (equal to death) and 1 (equal to full health). Thus, living 1 yr with a utility of 0.5 is equal to living half a year in full health. Utility scores can be assessed using interview-based techniques from decision analysis, e.g. time-trade off (TTO) and standard gamble (SG), or, particularly in large populations, descriptive instruments such as the EQ-5D [40].

The EQ-5D is self-administered, easy to use and has been validated in a large number of studies, including in RA [15, 18].

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics and mean costs (euros, 2004)</th>
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</thead>
<tbody>
<tr>
<td><strong>Malmö data</strong></td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>616</td>
</tr>
<tr>
<td>Patients &lt;65 yr</td>
</tr>
<tr>
<td>Sick pension (patients &lt;65 yr)</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Disease duration</td>
</tr>
<tr>
<td>No. of previous DMARDs</td>
</tr>
<tr>
<td>No. of patients on TNF inhibitors</td>
</tr>
<tr>
<td>Global VAS</td>
</tr>
<tr>
<td>HAQ</td>
</tr>
<tr>
<td>Mean utility</td>
</tr>
<tr>
<td>Mean total costs per patient</td>
</tr>
<tr>
<td>Direct costs</td>
</tr>
<tr>
<td>Informal care</td>
</tr>
<tr>
<td>Indirect costs</td>
</tr>
<tr>
<td>Early retirement (all patients)</td>
</tr>
<tr>
<td>Early retirement (patients &lt;65yr, mean age 53 yr)</td>
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<tr>
<td><strong>Stockholm data</strong></td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>1810</td>
</tr>
<tr>
<td>Patients &lt;65 yr</td>
</tr>
<tr>
<td>Sick pension (patients &lt;65 yr)</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Cost of early retirement</td>
</tr>
<tr>
<td>(patients &lt;65yr, mean age 47yr)</td>
</tr>
</tbody>
</table>
It addresses general domains of QoL using five questions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), with three levels of answers (no/some/severe problems). From these, descriptive health states were derived and assessed in the general population using TTO/SG to create a social tariff [42].

In view of the limited number of items in the questionnaire, no method of imputing missing values exists, and incomplete answers are excluded. The descriptive part of the EQ-5D was included in the follow-up survey and 541 complete answers were available.

### Results

#### Utilities

Utility scores were, as expected, significantly and independently correlated with both the HAQ and the global VAS ($P<0.001$). Patients at the same HAQ levels but with a VAS above 40 had consistently lower utilities than patients with scores below 40, as shown in Table 2.

#### Costs

As in previous analyses, total costs were significantly correlated with function (HAQ), as shown in Table 3, but the correlation with patients’ subjective assessment of disease severity was not obvious. Although a clear trend was found, the difference in cost between high and low VAS scores was not significant when controlled for function. In addition, sensitivity analysis introducing a 20% cost difference in each substate indicated a limited impact on total 10-yr costs. An exception to this was short- to medium-term work absence, which was highly correlated with VAS scores, but not HAQ, with a mean difference of 2400 euros between high and low scores.

In the model, we therefore apply the same costs to the substates, except for sick leave, for which different costs were used for states with high and low VAS scores, without differentiating by HAQ level.

#### Modelling results

Table 4 presents expected 10-yr costs and QALYs for patients starting at different levels of HAQ, using the gender distribution and mean age of the Lund cohort, as well as for the initial cohort distribution in that study. Results were obtained by Monte Carlo simulation (10,000 runs). Ten-year costs for patients starting in the mildest state (HAQ <0.6) amounted to 89,000 euros and increased by 65% for patients starting at a HAQ score of 2.1 or higher (147,000 euros). Mean costs for the Lund cohort were 106,000 euros. Expected QALYs over a 10-yr period were 5.52 for patients starting at HAQ <0.6, 3.95 for patients starting at HAQ >2.1, and 5.08 for the Lund cohort. Patients starting at HAQ <0.6 with consistently high VAS scores would have expected costs of 101,830 euros and 4.96 QALYs, while those with consistently low VAS scores would have costs of 81,603 euros and 6.01 QALYs.

#### Sensitivity analysis

Sensitivity analyses were performed using the Lund cohort distribution and are presented in Table 5. The model appeared to be very stable and essentially driven by function. The effect of increased mortality on costs and QALYs was very limited. Similarly, when costs for states with high disease activity were increased by 20%, total expected costs increased only very slightly. Age had a significant effect. Younger patients had substantially higher costs, due to higher indirect costs, and more use of biological drugs, and women had slightly higher costs overall than men. When progression to the next HAQ level was delayed by 10%, 10-yr costs decreased by around 3000 euros.

#### Discussion

In this paper, we present a new disease model that incorporates both functional capacity and a subjective measure disease severity, and that can be used to estimate the cost-effectiveness of new disease-modifying treatments in RA. When new clinical results (e.g. in different patient populations, over different time-frames, compared with different alternatives) become available, it is necessary to re-evaluate earlier cost-effectiveness estimates to base decisions on the best available data. Similarly, when knowledge about a disease progresses and new or different disease measures are used, these must be incorporated in any tool that is used to support decisions on resource allocation. In the field of RA, the introduction of potent disease-modifying treatments has provided new opportunities to investigate the causes underlying disease progression, and measures of both disease activity and joint erosion have been refined. As new data emerge, disease...
Effect of HAQ and DAS on costs and utilities

models to estimate costs and QoL must be adapted to incorporate the latest findings.

In an early analysis of patients treated with TNF inhibitors in clinical practice, we found that disease activity appeared to have an effect on utility, regardless of functional status [19]. However, the data set was too small to draw any firm conclusions. We therefore investigated this effect in a larger sample of 616 patients in an observational study, using the global VAS as a proxy for disease activity, and found it indeed to be highly significant. Thus, if models are to be used to analyse the cost-effectiveness of newer treatments with a pronounced effect on disease activity, such as the TNF inhibitors, it is necessary to incorporate the most current data.

Disease activity in RA has multiple dimensions and a composite score has been developed for its clinical assessment and measurement. However, the issue for economic models is the high variability of the economic parameters. This makes it necessary to use large data sets, for which it is often impractical to assess the DAS28. We have tried to overcome this limitation by using the patient global VAS as a proxy measure, as has been done earlier when assessing disease activity in data sets in which specific scores were not available, with a cut-off at 40 [5]. Clearly, the global VAS is a relatively crude measure that may incorporate the effect of other parameters, such as the patient’s ability to cope with disease activity and pain [48, 49]. Nevertheless, we found a highly significant correlation between the VAS and disease activity, independently of HAQ, in two different data sets with 932 observations. Using these data, we have further confirmed the cut-off at VAS 40. Correlating the patient global VAS with the DAS28 in the TEMPO trial [27], we found that a cut-off at a DAS28 of 3.2 corresponds to a score of 41 on the patient global VAS, while in a data set in Hungary it corresponded to 37.5. Thus, the use of the global VAS as a proxy for disease activity appears justified in the absence of a data set that contains all of HAQ, DAS28, EQ-5D and complete resource consumption.

The independent effect of the global VAS (controlled for function, age and disease duration) on utility is highly significant, and can therefore not be ignored in economic models. Contrary to this, its effect on costs was not significant, even if a trend towards higher costs with high VAS scores was found. This was the case even when patients treated with TNF inhibitors, who might have had low disease activity but high cost, were excluded. One explanation for this may be that RA patients are followed rather regularly, as almost all of them are treated with DMARDs and require monitoring. Painful inflammatory episodes may thus be taken care of during routine management. A further reason is probably that the drivers of costs, such as surgical interventions and the loss of work capacity are long-term costs and as such strongly related to function rather than inflammation. Lastly, in view of the large variation in costs, our sample may still be too limited to detect small differences.

As an exception, we found that short-term sick leave, which represented 14% of total costs, was related to the global VAS but not to function. This is not unexpected, and further supports the use of the global VAS as a subjective indicator of disease activity. Painful inflammatory episodes would indeed be expected to have an immediate effect on sick leave. The model therefore incorporates this effect. As the new treatments act strongly on inflammation, they may reduce sick leave across all levels of function, but not reverse other indirect costs, such as early retirement.

Resource utilization changes over time, particularly when new treatments are being used, and cost data must be updated. This was evident from the above analysis of TNF-treated patients in Sweden [19], where hospitalization and surgical costs were halved, leading to a reduction of almost 60% in direct costs other than TNF inhibitor treatment. However, total direct costs increased threefold, reducing the proportion represented by indirect costs to less than a third of total costs, compared with two-thirds in most published studies. However, such early treatment data can seldom be used in models that project to the long term and the future. In general, early users of a new treatment represent the most severe patients, with long-standing disease or who are refractory to current treatments, and these costs are unlikely to be representative.

Although resource consumption is available in the epidemiological study used in our model, costs such as community services, investments and informal care are not included. Also, usage in the first 10 yr of the study represents clinical practice in the 1990s. It is therefore preferable to combine disease progression in the Lund cohort with current management costs, as provided by the much larger survey in Malmö. There are, however, several issues to be considered. The treatments used in the 2002 survey are bound to be different from those used in the epidemiological cohort and it would also be expected that the use of more recent and more intensive treatments has an effect on disease development. Combining the two data sets could thus indeed be questioned. However, we have found in both samples that the only significant predictor of overall costs is functional status, regardless of how

### Table 4. Expected 10-yr costs (euros, 2004) and QALYs (discounted at 3%)

<table>
<thead>
<tr>
<th>Markov state</th>
<th>Expected costs (euros, 2004) Mean (S.D.)</th>
<th>Expected QALYs Mean (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting state</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.6</td>
<td>89 033 (4712)</td>
<td>5.52 (0.09)</td>
</tr>
<tr>
<td>0.6-1.1</td>
<td>104 197 (4640)</td>
<td>5.14 (0.10)</td>
</tr>
<tr>
<td>1.1-1.6</td>
<td>120 105 (5758)</td>
<td>4.72 (0.10)</td>
</tr>
<tr>
<td>1.6-2.1</td>
<td>137 784 (6547)</td>
<td>4.36 (0.13)</td>
</tr>
<tr>
<td>≥2.1</td>
<td>146 927 (6751)</td>
<td>3.95 (0.16)</td>
</tr>
<tr>
<td>Lund cohort</td>
<td>106 034 (5091)</td>
<td>5.08 (0.09)</td>
</tr>
</tbody>
</table>

1 euro = SEK 9.20.

### Table 5. Sensitivity analyses when varying key assumptions

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Expected costs (euros, 2004) Mean</th>
<th>Expected QALYs Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No excess mortality</td>
<td>107 085b</td>
<td>5.14b</td>
</tr>
<tr>
<td>Higher mortality</td>
<td>105 590b</td>
<td>5.09b</td>
</tr>
<tr>
<td>All female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 yr</td>
<td>114 779</td>
<td>5.12</td>
</tr>
<tr>
<td>60 yr</td>
<td>77 880</td>
<td>4.83</td>
</tr>
<tr>
<td>70 yr</td>
<td>41 337</td>
<td>4.47</td>
</tr>
<tr>
<td>All male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 yr</td>
<td>102 719</td>
<td>5.41</td>
</tr>
<tr>
<td>60 yr</td>
<td>69 821</td>
<td>5.12</td>
</tr>
<tr>
<td>70 yr</td>
<td>36 470</td>
<td>4.77</td>
</tr>
<tr>
<td>Direct cost 20% higher for states with VAS ≥40</td>
<td>106 645</td>
<td>5.08</td>
</tr>
<tr>
<td>15 yr follow-up</td>
<td>130 376</td>
<td>6.88</td>
</tr>
<tr>
<td>Transition probabilities to the next state</td>
<td>103 437</td>
<td>5.18</td>
</tr>
<tr>
<td>HAQ level reduced by 10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect of disease activity, patients starting in state 1 (HAQ &lt;0.6)</td>
<td>101 830</td>
<td>4.96</td>
</tr>
<tr>
<td>Consistently high disease activity</td>
<td>81 603</td>
<td>6.01</td>
</tr>
</tbody>
</table>

1 euro = SEK 9.20.

*The same cohort distribution as in the Lund cohort was used.
*Higher costs and higher number of QALYs due to a higher number of patients overall.
*Relative risk = 2.0 for low disease activity, 2.5 for high disease activity.
*Lower costs and higher number of QALYs due to the fact that mortality affects the more advanced states (3–5) and a higher number of deaths in these states will reduce the number of patients with high costs and low utility.
functional status has developed. In addition, when controlling for HAQ level, age and disease duration are insignificant, as they are highly correlated with HAQ. This justifies, in our view, the use of the more recent cost data.

It is expected that the new biological treatments delay the development of functional disability, and TNF-treated patients are therefore followed in registries such as the Swedish RA Registry. However, data to make comparisons with earlier cohorts will be available only after a number of years. Until then, differences in disease progression need to be modelled either by incorporating and extrapolating the changes seen in clinical trials or by investigating the effect of a hypothetical change, as we have done in this study.

The new model incorporates disease-specific mortality, but the effect on costs and utilities over 10 yr is limited. RA-specific mortality was based on the literature rather than on mortality data in the Lund and Malmö cohorts. To estimate the relative mortality risk by both HAQ level and disease activity requires very large data sets, and using average findings from a number of different studies is therefore more adequate.

Costs in the new model are higher overall than in previous estimates. In particular, costs for patients starting in the mild states have increased by 20–30%, driven by direct costs and the use of biological agents. Costs for a patient group similar to the Lund cohort have increased by 12%. Contrary to this, costs for patients entering the model in more advanced states are similar, despite the more frequent use of biological drugs. This is explained by considerably lower indirect costs because fewer patients are on early retirement in this new model, compared with the earlier data from the Lund cohort.

The overall number of QALYs over 10 yr for the Lund cohort is similar to the estimate in the previous model, despite the incorporation of the effect of the additional measure of disability. However, patients starting with more advanced functional disability have around 0.3–0.4 QALYs less than in the previous model, illustrating the effect of a high proportion of patients with high VAS scores in these states and therefore lower utility. The strong effect of the subjective assessment of disability is, however, best illustrated when comparing patients starting at the same level of functional capacity but with either consistently high or consistently low VAS scores. The difference in expected costs over 10 yr is around 20 000 euros, driven by short-term work absence, and more than 1 QALY (both discounted at 3%). Thus, any cost-effectiveness estimates of drugs with an effect on disease activity must take these differences into account.

Owing to the large data set used, the uncertainty in the cost and utility estimates in this new model is limited, as evidenced by the small standard deviations. The main uncertainty resides in disease progression, which may be affected by the new treatments, but new data sets are required to overcome this. Also, we did not have a data set with actual disease activity scores that also contained costs and utilities and used a proxy measure.

Nevertheless, the current model incorporates the best currently available data and provides a new opportunity to estimate costs and outcomes for treatments with an effect on disease activity.

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References


Key messages

- A new cost-effectiveness model is presented that incorporates for the first time both the effects of functional impairment and of patients' subjective assessment of disease severity and activity on costs and utilities, as a useful tool for the economic evaluation of treatments that have an effect on disease activity and progression.

Effect of HAQ and DAS on costs and utilities