Cost-of-illness of rheumatoid arthritis and ankylosing spondylitis

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ABSTRACT

Objective. *To assess, quantify and summarise the cost of illness of rheumatoid arthritis (RA) and ankylosing spondylitis (AS) from the societal perspective.*

Methods. *Original studies reporting costs of RA or AS were searched systematically. Both cost-of-illness studies and economic evaluations of therapies were included. Studies were appraised for patient and study characteristics, type of costs and actual costs. Reported costs were aggregated by cost categories and overall mean costs were summarised by cost domain (healthcare, patient and family, and productivity costs).*

Results. *Overall mean costs of RA (€14,906 per year) were above that of AS (€9,374 per year), while the relative distribution of costs over cost domains was approximately similar. For both diseases, productivity costs based on the human cost approach were 3 to 10 times higher than the friction costs and accounted for more than half the total costs of both diseases.*

Conclusion. *Productivity costs constitute the largest part of the total cost-off-illness of RA and AS reflecting the high burden of the disease on work participation. Although total and direct costs of illness in RA were higher than in AS, the average age of AS patients was 10 years lower and therefore, lifetime costs associated with AS may actually be equal or higher.*

Introduction

Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are chronic inflammatory rheumatic diseases characterised by pain, stiffness and functional limitations. These impairments are associated with various socio-economic consequences for patients, their environment and society, such as an increased healthcare utilisation, a need for formal and informal care, and a reduced productivity or ability to work among patients (1-8). Recently, new drug compounds such as agents against tumor necrosis factor antagonists (TNF inhibitors) have been introduced with a strong effect on the inflammation in RA and AS and a clear potential to arrest radiographic damage in RA. However, their use is constrained by high medication costs, being €9,000–18,000 per year per patient (9). The challenging question is whether the costs of these drugs can be offset, at least partially, by savings in the costs-of-illness.

The present study aimed to provide an overview of the economic consequences of RA and AS, based on evidence from literature, and the relative contribution of different cost categories to the total disease costs. This review obtained cost data from bottom up cost-of-illness (COI) studies (*i.e.* based on individual patient data) and intervention studies, such as cost-effectiveness analysis or cost-utility analysis. This resulted in the following research questions: What type of economic consequences, related to RA and/or AS are reported in COI studies or intervention studies? What are the costs related to RA and/or AS and the variation in costs reported in COI studies or intervention studies?

Methodology

The search strategy

Abstracts were retrieved from the databases Medline, Embase and Econlit (EBSCO) through a meta-search in July 2007 using the terms 'Rheumatoid arthritis' or 'Ankylosing spondylitis' in combination with 'cost-of-illness', 'cost effectiveness', 'cost utility' or 'cost analysis' in the title, abstract or key words. Papers without abstracts, non-English papers and abstracts from conference papers were excluded. Two of the authors used the abstracts to independently assess the papers' potential relevance to this review. All authors were involved in this review

process. Reasons to exclude abstracts were: 1) no information on RA or AS; 2) no costs reported in abstract; 3) no primary data reported (literature reviews for example).

Full transcripts were obtained of all abstracts considered potentially relevant to this study by one or both reviewers. Subsequently, one reviewer (LF) assessed the full papers. In case of uncertainty, the opinion of a second reviewer was solicited. Exclusion criteria for full papers were: 1) no primary data reported.; 2) no costs quoted in the results section, no breakdown of costs, or incremental costs of interventions only; 3) health system distinct (non-western countries) or patient population unrepresentative (<30 patients); (4) Top-down approach adopted in COI study (for instance, costs based on health insurance statistics and not on individual patient data). The reference lists of retrieved papers were checked for other relevant studies.

Data handling

Study and patient population characteristics, type of costs, cost rates, and mean costs were obtained using a data extraction form. Costs were categorised using a cost matrix for RA developed by Merkesdal *et al*. (10) as a basis. Main cost domains distinguished in the current extraction form were: healthcare costs, patient and family costs, and productivity costs. Two methods were used to assess productivity costs: the human capital approach (HCA) and the friction cost approach (FCA) (11, 12). As differences between the methods in costs of short-term absence or sick leave tend to be small, we aggregated short-term productivity costs. Substantial differences can be found in productivity costs of long-term sickness, disability to work, and early retirement, and these costs were presented separately for the two approaches.

Extracted costs were annualised and converted to 2006 EU € using the Consumer Price Indices of the relevant countries and the 2006 Purchasing Power Parities between these countries and the EU average (13). Mean costs in tables represented the mean of costs reported by the various studies. Interquartile ranges (IQR) of costs, *i.e*. the 25th and 75th percentile, were also presented. For studies based on RCTs, weighted average costs of the treatments were used, based on the number of patients per treatment. These weighted costs from RCTs were included in the calculation of the overall mean costs.

Results

The search

Six hundred and three (603) titles with abstracts on RA or AS were obtained through the meta-search. 89 studies on RA and 11 on AS fulfilled the abstract inclusion criteria. The assessment of full transcripts resulted in 25 papers on RA and 7 on AS considered suitable for this review. One paper (14) contained cost data on both RA and AS. Inspecting the reference lists of papers resulted in one additional study on RA (15). Another paper on RA (16) was retrieved as it provided additional background data on a study (17) already retrieved. Hence, in total, 26 independent studies presenting original cost data on RA (14, 15, 17-40), and 7 studies on AS (14, 23, 41-45) were included.

Study characteristics

Most published studies on RA and AS in this review were COI studies (Table I). Only seven studies on RA (17, 22, 26, 28, 33-35) and one on AS (41) were conducted within a RCT setting. These were all cost-effectiveness studies, occasionally along with a cost-utility study. Four studies on RA (19, 26, 30, 46), but no studies on AS, reported costs of TNF inhibitors for disease treatment. Most studies considered disease-related costs only and excluded other healthcare expenditures (15, 17, 21, 22, 25, 31, 32, 37, 38). Given the large number of co-morbidities associated with RA and AS, and the difficulty to attribute healthcare expenditures to a

Table I. Characteristics of published studies on the economic consequences of rheumatoid arthritis and ankylosing spondylitis.

	RA	AS
Total number of published studies	26	7
Cost-of-illness studies	19	6
With costs of TNF-inhibitors	3	0
No costs of TNF-inhibitors	16	6
Cost-effectiveness studies	7	1
With costs of TNF-inhibitors	1	0
No costs of TNF-inhibitors	6	1
Disease-related or all healthcare costs		
Disease-related costs	16	6
All healthcare costs	10	1
Patient characteristics		
All patients	19	6
Working population	3	1
Patients with early disease (< 3 years)	4	0
Size of patient population (p)		
$30 < p \leq 200$	9	1
$200 < p \leq 1000$	12	5
$1000 < p \leq 8000$	5	1
Geographical region		
Northern America	9	2
Netherlands	6	1
Germany	4	1
Other EU countries	7	3
Year of publication		
1988 – 1997	2	0
1998 – 2002	6	1
2003 – April 2007	18	6
Time horizon (t)		
$t \leq 6$ months	9	1
6 months $< t \leq 1$ year	10	3
1 year $< t \leq 3$ years	7	3

particular disease, few studies preferred to combine all healthcare expenditures incurred by RA or AS patients (19, 27, 30, 39, 47), or presented both types of expenditures (24, 40). In the latter case, we only used disease-related costs for analyses as this was the most common approach. Most studies included RA or AS patients of all ages over 18 years. The presence of severe co-morbidities or pregnancy was often applied as an exclusion criterion. Some studies on RA included patients of working age only (<65 years) (25, 28, 29) or patients with early RA only (17, 21, 29, 31). The number of patients on which cost assessments were based greatly varied between studies. Two studies on RA (11, 14) included 4351 and 7527 patients. Many studies were conducted in the Netherlands (15, 22, 34, 35, 37, 47), Germany (14, 28, 29, 32), the U.S.A. (38, 40, 48), Canada (11, 18, 26, 27), and fewer in other EU countries (17, 20, 21, 23-25, 39), including Sweden, Belgium, France, Spain and Italy. The number of cost studies of RA has rapidly increased in recent years. All studies in this review on AS were published in 2000 or later. The studies' time horizons (i.e. the time over which costs of RA or AS incurred by patients was measured) varied between 3 months and 3 years. The average age of patients with RA was 57 years, while that of AS patients was 47 years. On average, 76% of RA patients was female, while 69% was male among AS patients.

Table II. Mean healthcare and patient & family costs of rheumatoid arthritis and ankylosing spondylitis, the associated inter-quartile range (IQR), and the number of studies (n) on which the costs were based (€ per patient per year).

	Rheumatoid arthritis			Ankylosing spondylitis		
	n	Mean	0.25 – 0.75 IQR	n	Mean	0.25-0.75 IQR
Healthcare costs	**23**	**4170**	**2756-4561**	**6**	**1992**	**1359-2474**
Outpatient costs	23	2981	1754-3660	6	1400	1114-1419
Visits to physician	22	527	288-718	6	301	236-306
General Practitioner	6	105	53-158	2	38	38-39
Rheumatologist	6	314	158-425	2	158	125-192
Other specialist physician	8	153	46-234	2	156	125-188
Non-physician service utilisation	15	402	106-560	5	428	197-513
Physiotherapist	6	365	165-584	3	307	225-442
Other therapist	4	265	81-411	3	43	34-52
Clinical nurse specialist	3	204	50-283	0		
Social worker / psychologist	2	132	80-184	0		
Emergency room visit	7	133	42-194	1	0	
Medication	23	1567	605-1652	6	628	296-701
NSAIDs	6	287	94-499	1	518	
Steroids	5	48	13-70	0		
DMARDs	7	694	267-953	2	661	367-954
TNF inhibitors	4	3820	2602-4408	0		
Gastro-protection	3	224	85-299	1	87	
Analgesics	4	67	22-87	1	93	
Osteoporosis drugs	1	38		0		
Other medicines	2	253	209-296	1	344	
Diagnostic procedures	18	370	177-474	3	164	128-219
Radiographs	6	256	131-300	2	81	68-95
Other procedures	7	206	37-253	1	92	
Outpatient surgery	13	114	36-139	4	48	18-76
Inpatients costs	22	1243	446-1649	6	592	245-983
Acute hospital facilities	16	1236	431-1519	2	499	372-627
Surgery	6	256	162-239	0		
Non-surgery	5	279	237-404	0		
Non-acute hospital facilities	9	171	58-322	2	204	121-286
Patient and family costs	**19**	**2284**	**628-3092**	**6**	**1104**	**541-1431**
Transportation	8	70	28-102	2	54	38-71
Home care services	13	730	98-984	5	564	257-849
Home remodelling	1	288		0		
Devices and aids	14	446	65-297	3	230	37-332
Non-medical practitioner	7	131	38-220	5	400	32-798
Patient time	1	1614		1	612	
Informal care by friends and family	9	1969	450-2471	1	273	
Other costs	9	907	480-937	1	187	

Costs

Healthcare expenditures of RA were greater than patient and family costs (Table II). Inter-quartile ranges suggested that variation between studies in healthcare costs was less than in patient & family costs. Within healthcare costs, outpatient costs exceeded inpatient costs. An important component of outpatient costs were medication costs. The breakdown of medication costs highlighted the contribution of TNF inhibitors to the total medication costs. Mean costs of TNF inhibitors, reported by four studies (19, 26, 30, 46), were more than double the overall mean expenditure on medication. Inpatient costs were primarily driven by expenditures on acute hospital facilities. Non-acute hospital facilities represented minor costs, as only few patients made use of such facilities. Within patient & family costs, large costs were reported for patient time, informal care by friends and family and home care services. However, the size of these costs greatly depends on the method and cost rates used to estimate the costs. For instance, the value of time varies a lot between studies. Moreover, the cost estimation of patient time was based on one study only. These factors contributed to the wide IQR of patient and family costs of RA, relative to the IQR of total healthcare costs

Healthcare and patient and family costs reported in studies of AS were also substantial (Table II), albeit slightly below those of RA. Main outpatient healthcare expenditures constituted of medication costs, visits to physicians and non-physician service utilisation. Prescriptions of NSAIDs and DMARDs were major contributors to the total medication costs. None of the studies on AS assessed the costs of TNF inhibitors. These medicines could strongly increase the medication and total healthcare costs of AS if prescribed more frequently in the future. Within inpatient costs, expenditures on acute hospital facilities were greater than

Table III. Productivity costs of RA and AS, calculated through the HCA or the FCA: number of studies reporting costs (n), mean costs, and inter-quartile range (IQR) associated with the mean costs (€ per patient per year).

	n	Mean	0.25 – 0.75 IQR
Rheumatoid arthritis (n=16)			
Short-term absence / sick leave	6	2770	855-2378
Work disability / early retirement (HCA)	4	6467	4195-8999
Total productivity costs (HCA)	14	8452	4144-11566
Work disability / early retirement (FCA)	2	865	412-1067
Total productivity costs (FCA)	4	1441	702-1307
Ankylosing spondylitis (n=6)			
Short-term absence / sick leave	4	913	388-1079
Work disability / early retirement (HCA)	4	5657	4777-7271
Total productivity costs (HCA)	5	6278	5111-7725
Work disability / early retirement (FCA)	2	884	706-1062
Total productivity costs (FCA)	2	2271	1572-2970

costs of non-acute hospital facilities. Within patient and family costs, large costs were recorded for home care services, alternative therapies, and devices and aids. While patient time also represented high costs, these were measured by one study only.

Work disability/early retirement costs and total productivity costs calculated with the HCA were 3 to 10 times higher than the friction costs (Table III), which is in line with results from literature (12). Most studies on RA used the HCA only to assess total productivity costs (11, 14, 17, 18, 20, 21, 24, 25, 28, 29, 31-33, 46, 47). Three studies also evaluated the friction costs (11, 14, 47), while one study presented friction costs only (28). The distribution of costs of short-term absence/sick leave of RA was skewed due to one study presenting very high annual costs of short-term absence/sick leave (€8,452 patient^{-1} y^{-1}) (29). This study assessed productivity costs of patients with early RA, which usually have high costs for short-term absence and low costs for work disability/early retirement. Excluding this study gave a mean cost for short-term absence/sick leave of €1,352 patient^{-1} y^{-1}. A large variability was also observed in total productivity costs. An upper value was retrieved from a Swedish study estimating the total productivity costs of RA at €23,690 patient^{-1} y^{-1} (21). A study from Spain presented total productivity costs of €629 patient^{-1} y^{-1} (24). Both studies used the HCA and this difference was primarily the result of variation in assumed wages to value time absent from work. Five studies on AS assessed the overall productivity costs using the HCA (14, 23, 42, 44, 45). One study applied both the HCA and the FCA (14), while another study used the FCA only (41). Total productivity costs of AS were slightly below those of RA.

Mean total cost (the sum of the total healthcare, patient and family and productivity costs (HCA) in Tables II & III) was €14,906 per patient per year for RA and €9,374 per patient per year for AS. Productivity costs (HCA) accounted for 57% of the total costs of RA and for 66% of the total costs of AS. This large share of productivity costs in the total costs reflected the high burden of both diseases on work participation.

Discussion

While annual societal costs per patient were higher for RA for almost all cost categories than for AS, the average age of onset of AS is about 15 years earlier than of RA patients, suggesting the lifetime costs of AS may well be equal or higher than that of RA. As yet, no study has looked at this issue. Notwithstanding, this is relevant when assessing the long-term costs-effectiveness of interventions. Medication costs were the major contributors to the total healthcare costs of RA and AS. Productivity costs had a very large share in the total costs of both diseases, but varied on the methodology and cost rates applied.

This review has clear limitations. Studies fulfilling the inclusion criteria were not rated on methodological qualities, and consequently studies with different methodological designs were treated equally. This approach was chosen given the difficulty to define objective criteria for rating methodological qualities of cost studies. In addition, the large number of studies available on RA (26) implied that describing each study in sufficient detail to explain variation in costs between studies would go beyond the study's scope. Notwithstanding, when different costing methodologies had a large impact on the cost estimates (*e.g.* different approaches used to assess productivity costs), this was highlighted. Fewer studies on costs of AS were retrieved. Here, a more narrative approach and a more detailed assessment of the differences in costs would have been feasible (51). Our approach was supported by the fairly narrow inter-quartile ranges of mean costs, especially of healthcare costs, suggesting that mean costs of RA and AS among large groups of patients was reasonably stable, irrespective of the methodology followed to collect or present data. The variation in costs between patients within studies was often larger.

The expected rise in the use of TNF inhibitors for RA and AS treatment in the near future is likely to result in a strong increase in medication costs as already shown by several studies (9, 50, 51). On the long term, however, treatment with TNF inhibitors will reduce functional disabilities caused by RA or AS, which in turn can result in reduced productivity costs. However, the link between better treatment effects and reduction of the long-term productivity costs has not been well established. Therefore, future research on the economic consequences of RA and AS should focus on assessing the long-term productivity costs of the diseases, particularly in relation to the clinical and economic impact of medicine treatments.

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Key messages

1. Productivity costs constitute the largest part of the total cost-off-illness of RA and AS.
2. Overall mean patients costs of RA (€14,906 per year) were above that of AS (€9,374 per year).
3. The lifetime costs of AS, compared to RA, may however be equal or higher due to the earlier onset of AS.

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