Systematic literature review on economic implications and pharmacoeconomic issues of rheumatoid arthritis

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ABSTRACT

Objective. To provide a state of the art of economic analyses applied to rheumatoid arthritis (RA).

Methods. A systematic literature review on economic consequences and pharmacoeconomic issues of RA was performed.

Results. 127 valid articles were examined in this review. Generally, the financial impact of RA is substantial for health-care systems and society worldwide, although differences exist among national economies. Both direct and indirect (i.e., loss of productivity) costs contribute to economic burden of RA and must be taken into account when estimating overall impact to society. Disease severity, disease activity, age, and socioeconomic status have been found to be the most relevant predictors of cost increase in RA. Moreover, introduction of biological anti-rheumatic agents has significantly raised direct medical costs in certain patients, but has also led to marked improvements in reducing disease activity, joint damage, and productivity loss in many of these patients. RA has also a significant impact on all aspects of quality of life; recent publications on health utility scores showed RA to be one of the diseases associated with poorest quality of life.

Conclusions. RA represents a clinical and economic burden for healthcare systems. Although attributable RA costs have been extensively evaluated over the last decades, several issues, especially concerning the use of expensive therapies, must be addressed and frequently updated. Future research should also provide health economic evidence from usual practice settings, and on the economic impact of different therapeutic approaches to pursue specific clinical targets in individual patients.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease affecting approximately 0.05–1% of the population (1, 2). The course of RA is variable, but for a substantial proportion of patients it is characterised by persistent pain and stiffness, progressive joint destruction, functional disability, and premature mortality (3). RA also presents a serious socio-economic burden in terms of both direct medical and non-medical costs, and indirect costs (i.e., productivity loss, premature mortality, and burden for caregivers) (4-9).

The introduction of early therapy with disease-modifying anti-rheumatic drugs (DMARDs), particularly widespread use of methotrexate, led to substantial improvement in status of many patients. Nonetheless, about 10–40% of patients have incomplete responses to methotrexate and other DMARDs, for whom biological therapies have led to marked improvements in disease activity control and prevention of joint damage. However, biological therapies are far more costly than traditional DMARDs, and the higher direct medical costs limit prescription of biologic agents in RA. Market access conditions such as reimbursement status, level of co-payment, prescribing restrictions, will impact payers’ level of acceptance of biologic agents for specific patients. As per-capita healthcare expenditures reflect payers’ willingness to pay, prescription of biological drugs is much more developed in high-income countries (10).

The high societal costs of RA and new biological therapies have led healthcare payers and providers to increase their level of attention on this condition, particularly in the current period of budget constraints. By using cost-effectiveness analysis to evaluate the economic “value” of a drug, public payers dictate to some extent what treatments can

Competing interests: L.G. Mantovani received an institutional research grant from Pfizer and is a member of the Advisory Board for MSD, and Pfizer; the other co-authors have declared no competing interests.
or cannot be charged on their budget. This is particularly important in the RA treatment landscape, where few patients could afford costs of biological therapies without health insurance, be it public or private.

In particular, GRADE (Grading of Recommendations Assessment, Development and Evaluation) encourage incorporation of economic issues in RA recommendations regarding treatment (11). We systematically reviewed existing economic studies in RA to better understand the economic consequences of this disease and its treatment, as presented in this report.

Materials and methods
Search strategy and inclusion / exclusion criteria
To collect and review the evidence, we performed a systematic literature review aimed to select economic evaluations in RA. In order to focus on the most recent clinical practice, we included studies, analyses and reviews on RA economic topics published over the last 5 years (from May 2007 until June 2012) through a MEDLINE search (however some publications older than 5 years mentioned in selected reviews could have been reported in this article). As the aim of the review was to perform an assessment of therapeutic classes and not active principles individually, head-to-head studies comparing single active principles were not included. To maximise retrieval of all pertinent papers we applied medical subject headings (“MeSH”) terms, or keyword searches when at all appropriate. Box 1 and Table 1 provide details of the search strategy. After scanning all titles and abstracts, we retrieved the full text for all potentially relevant studies.

Data review and analysis
Two members of the review team examined studies in a three-step process. First, the title list was considered; second, abstracts of those that passed the title review were examined; third, potentially relevant articles were reviewed. Disagreement between the two reviewers was resolved by consensus of a third party. Data from eligible studies were extracted and a spreadsheet was used for data entry. The articles were also categorised according the classification illustrated in Figure 1.

Results
We screened 505 non-duplicate citations (last update: May 25, 2012), 378 of which (74.9%) were excluded as they did not meet pre-defined inclusion criteria. 127 economic evaluations were included, 19 of which (15%) were reviews. Research details are shown in Figure 1. These retrieved articles were NOT hand searched for further references.

Costs of RA
A large number of economic evaluations have been performed in recent years to assess the burden of RA for patients, healthcare providers (public and private), and society in general. Tables II and III summarise main findings with regard of direct and indirect costs. Of course, methodological approaches and primary objectives vary considerably across these studies, so that a homogenous comparison is complex and difficult to perform, but a comprehensive overview may be informative. Some recent reviews attempted to compare RA costs across different countries or to calculate average costs combining results of national studies. Boonen et al. (23) performed a systematic review of 26 cost-of-illness studies, mainly conducted in Western Europe, with the aim to derive a weighted average annual cost of RA. Considering the different data sources and weighting results by the timing of the study, the authors found that annual healthcare and non-healthcare costs were €4,170 (inter-quartile range: €2,756–€4,561), with out-patient costs being the cost driver (€2,981). Another systematic review of RA costs across different countries was reported by Lundkvist et al., in their in 2008 (2). Annual total economic burden (direct costs + indirect costs + informal care), was estimated to be €41.631 billion in the US, and €45.263 billion in
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<td>2011 (USA)</td>
<td>Per patient annual costs: - Group 1 (patients receiving a single anti-TNF: drug costs=$7,058; RA related costs=$13,312) - Group 2: patients switching from anti-TNF: drug costs=$8,340; RA related costs=$15,048 - Costs in Group 2 were significantly higher than in Group 1</td>
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<td>Per patient annual costs: - Total costs (direct + indirect): €4,280 in 1997-98; €3,830 in 2002 (p&lt;0.05 for the difference) - Higher costs in 2002 vs. 1997-98; p&lt;0.001 for medications and hospitalisations</td>
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*Data taken from abstracts of selected articles.*

Europe). Per-patient annual costs were around €21,000 in the US and €13,500 in Europe (Fig. 2 shows costs for US and larger European countries). In Europe, medical costs accounted for about one-third of overall expenditure; the majority of costs were direct costs (49% of total costs), production losses (32%) and informal care (19%). Costs in the United States were considerably higher than in Europe, due to a higher use of biological DMARDs. Results highlighted relevant cost variability across countries, potentially attributable to different factors: i) proportions of patients treated with biological drugs, ii) differences among patients on disease severity, level of comorbidity.

Several studies have demonstrated that disease severity and functional disabili-ty are significant predictors of increased direct and indirect costs in RA popula-tion. Lundkvist et al. (2) highlight the importance to correlate RA costs to the year of publication. In more recent cost-of-illness studies, enrolled patients had a higher likelihood to be treated with new, high cost, biological therapies, compared to older studies in which more RA patients were treated with traditional DMARDs (e.g. methotrexate). Many recent cost-of-illness studies were focused on the influence of new generation treatment with biological agents (e.g. anti-TNF, rituximab, abatacept) on healthcare direct costs for patients with RA (51, 59, 77, 135).

Several studies evaluating direct medical costs found that introduction of biological treatments for RA has increased drug-related costs (59), but reduced the rate of out-patient visits and hospital admissions (135). Finally, the adoption of more complex patterns of treatment such as anti-TNF switching or usage of other biologic agents after anti-TNF failure, has led to a rapid increase of overall higher medical costs compared to the previous decade. A study conducted in 2011 in the USA (19) revealed that switching from one anti-TNF drug to another during the first year of treatment, would cost more than maintaining patients on the same anti-TNF therapy as annual RA-related prescription drug costs ($8,340 vs. $7,058; p=0.012), RA-related healthcare costs ($15,048 vs. $13,312; p=0.008), and total healthcare costs ($26,697 vs. $21,381; p<0.001).
### Table III. Main findings from studies evaluating indirect costs in RA*.

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<td>Lost working days (per-month), attributable to medication errors: - 3 days/month</td>
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<td>Aceves-Avila FJ (63)</td>
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<td>Evaluation of effect medication errors on productivity loss, in rheumatology patients (292 out of 381 had RA)</td>
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<td>Langley PC (18)</td>
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<td>Neovius M (64)</td>
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<td>Per patient annual costs: - Total costs: US$ 9,286 - Indirect costs: 60% of total costs</td>
<td>Per patient annual costs: - Total costs: US$ 9,286 - Direct costs: 40% of total costs</td>
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<td>Bowman SJ (69)</td>
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<td>Per patient annual productivity costs: - pSS patients: £7,677 - RA patients: £10,444 - Community controls: £892</td>
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<td>Franke LC (35)</td>
<td>2009 (Netherlands)</td>
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<td>2009 (Netherlands)</td>
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Some studies evaluated costs (or resource consumption) of RA by disease severity/activity. Disease activity progression was found to predict an increase of costs (21, 41). A French study published in 2011 (29) assessed the use of direct medical resources, excluding drugs, according to level of disease activity (using DAS score as the stratification variable). Results indicated that costs for patients achieving remission were €771 over the first 6 months period and €511 during the next 6 months period. For patients achieving a low disease activity state, costs were estimated at a €905 for the first 6 months and €696 for each 6 months period. Finally, patients still in moderate to high disease activity had higher costs (€1,215 for the first 6 months). In the same year, a similar study conducted in Sweden (27) analysed the relationship between the level of disease activity at 3-month follow-up and costs over the following 4 years. Patients with low disease activity score levels incurred relatively low direct costs (€2,760 per year 1; €2,447 per year 2; €1,693 for year 3 and €2,073 per year 4) and patients with moderate to high disease activity score levels incurred higher direct costs (€4,147 per year 1; €3,173 per year 2; €3,085 per year 3 and €3,666 per year 4) independent of age and gender. Some studies have also examined out-of-pocket expenditure. In Belgium, long-standing RA patients (>12 years since diagnosis) spent more than twice, compared to early-diagnosed RA patients (<1 year: €1,098 vs. €469: (137, study published in 2005, included in article ref. 23). Out-of-pocket expenditures were estimated to be AUS$1,523 per patient per year in Australia; higher expenses were seen with increasing disability and in women (138, study published in 2002, included in article ref. 23). A large US observational study in early RA showed that one of three working patients voluntarily retired within the first 2 years after diagnosis, while another study found even higher figures (percentage of patients leaving work by 2.5 years and 6 years from diagnosis: 40% and 53%, respectively) (140, study published in 2007, included in article ref. 23). A large US observational study on work disability in RA (average duration of follow-up: 12.8 years) found an incidence rate of 8.7% for stopping work and 4.0% for stopping and not resuming work (141, published in 2007, included in article ref. 23). Estimation of indirect costs depended on the approach adopted: loss of productivity amounted to €8,452 using human capital approach vs. €1,441 using friction cost approach. Accord-
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Fig. 2. Distribution of costs from a recent cost-of-illness review (adapted from 2).

ing to Lundkvist’s review (2), indirect costs were €16,584 billion per year in Europe and €8,716 billion per year in the US. Per patient annual values were quite similar: €4,300 in Europe and €4,400 in the US. However, the average value for Europe is the result of very different estimations. In general terms, studies conducted in Western Europe reported much higher indirect costs than Eastern countries. The highest value has been reported for Germany (€11,400), perhaps a country with one of the most developed public welfare system. Variability of indirect costs across countries might be attributable to different reasons, such as social security systems and welfare, clinic conditions of enrolled patients, duration of follow-up, which could realistically have affected productivity loss. Increasing age, manual work, larger impact on physical function (measured by the Health Assessment Questionnaire, HAQ), level of co-morbidity and duration have been found statistically significant predictors of increased indirect costs (142, 143 studies published prior to 2007, included in article ref. 75). There were also geographic differences, indicating the importance of social security systems and unemployment rates. For example, a study comparing patients with early RA in Finland and the USA found that Finnish patients had higher rates of work disability (expressed as probability of working at 36 months: 0.84 vs. 0.89; p<0.02) despite better scores for pain and function. This was attributed to less stringent criteria for receiving disability benefits in Finland (144, study published in 2006, included in article ref. 75).

Although these methodological issues can determine different results, it is acknowledged that RA is strictly related to work limitations, high rates of absenteeism and presenteeism. Therefore most studies highlight the opportunity of including these type of costs and adopt a broad economic perspective when evaluating the economic burden of RA and comparing cost-effectiveness of different alternatives for patient management.

Quality of Life in RA

Different generic and specific quality-of-life measures have been used to assess RA. The most widely used were Short-Form (SF) 36, EuroQoL (EQ-5D) and the HAQ. RA has a significant impact on all components of the SF-36. The most recent review, published in 2011, reported 17 observational studies and 6 randomised controlled trials (79) using SF-36 to evaluate the impact of RA on quality of life assessed. These results come from data of 5,090 patients with a mean age of 56 years (range 43–64) and mean disease duration of 9.5 years (range <1–16) and showed that physical component scores (PCSs) were lower than mental component scores (MCSs), with the exception of vitality. The lowest scores were seen for the role physical domain. Poorer quality of life scores were associated with higher disease activity.

Data from trials have showed that biological drugs provide greater benefits in PCS scores (weighted mean difference of 4.55: 95% confidence interval (CI) 3.80–5.31; p<0.00001) compared with MCS scores (weighted mean difference of 2.59 (95% CI 1.66–3.52, p<0.00001).

The HAQ is widely used in RA because of its effectiveness in measuring patient function. Total score of the HAQ ranges from 0 to 3, with scores of 0–1 indicating mild/moderate disability, 1–2 moderate/severe disability and 2–3 severe/very severe disability (145). In RA, an improvement of at least 0.22 is considered indicative of improved functional status (146, 147). Moreover, HAQ scoring variations are strongly correlated with EQ-5D, SF-6D, and Health Utilities Index (HUI)-3 (148). HAQ scores are traditionally increased over time at varying rates (Figure 3), although in general, at slower rates in recent years. HAQ score is high in patients with active disease (149, 150), and it lowers with the improvement of inflammatory synovitis. In addition HAQ is affected by joint damage with a strong correlation, in established RA, between HAQ scores and measures of erosive damage (149). Other factors associated with higher HAQ scores include depression, low socioeconomic status (151, 152) and co-morbidities (153). As the EuroQol is used to evaluate health costs, it is interesting to observe that this index is closely associated with socioeconomic deprivation. An analysis of EuroQol scores in a trial of intensive DMARD treatment by Harrison et al. (155) showed that RA patients who have high levels of deprivation have low EuroQol scores compared to patients with low levels of deprivation. There is also strong evidence that EuroQol scores are worse in RA patients with multiple co-morbidities (156).

Many studies have evaluated utilities to assess QoL in RA patients (18, 84, 85 98). Moreover, utilities have been used in cost-utility analyses comparing pharmacological alternatives (38, 108). A comparison of utilities across studies is extremely complex, due to different clinical and demographic characteristics of RA populations. However these
studies unanimously confirm that RA determines a reduction of mean utility values compared to general population. In their review, Lundkvist et al. (2) report a mean utility of 0.500, a value quite similar to the utility for chronic ischaemic heart diseases and multiple sclerosis (0.558 and 0.555 respectively, for subjects evaluated in the in-patient setting, and worse than conditions such as gastro-esophageal reflux disease (0.671) and non-insulin-dependent diabetes mellitus (0.764). There are limited data about changes in EuroQol with disease duration and most of the prospective data about changes in EuroQol scores focus on the effects of drug treatment. A study of intensive DMARDs treatment in established stable RA by Symmons et al. (157, published in 2005, included in article ref. 79) showed that there were small declines in EuroQol scores over 3 years, with mean changes of 0.03 per year, which is approximately the same as the 1% of maximal score annual worsening in HAQ. Changes of 0.1–0.2 of the EuroQol are considered as clinically relevant. The impact of biologics on EuroQol scores was shown in an observational study carried out in Sweden, indicating larger changes with the first TNF inhibitor compared to second and third inhibitors cycle (scores: 0.45, 0.64, and 0.52 respectively) (154). So far there is relatively little information about changes in EuroQol in trials of biologics.

Cost-effectiveness analyses in RA

The high-cost of new biologic therapies has raised several concerns on their prescribing cost-opportunity. In particular, health-economists have tried to address under which conditions (monotherapy vs. combination with conventional DMARDs, first vs. second line treatment) usage of biologics is sustainable from an economic viewpoint (158), including several systematic reviews to assess cost-effectiveness of different therapeutic strategies of RA, including biologic agents (79, 103, 105). Nevertheless, a clear assessment of cost effectiveness is difficult due to the high variability of methodologies and approaches used. Results vary according to adopted perspective (payer perspective vs. societal perspective), choice of comparators (head-to-head vs. placebo controlled settings), and type of selected patients (e.g. patients with severe or highly active disease vs. remitted patients).

Summarising, the above-mentioned reviews suggest that usage of biologics (mainly TNF antagonists) either in monotherapy or in association with DMARDs, would not be recommended in RA naïve patients, due to high incremental cost-effectiveness ratios vs. alternatives (mainly methotrexate and other traditional DMARDs), along with evidence that similar efficacy with small molecule traditional DMARDs is seen in 50–80% of patients, and higher levels of adverse events are seen with biological agents. Feely et al. (34) confirm these findings, also highlighting the importance of early initiation with conventional DMARDs to improve cost-effectiveness of the intervention. On the other hand, the usage of these new-generation agents (both in monotherapy and in combination with MTX) is cost-effective compared to DMARDs in patients who have failed DMARD treatment or for whom DMARDs treatment is contra-indicated, using a willingness to pay threshold of £50,000 per QALY (105). However in one of these reviews (103), the authors argued that cost-effectiveness results were favourable for biologics due to the choice of drug as second line treatment comparator (in most cases methotrexate, the same agent used in first line treatment), and that more appropriate design should be set up to confirm these findings. Brennan et al. modeled cost-effectiveness of anti-TNFs vs. conventional DMARDs in patients who failed two traditional disease-modifying anti-rheumatic drugs (121). Therapy with anti-TNF was found cost-effective (£23,882/QALY gained for the base case), with 84% probability to be below the accepted threshold of £30,000. The two main issues, early treatment with conventional DMARDs and switch to biologics after (at least one) conventional DMARDs failure, have been simultaneously evaluated by Finckh et al. (113), who compared three different therapeutic strategies: i) “pyramid” strategy with initial nonsteroidal anti-inflammatory drugs, patient education, pain management, and low-dose glucocorticoids, and disease-modifying antirheumatic drugs (DMARDs) at 1 year for non-responders; ii) early DMARD therapy with methotrexate (159); iii) early therapy with biologics and methotrexate. In this study early DMARD treatment was more cost-effective (lower ICER) than early biologic treatment, vs. pyramid strategy, used as reference.

Discussion

As all inflammatory connective tissue diseases, rheumatoid arthritis is a chronic disease with a relevant burden for national healthcare services, healthcare providers, and society in general.

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Fig. 3. Annual HAQ progression in 14 studies published between 2000 and 2010 (adapted from 79).
The definition of appropriate time-frames to adopt biological therapies based on clinical manifestations, on the identification of novel biomarkers as well as economic considerations, would represent, in the next years, the main challenges for health economists involved in decision making support in RA and other rheumatic diseases (163-169).

References

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(4-9, 160, 161). Factors like the high epidemiological impact, the relatively young age at disease onset, the status of chronic-degenerative disease, the high rate of comorbidities and effects on patients’ disability and work productivity, have drawn payers’ attention over the years. The level of attention on this condition has increased with the introduction of new therapies, characterised by much higher costs than conventional DMARDs.

The main findings of our review can be summarised as follows:

- RA is a widespread disease, with an average prevalence rate of almost 0.5–1%, and an overall population of around 6.7 million RA patients in Europe and North America.
- RA impact on patients’ QoL is considerable, with RA patients regularly scoring amongst the groups with lowest utility values. Mean utilities in population samples of RA patients have been estimated at between 0.45 and 0.55. Only multiple sclerosis appears to have a similar effect on QoL among studied diseases. Moreover RA accounts for for 0.8% of all DALYs lost in Europe.
- RA-attributable direct health care costs have been estimated at €14 billion per year in Europe. Productivity loss expenditure for both employers and employees significantly contributes to increase societal costs.
- RA management costs increase with increasing disease severity, in particular with functional disability. In the early years from the introduction of the biological drugs, utilisation patterns rapidly have increased from year to year, and the impact of these drugs compared with traditional DMARDs is considerable.
- Economic evidence suggests that biologic agents generally are cost effective compared to DMARDs for RA in adults in selected populations at a willingness to pay threshold of $50,000 per QALY.

In the future, health-economic research should focus on the evaluation of acquisition costs of biologic agents, and should adapt the results to local health-care settings (162) or designing ad-hoc studies taking into account real practice data.


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