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

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.

Box 1 Search terms and strings

("rheumatoid arthritis"[TIAB]) AND ("cost" OR "economic" OR "cost of illness" OR "burden" [TIAB]) AND ("Humans"[Mesh])

Table I. Search inclusion/exclusion criteria.

Inclusion	Exclusion
Including quantitative assessment	Including qualitative assessment only
Informing about the economic impact of RA	Article non in English
Informing about the economic analysis of RA treatments	Head-to-head drug pharmacoeconomic comparisons
Published from May 2007 until June 2012	Published before May 2007

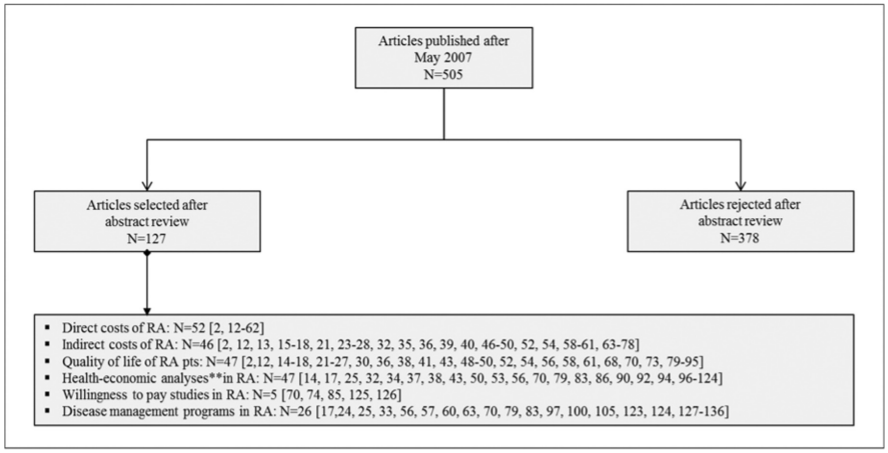

Fig. 1. Strategy search results*.
*The sum of articles by category is not equal to 127 as some categories are not mutually exclusive.
**Includes cost-effectiveness, cost-utility, cost-benefit, cost-minimisation and budget impact analyses.

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.

Results

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 (interquartile 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

Table II. Main findings from studies evaluating direct costs in RA*.

Main Author	Year of publication (Country)	Summary of results	Methodological notes
Lee TJ (12)	2012 (South Korea)	Total annual costs by functional severity: - Class I: 4,230,204 Korean won - Class II: 7,250,674 Korean won - Class III: 8,046,434 Korean won - Class IV: 8,206,215 Korean won	Evaluation of direct medical + non-medical + indirect costs (societal perspective)
Simons WR (13)	2012 (USA)	Per patient annual costs by year: - $4,422: year I - $2,902: year II - $1,882 year III	Evaluation of healthcare direct costs during three consecutive years
McBride S (19)	2011 (USA)	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=$15,048 - Costs in Group 2 were significantly higher than in Group 1	Evaluation of drug costs and total healthcare costs (during first year since anti-TNF initiation)
Metsios GS (21)	2011 (UK)	Significant predictors (p<0.05) of increased number of hospital admissions / increased length of stay: - Disease activity (measured with disease activity score: DAS28) - Physical activity (measured with International Physical Activity Questionnaire)	Evaluation of hospital number of admissions and hospital length of stay (regression analysis)
Zhu TY (26)	2011 (Hong Kong)	Per patient annual costs: - Total costs: US$ 9,286 - Direct costs: 40% of total costs	Longitudinal evaluation (follow-up=10.8 years) of direct + indirect costs
Kirchhoff T (28)	2011 (Germany)	Per patient annual costs: - Total costs (direct + indirect): €4,280 in 1997-98; €3,830 in 2002 (p>0.05 for the difference) - Higher costs in 2002 (vs. 1997-98; p<0.001) for medications and hospitalisations	Evaluation of direct medical + indirect costs (societal perspective) in two different periods: 1997-98 *vs*. 2002
Beresniak A (29)	2011 (France)	Per patient 6-months costs: - Remitted patients (DAS28 ≤ 2.6): €771 - Low disease activity state (DAS28 ≤3.2): €905 - Moderate to high disease activity (DAS28 >3.2): €1,215	Evaluation of 6-months direct costs (excluding drugs), by disease severity (measured with Disease Activity Score 28-joint count)
Maravic M (31)	2011 (France)	Management costs: - Overall impact 2007: €222 million - Per patient impact (2007): range €6,451-19,618	Real-life evaluation of drug costs in RA patients biotherapies (adalimumab, etanercept, infliximab)
Brach M (32)	2011 (Switzerland)	Per patient annual direct costs: - CET: €7,945.34 - SET: €5,619.25	Evaluation of direct costs in two different groups of patients (cognitive-behavioural group therapy, CET, and supportive-experiential group therapy, SET)
Franke LC (35)	2009 (Netherlands)	Per patient annual costs: - RA: €14,906 - Ankylosing spondylitis: €9,374	Comparison of direct medical + family burden + indirect costs (societal perspective) in RA vs. ankylosing spondylitis
Boonen A (36)	2009 (Netherlands)	Qualitative assessment: - RA is associated to higher direct costs than ankylosing spondylitis - Main cost predictor of increased costs: reduced physical activity	Evaluation of direct and indirect cost predictors in RA and ankylosing spondylitis
Saraux A (37)	2010 (France)	Per patient 6 months direct costs: - Patients remitted/ achieving low disease activity: €905 - Patients NOT achieving low disease activity: €1,215	Evaluation of 6-months direct costs, by achievement of remission/or low disease activity
Kobelt G (38)	2009 (Sweden)	Direct + indirect costs over 10-year period: - US$336,000	Modelling the 10-year direct + indirect costs of RA patients receiving biological drugs
Tanaka E (41)	2009 (Japan)	Out-patient healthcare costs: - JPY271,498 in 2000 - JPY292,417 in 2004 - +7.7% increase from 2000 to 2004 - Predictors of increased out-patient costs: aging, longer RA duration, higher Disease Activity Score of 28 Joints (DAS28), and higher Health Assessment Questionnaire (J-HAQ) score	Evaluation of out-patient healthcare costs before introduction of biological therapies (from 2000 to 2004)
Malhan S (42)	2010 (Turkey)	Per patient annual direct costs: - Total direct costs: €2,669.14 - Out-patient costs: €240.40 - Cost for single hospital stay: €87.76 - Costs per medication: €2,238	Evaluation of direct healthcare costs, using reimbursement agencies perspective
Flipon E (44)	2009 (France)	Per patient annual costs: - €5,928 in RA patients - €2,424 in patients with undifferentiated arthritis - Early predictors of increased total costs (p<0.05): higher pain and presence of rheumatoid factor	Evaluation of direct medical + indirect RA attributable costs (2003 data)
Joyce AT (45)	2009 (USA)	Per patient annual direct costs: - RA+CVD patients: US$14,145 - RA+CVD+depression: US$13,513 - RA+depression: US$12,225 - RA alone: US$11,404	Evaluation of direct healthcare costs in patients with RA with or without comorbidities (CVD: comorbid cardiovascular disease, Dep: depression)
Silverman S (46)	2009 (USA)	Per patient annual direct costs: - RA patients: US$10,716 - FM patients: US$10,911 - RA+FM patients: US$19,395	Evaluation of direct healthcare costs in patients with RA, fibromyalgia (FM), or both conditions

Main Author	Year of publication (Country)	Summary of results	Methodological notes
March LM (48)	2008 (Australia)	Qualitative assessment: - Reduction of out-of-pocket costs and service utilisation during the first year after TKR and THR patients	Evaluation of out-of-pocket expenditure (patient's perspective) in RA patients undergoing total knee replacement (TKR) or total hip replacement (THR) surgery
Kobelt G (49)	2008 (France)	Per patient annual costs: - Direct healthcare costs in societal perspective (health insurance + patient): €11,757 - Direct costs in health insurance perspective (€9,216) - Direct non-medical costs in societal perspective (health insurance + patient): €11,757	Evaluation of direct medical + non-medical + indirect costs (societal perspective)
Favalli EG (51)	2008 (Italy)	Per patient annual treatment costs: - Without vial optimisation: €8,454.65 - With vial optimisation (reducing drug wastage): €7,505.85	Evaluation of treatment costs in RA patients receiving a biological therapy (infliximab)
Chermont GC (52)	2008 (Brazil)	Per patient annual costs: - Total costs: US$424.14 - Direct costs: 95% of total costs - Drug costs: 59% of total costs - Indirect costs: 5% of total costs	Evaluation of direct + indirect costs for RA patients and health public service (societal perspective)
Al MJ (53)	2008 (Netherlands)	Per patient 6-months treatment costs: - Celecoxib: €255 - NSAIDs: €166 - NSAID+misoprostol: €285 - NSAID+H(2)RA: €284 - NSAID+PPI: €243 - Arthrotec: €187	Evaluation of treatment costs in RA patients receiving celecoxib, nonsteroidal anti-inflammatory drugs (NSAIDs), alone or in combination with gastro-intestinal drugs (misoprostol, histamine-2 receptor antagonists: H(2)RA; proton pump inhibitors: PPI, Arthrotec)
Khanna R (55)	2007 (USA)	Medical costs covered by Medicare: - $2,379 per year Patients with ≥1 prescription: - Narcotic analgesic: 67.8% - Nonsteroidal anti-inflammatory drugs: 58.8% - Oral steroid: 48.3% - Disease-modifying anti-rheumatic drug: 40.1% - Biologic agent: 12.4%	Evaluation of resources consumption and medical services covered by Medicare in RA US patients
Lundkvist J (2)	2008 (Multi-countries)	Total health costs:- €45.3 billion/year in Europe - €41.6 billion/year in the US	Review of RA cost-of-illness studies measuring direct and/or indirect costs, or evaluating overall economic burden
Juillard-Condat B (59)	2007 (France)	Annual RA costs: - Total costs: €15,148.57 after etanercept initiation - Total costs: €5,248.95 prior to etanercept initiation - Drug costs: €9,995.23 after etanercept initiation - Drug costs: €120.12 prior to etanercept initiation - No difference between indirect costs before and after therapy initiation	Evaluation of direct + indirect costs for RA patients, prior and after treatment initiation with etanercept
Jacobsson LT (61)	2007 (Sweden)	Annual RA costs: - Total costs: €12,020 - Direct costs: 41% of total costs (mainly drugs, community services and hospitalisations	Evaluation of direct + indirect costs for RA patients (2002 data)

*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 disability are significant predictors of increased direct and indirect costs in RA population. 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*.

Main Author	Year of publication (Country)	Lost working days: summary of results	Economic impact of productivity loss:summary of results	Effects on working rate retirement/disability pensions: summary of results	Methodological notes
Simons WR (13)	2012 (USA)	Lost working days attributable to RA: - 4.86 days: year I - 1.70 days: year II - 2.99 days year III	Reduction of annual income: - $2,404: year I - $2,207: year II - $1,212: year III	Rate of employment in RA patients: - 36.8%: year I - 39.5%: year II - 44.0%: year III	Evaluation of working status and productivity loss during three consecutive years
Hallert E (27)	2012 (Sweden)			Rate of disability pensions (DP): - 1990: 1.9% of total DPs - 2000: 1.5% of total DPs - 2009: 1.0% of total DPs	Evaluation of disability pensions attributable to RA over three decades, using the Swedish National Social Insurance Register
Aceves-Avila FJ (63)	2011 (Mexico)	Lost working days (per-month), attributable to medication errors: - 3 days/month			Evaluation of effect medication errors on productivity loss, in rheumatology patients (292 out of 381 had RA)
Langley PC (18)	2011 (China)			Likelihood of workforce participation: - About 8%	National survey evaluating QoL and workforce participation in RA patients
Neovius M (64)	2011 (Sweden)	Annual sick leave and disability pension days: - DMARD monotherapy: 78 days - DMARD combination: 132 days - Biological therapies: 190 days		Rate of disability pensions (DP), before therapy initiation: - DMARD monotherapy: 10% - DMARD combination: 12% - Biological therapies: 43%	Evaluation of sick leave and disability pension rates from national registers, over the period 1999-2007 (RA population stratified by type of therapy)
Neovius M (65)	2011 (Sweden)	Annual sick leave and disability pension days: - 43 days/year: year I from diagnosis - 77 days/year: year II from diagnosis - 147 days/year: year III from diagnosis - 116 days/year: year III from diagnosis			Comparison of progression of sick leave and disability pension rates over time, from national registers, in RA patients diagnosed during the period 1999-2007
Zhu TY (26)	2011 (Hong Kong)		Per patient annual costs: - Total costs: US$ 9,286 - Indirect costs: 60% of total costs	Per patient annual costs: - Total costs: US$ 9,286 - Direct costs: 40% of total costs	Longitudinal evaluation (follow-up=10.8 years) of direct + indirect costs
Kirchhoff T (28)	2011 (Germany)		Per patient annual productivity costs: - €1,480 in 1997-98; €850 in 2002 ($p<0.05$ for the difference)		Evaluation of direct medical + indirect costs (societal perspective) in two different periods: 1997-98 *vs*. 2002
Bowman SJ (69)	2010 (UK)		Per patient annual productivity costs: - pSS patients: £7,677 - RA patients: £10,444 - Community controls: £892		Model estimation of indirect costs in three groups of women: RA patients, primary Sjögren's syndrome (pSS) patients, community controls
Sokka T (70)	2010 (Multi-countries)			Probabilities of continuing to work: - 80% at 2 years - 68% at 5 years	Longitudinal evaluation of probabilities of continuing to work in patients with RA
Franke LC (35)	2009 (Netherlands)		Per patient annual costs: - Total costs in RA: €14,906 - Indirect costs in RA: more than 50% of total costs - Productivity costs higher if human cost approach adopted (vs. friction costs)		Comparison of direct medical + family burden + indirect costs (societal perspective) in RA vs. ankylosing spondylitis
Birnbaum H (72)	2009 (USA)		Per patient annual productivity costs: - Adalimumab: $9,071 - Other RA therapies: $16,335 - Cost for reduced productivity: 57% of total indirect costs - Costs for absenteeism/ disability 21% of total indirect costs - Costs job turnover: 21% of total indirect costs		Model estimation of indirect costs in RA patients receiving adalimumab *vs*. other RA therapies
Hoving JL (73)	2009 (Netherlands)		Per patient weekly productivity gain vs. baseline: - +€169 ($p<0.05$)		Evaluation of productivity in RA patients after a 6-months treatment with TNF inhibitors

Main Author	Year of publication (Country)	Lost working days: summary of results	Economic impact of productivity loss:summary of results	Effects on working rate retirement/disability pensions: summary of results	Methodological notes
Zhang W (66)	2008 (Canada)	Per patient productivity gain vs. baseline: - Absenteeism: -0.5 workdays per 2 weeks - Unpaid work productivity: -3.5 workdays per 2 weeks			Evaluation of productivity in RA patients after a 12-weeks treatment with adalimumab
de Azevedo AB (76)	2008 (Brazil)		Per patient annual indirect costs: - US$ 2,423.51	Impact on working status: - Retired early due to RA: 24.5% - Sick leave due to RA: 32.3%	Evaluation of indirect costs and impact on working status in RA patients
Kobelt G (49)	2008 (France)		Per patient annual indirect costs: - Total costs: €5,076 - Indemnity payments: €1,944	Impact on working status: - Retired early due to RA: 34%	Evaluation of direct medical + non- medical + indirect costs (societal perspective) and working status
Chermont GC (52)	2008 (Brazil)		Per patient annual costs: - Total costs: US$424.14 - Indirect costs: 5% of total costs		Evaluation of direct + indirect costs for RA patients and health public service (societal perspective)
Shanahan EM (78)	2008 (Australia)		Personal annual income: - RA patients: AUS$22,400 - General population: AUS$38,000		Evaluation of annual personal income in RA patients, compared *vs*. general population
Jacobsson LT (61)	2007 (Sweden)		Annual RA costs: - Total costs: €12,020 - Indirect costs: 59% of total costs		Evaluation of direct + indirect costs for RA patients (2002 data)

*Data taken from abstracts of selected articles.

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 US study linked out-of-pocket expenditure to health outcomes, showing that adherence to drug treatment, particularly for expensive drugs, was lower in patients with the highest co-payments or co-insurance (47).

Over the past five years, 45 studies reporting the impact of RA on work loss and work disability have been published. Almost all studies found that productivity loss (*i.e*. absenteeism and presenteeism) in RA determines relevant expenditure for both employers and employees, but work disability rates and associated indirect costs vary across studies. A recent review published in 2011 evaluated 12 cross-sectional and 9 longitudinal studies aimed to measure indirect costs or lost working days (23). One of the studies examined in this review (139) reported that RA patients had an increased risk to lose working days/retire, compared with matched controls (odds ratio; OR: 1.2–3.4). Three longitudinal studies 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-

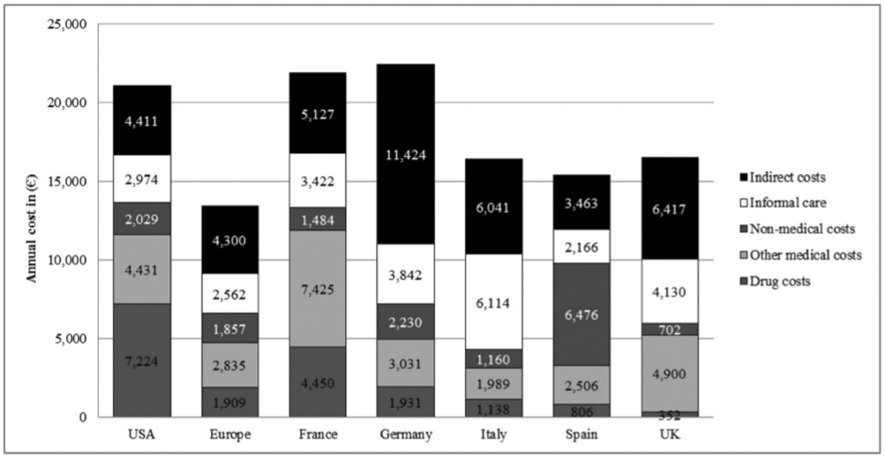

Fig. 2. Distribution of costs from a recent cost-of-illness review (adapted from 2).

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

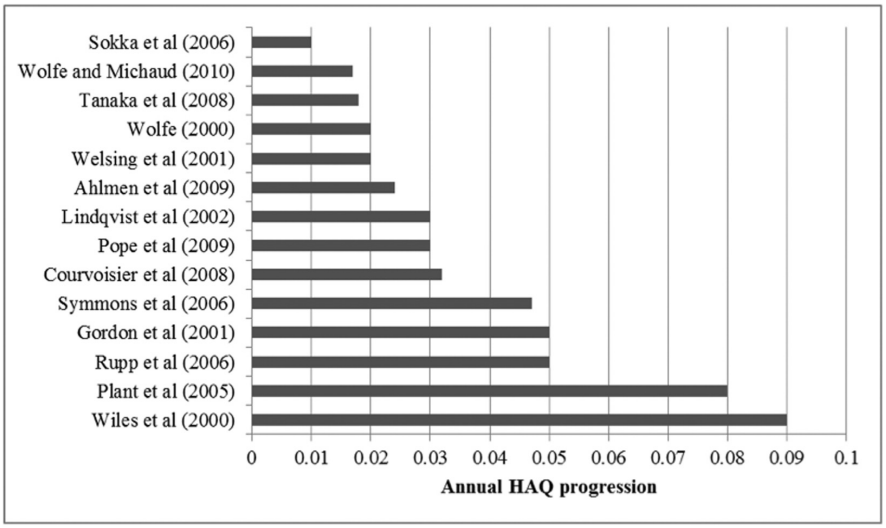

Fig. 3. Annual HAQ progression in 14 studies published between 2000 and 2010 (adapted from 79).

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 view point (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

(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 healthcare settings (162) or designing ad-hoc studies taking into account real practice data.

The definition of appropriate timeframes 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).

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