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

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ABSTRACT

The introduction of anti tumour necrosis factors-α (TNF-α) agents has greatly advanced the management of psoriatic arthritis (PsA). Functional disability in patients with PsA may result in significant impairment of Quality of Life (QoL), psychosocial disability and productivity loss. Although many patients respond adequately to methotrexate and other therapies, in patients who have incomplete responses, anti TNF-α agents reduce inflammation and minimise joints damage, increasing functional capacity and QoL, and decreasing the progression rate of structural damage in peripheral joints. Because of the high costs associated to anti TNF-α agents therapy, an increasing number of economic evaluations have been performed over the last few years, and several cost-of-illness and cost-effectiveness studies have been published concerning use of anti TNF-α agents in management of PsA. We performed a systematic literature review to better understand the pharmacoeconomic perspective of PsA. The pharmacoeconomic studies analysed have demonstrated the high socioeconomic burden of PsA and that TNF-α blockers treatment options provide value for money in the musculoskeletal and cutaneous manifestations of psoriatic disease.

Introduction

Psoriatic arthritis (PsA) is a heterogeneous chronic, progressive, inflammatory arthropathy of the peripheral joints, peripheral entheses, synovial sheaths of tendons, and spine associated with psoriasis of the skin or nails (1, 2). PsA has a variable presentation and course (3). Patients with PsA may also experience eye and gastrointestinal involvement (4, 5). In addition, patients with PsA or psoriasis have a higher rate of metabolic syndrome, obesity, hypertension, hyperlipidemia, cardiovascular diseases, type 2 diabetes and insulin resistance than the general population (6).

PsA was considered a rare and mild disease until the past few decades. Around 30% of patients affected by psoriasis have musculoskeletal manifestations (1, 7). However, the prevalence of PsA is still difficult to estimate (1, 8).

Over the past 2 decades, evidence has accumulated that PsA is: 1) erosive and deforming in 40% to 60% of patients with joint damage emerging in the first year of the disease onset and 2) a severe disease in at least 20% of patients with progression of joint damage (9-12).

Functional disability in PsA may lead to significant impairment of Quality of Life (QoL), psychosocial disability and productivity loss (1, 13-15), as in other rheumatic diseases. PsA also is associated with increased mortality rates compared with general population (16).

Therapies for PsA have been inadequate in many patients until few years ago. Non-steroidal anti-inflammatory drugs are helpful in relieving pain symptoms, but have little or no effect on slowing radiographic joint damage. Local corticosteroid injections provide useful support for mono- and oligoarthritis, while the use of systemic low-dose glucocorticoid treatment may be helpful, though, as in other rheumatic diseases, not supported by randomised clinical trial data (17). Methotrexate (and sometimes other disease-modifying anti-rheumatic drugs (DMARDs), the second-line treatment in PsA management, control symptoms in many patients, but do not control symptoms or slow radiographic progression in some patients (18), though rigorous estimates are not widely available.

Anti tumour necrosis factors-α (TNF-α) agents provide an important new treatment option for management of PsA (19). Anti TNF-α greatly reduce

inflammation and slow radiographic joint damage, increasing functional capacity and QoL (20-23).

On the other hand, anti TNF-α are very costly, and long term use is required, as discontinuation often results in a disease flare. Further, the use of these agents can lead to serious infections, however this is balanced by reduced joint replacement and productivity losses (24-26).

The high costs associated to anti TNF-α agents, as seen with introduction of medical devices and major technologies in health care (27-30), has stimulated an increasing number of economic evaluations in recent years. Several cost-of-illness and cost-effectiveness studies concerning anti TNF-α in in PsA have been reported, as examined in this review.

Methods

Search strategy

In June 2012, we searched the literature for articles with an English language abstract on PsA costs and cost-effectiveness using the MEDLINE (PubMed) database. We limited our search to articles published between February 2009 and May 2012 to update a previous review on PsA costs and cost-effectiveness by Olivieri and colleagues (2). We chose to update the review of Olivieri *et al*. because it focuses on the same objective and reports the same type of articles that are included in our review. Terms included in Medline (PubMed) search were: "cost AND psoriasis arthritis"; "cost-effective AND psoriasis arthritis"; "cost-utility AND psoriasis arthritis"; "economic analysis AND psoriasis arthritis"; "economic evaluation AND psoriasis arthritis"; "Cost of illness AND psoriatic arthritis" and "burden AND psoriatic arthritis".

After this first step, we conducted a manual research on the references of all articles found with the PubMed research.

Inclusion criteria

To be included in the review, articles were required to report 1) information concerning PsA costs and/or data on effectiveness and costs of anti TNF-α treatment in PsA patients and 2) abstract was required to be in English.

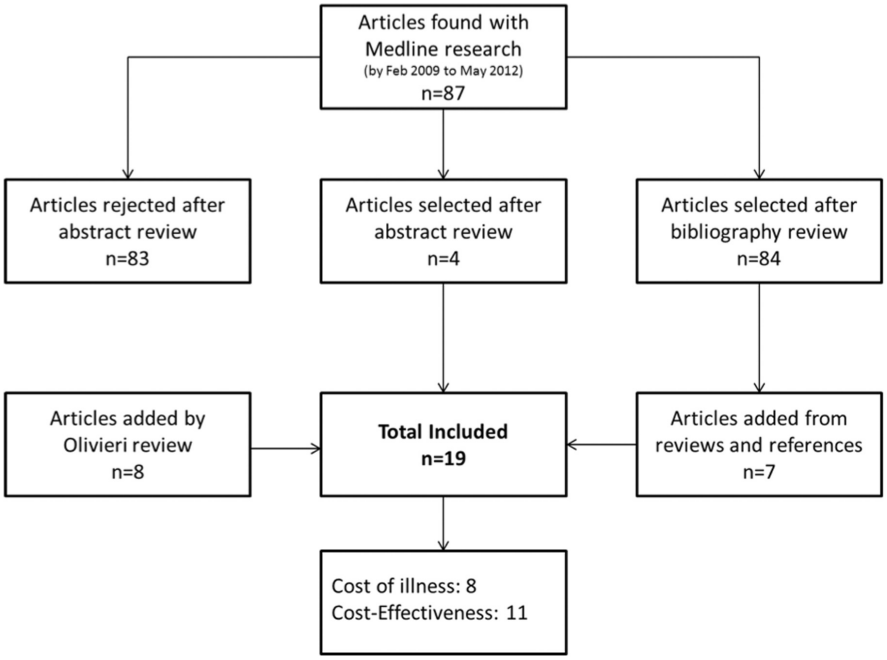

Fig. 1. Flow chart of study selection.

Results

Studied identified

We identified 87 articles from the PubMed search. Eighty-four articles were added from the manually research of the references reported in the 87 articles identified. A total of 171 abstracts were reviewed, of which 160 were excluded because they did not meet inclusion criteria. Therefore, 11 full-text articles met the inclusion criteria, and were reviewed. Further, all 8 studies reported in the Olivieri and colleagues' review (2) were included in this review (Fig. 1). In the end, 8 Cost of Illness and 11 Cost Effectiveness studies were selected. Only one study was included in both categories.

Cost of illness in psoriatic arthritis

Eight published analyses quantify the economic burden of PsA were considered valid for our review (Table I) (13, 26, 31-36). Most of the studies in these reports identified direct (hospitalisations, out-patient and physician office visits, prescription and over the counter-OTC medication, medical procedures, etc.) and indirect costs (loss of productivity, etc.) (13, 26, 32, 34-36). Two studies were identified that assessed only direct costs of disease (31, 33).

Patients with PsA are significant users of health care resources all over the world. In a 2002 study conducted in the USA, Javitz *et al*. estimated the direct costs of care for psoriasis and PsA among adults (31). The annual cost of illness for the 1.4 million patients with clinically significant disease, selected from publicly available health databases (the Health and Nutrition Examination Survey, National Hospital Discharge, Medicare Public Use Files, National Ambulatory Medical Survey and the National Hospital Ambulatory Medical Care Survey), was $US 649.8 million ($US 86.8 million for out-patient medical visits, $US 27.4 million for photochemotherapy, $US 147.9 million for dermatologic prescription drugs, $US 30.5 million for hospitalisations, $US 357.2 million for OTC medications).

In 2006, Huscher *et al*. compared direct and indirect costs of illness in several rheumatic diseases in Germany. Average annual costs for PsA were 3.156€ per patient (32), lower for these patients than for patients with rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis. The total annual costs increased to €11.075 when indirect costs were considered and assessed using the Human Capital Approach, whereas the annual costs increased only to €5.570 when indirect costs were assessed using the Frictional Cost Approach. The authors concluded

Table I. Cost-of-illness studies of PsA.

References	Data provided	Population characteristics	Results
Javitz *et al*. (2002 (31))	Direct medical costs (hospitalisations, out-patient and physician office visits, out-patient and office procedures, prescription medications, and over-the-counter medications) from the societal perspective.	n=1.4 million with psoriasis or PsA, adult patients	Total direct costs of illness: $649.6 million. A much greater percentage is represented by the dermatologic prescription drugs: $147.9 million (23%) over-the-counter medications: $357.2 million (55%). Total annual costs were in the order of $452 per person with clinically significant psoriasis or nearly $718 per person with clinically significant and active psoriasis.
Huscher *et al*. (2006 (32))	Direct (data of out-patients) and indirect costs from the societal perspective.	n=908 patients with PsA, aged18–65	Mean annual costs in PsA were: Direct cost: 3.156 €/patient-year Indirect cost(HCA): 11.075 €/patient-year Indirect cost(FCA): 5.570 €/patient-year
Olivieri *et al*. (2008 (26))	Direct (in-patient and out-patient) and indirect costs from the national health system and societal perspective.	n=107 patients with different forms of PsA and inadequate DMARDs' response, undergoing TNF-α antagonists treatment, age older than 18	With the societal prospective, the total cost in the 6 months before the beginning of the study was 1519.17€ per patient: 41.5% attributable to cost of drugs. The mean overall direct and indirect costs were €942.87 and €576.30, respectively. In the last 6 months of therapy, the direct cost increased by €5052.
Brodszky *et al*. (2009 (13))	Direct medical (cost of hospital admissions, including surgery and out-patient) and non-medical costs as well as production losses from the societal perspective.	n=183 patients with PsA, aged older than 18 years	The annual average total costs per patient were 5.574 €/patient-year: direct costs 2.670€ and indirect costs 2.904 €.
Barra L *et al*. (2009 (33))	Direct costs (out-patient) from a societal perspective.	n= 57 patients with PsA on 297 enrolled in the study, adult patients	The average of total annual direct cost to achieve minimal clinically important difference (MCID) for PsA were: 39.937 $ in the first year 50.535 $ in the second year 39.121 $ in the third year
Zhu TY *et al*. (2010 (34))	Direct (in-patient and out-patient) and indirect costs from the societal perspective.	n=125 patients with peripheral and axial PsA, adult patients	The estimated average annual direct costs were $4.141 per patient. Costs of in-patient care accounted for the largest component of direct costs (27%), followed by costs of visits to healthcare providers (25%). The average indirect costs were $ 5.321 per patient-year.
Poole CD *et al*. (2010 (35))	Direct (hospital in-patient care and out-patient) and indirect costs from the societal perspective.	n= 356 patients with PsA were identified in the British Society of Rheumatology Biologics Register (BSRBR) and 4492 in The Health Improvement Network (THIN), adult patients	The total annual health care costs ranged from £ 11 to £ 20.782 with a mean of £ 1.446 per person.
Kvamme MK *et al*. (2012 (36))	Direct out-patient and in-patient and indirect costs from the societal perspective	n=374 patients with PsA treated with DMARDs, adult patients	Total 2-year costs for patient with PsA were: 64.500 € with synthetic treatment and on biologic treatment 111.200 € with biologic treatment.

that the costs were higher in patients with greater functional disability and disease duration.

In Italy, Olivieri *et al*. estimated the cost of illness per patient with PsA who experienced an incomplete (or inadequate) response to the traditional therapy (26). In the 6 months before the start of anti TNF-α treatment, the total cost (direct and indirect) was €1.519,17 per patient, amounted to €3.038 per patient-year, a lower value compared to the total cost estimated by Huscher *et al*. in Germany. In Olivieri's study, after 12 months of anti TNF-α therapy, there was an increase of €5,052.34 of direct costs due to the cost of anti TNF-α agents, which was only partially compensated by the reduction of €413.34 of indirect costs (26).

More recent studies confirmed that indirect costs are an important component of the total costs for PsA patients. Indeed, in the study by Brodszky *et al*., the annual average total cost per patient was €5.574 per year: direct costs €2.670 and indirect costs €2.904 (48% and 52%, respectively) (13). In this study, the direct costs were probably underestimated because patients receiving biologic therapy were excluded from the analysis. Once again, both direct and indirect costs of PsA increased in patients with poorer physical function and higher disease activity, similar to findings by Huscher *et al*. (32).

As noted above, anti TNF-α therapy has provided important new treatment options for inflammatory arthritis which are quite expensive. Therefore, studies have examined whether additional costs incurred in patients taking anti TNF-α drugs are offset by reduction of joint replacement and work loss (26, 31).

In 2009, Barra *et al*. conducted a study in which they considered only direct costs in patients with PsA. In this study, the annual direct costs per patient with PsA were: 21.243 $US during the first year, 21.688 $US during the second, and 21.613 $US during the third (33). They concluded that anti TNF-α medications are very costly, approximately 20.000 $US per year.

Zhu *et al*. confirmed that the socioeconomic burden of PsA is considerable (34). Anti TNF-α agents which are substantially more expensive than traditional medications, have the capacity to reduce indirect costs and some direct costs by reducing disease activity and improving function and QOL. The average annual direct and indirect costs were $US 4.141 and $US 3.127, respectively. Also Poole *et al*. underline the high economic burden of PsA (35). The average annual health care costs associated with PsA in UK was estimated to be £1.444 per person. Prescription costs and secondary care episodes each accounted for more than one third of total care costs. The study suggests that the economic burden associated with PsA may be more important compared with other inflammatory disorders (rheumatoid arthritis), perhaps attributable to differences in methods. However, this conclusion is not in agreement with results of other studies in Germany (32) and Hungary (13), where health care costs for PsA were found to be lower than the costs associated with rheumatoid arthritis using a similar methodology.

As reported in the previous studies included in our review, treatment of people with PsA resulted in considerable financial costs which varied markedly by disease severity. A decision model developed by Kvamme *et al*. (36) estimated the total cost for patients with PsA treated with DMARDs. Total 2 year costs were similar across diagnoses for patients treated with synthetic treatment (€64.500), but almost double in patients treated with biologic agents (€111.200).

Cost-effectiveness of anti TNF-α Treatment

Eleven studies have been published concerning cost-effectiveness analysis of anti TNF-α agents in PsA (26, 37-46). Ten were decision models (36-45), based on anti TNF-α randomised controlled trials (RCTs) data (20, 47-53), and all the cost-effectiveness analysis used Quality Adjusted Life Years (QALY) as a measure of effectiveness. Most studies were conducted to perform indirect comparison between different anti TNF-α agents, using in many cases "palliative care" as comparator (37-42, 44, 45). As the aim of our review was to perform an assessment of therapeutic classes and not active agents individually, results of these comparisons between different anti TNF-α biological are not reported in detail. However, these studies showed an absolute values of effectiveness (utility) and costs similar to those observed in the studies comparing anti–TNF-α drugs with other pharmacological classes.

Of the 11 eleven studies identified, 3 performed a comparison between anti TNF-α and other therapeutic options (26, 43, 46), summarised in Table II.

Bansback *et al*. (43) estimated potential longstanding benefits on health status of a TNF-α antagonist compared to conventional DMARDs. In this study, the British Society for Rheumatology guidelines were used to identified the patients who responded inadequately to conventional DMARDs therapy over a time horizon of 10 years. The model generated a cost per QALY gained for TNF-α antagonist approximately between €28.000 and €38.000 in comparison with DMARDs therapy (43).

Olivieri *et al*. (26) evaluated cost-effectiveness of the anti TNF-α class in patients with PsA who experienced incomplete (or inadequate) responses to traditional therapy. Time horizon used was 1 year. At the end of the follow-up, an increase of direct costs due to anti TNF-α agents was balanced partially by a decrease in indirect costs. The authors stated that, in the last 6 months of the follow-up, the direct cost increased by €5,044 from Italian NHS point of view and by €4,638 in term of social cost. A gain of 0.12 QALY, assessed with the EQ-5D, produced an Incremental Cost-Effectiveness Ratio (ICER) of €40,876 and €37.591 per QALY, for the Italian NHS and the society respectively. Moreover the authors declared a utility value affected by disease activity and functional disability status which was more severe than traditionally recognised, due to the negative effect of psoriasis on patients' health related quality of life.

Sizto *et al*. (46) analysed cost-effectiveness and optimal treatment sequence for moderate to severe psoriasis considering short and long term efficacy and costs using data available. The PASI response rates from 22 randomised controlled trials of anti TNF-α and non-biologic agents with European regulatory approval were considered. Short-term efficacy was based on relative probabilities of each treatment to achieve PASI response (50 /75 /90), obtained through a meta-analysis of trial results. Treatment benefits were determined by the relationship between PASI response and the EQ-5D health utility measure. ICERs were calculated and treatments ranked relative to supportive care. Biological treatment provided the most incremental QALYs, and non-biologic systemic agents were less beneficial but cost saving. Non-biologic systemic agents were considered the first treatments in the optimal sequence. However, this model does not account for adverse events, because of a lack of data concerning long-term safety. Biologic agents were indicated when conventional systemic treatment was inadequate or patients experienced adverse events with conventional treatment.

Conclusion

PsA incurs a high socioeconomic burden, similar to other rheumatologic diseases (58-64). Cost-effectiveness studies of TNF-α inhibitors have demonstrated that these drugs are cost-effective on both the musculoskeletal and cutaneous manifestations of psoriatic disease, offering good value for money.

Table II. Summary of Cost-Effectiveness Analyses.

References	Study design	Population characteristics	Intervention/drugs compared	Results: ICER (Cost/QALY)
Bansback *et al*. (2006 (43))	Model comparing: an anti TNF-α drug to a combination of DMARDs therapy. Time horizon: 10 years.	Study population was based on data coming from randomised controlled trials and from a local cohort of patients. (20, 54)	Anti TNF-α agents and DMARDs.	Anti TNF-α *vs*. DMARDs £37,066 Anti TNF-α *vs*. DMARDs £28,189 Authors stated that benefits in term of health status of the TNF-α Antagonist are greater than conventional DMARDs.
Olivieri *et al*. (2008 (26))	Cost of care analysis, conducted from societal perspective. Time horizon: 1 year.	107 patients with different forms of PsA and inadequate response to conventional treatment.	Anti TNF-α agents and DMARDs.	Anti TNF-α *vs*. DMARDs (Considering only the Direct cost): €40,942.78 Anti TNF-α *vs*. DMARDs (Considering the NHS point of view): €40,876.90 Anti TNF-α *vs*. DMARDs (Considering Society's point of view): € 37,591.01 The cost–effectiveness acceptability curve suggested that if decision makers' willingness to pay per QALY was €45 000, then anti-TNF treatment would be cost effective in 82% of the cases. Moreover, it would be increased to 97% if the threshold for willingness to pay was raised to €60 000.
Sizto *et al*. (2009 (46))	Model comparing: anti TNF-α drug to non-biologic systemic therapy. Time horizon: the model considered both assessment period (time used to assess if treatment works) and the treatment period (pertaining to patients in whom treatment work).	Patients with moderate to severe psoriasis, who followed a clinical pathway in accordance with guidelines in the U.K. (55-57)	Anti TNF-α agents, non-biologic systemic therapy.	ICERs compared with supportive care were calculated. Anti TNF-α provided the most incremental QALYs, on the other hand non-biologic systemic agents were less beneficial but cost saving. Authors stated that in the optimal treatment sequence non-biologic agents were considered the first treatments option. However, this model does not account for adverse events, because of a lack of evidence on long-term safety.

Anti-TNF-α drugs, which are considerably more expensive than conventional drugs, reduce disease activity and improve QoL and, therefore, appear to reduce overall costs, with greater direct costs of drugs offset by reduced indirect costs due to PsA.

Future studies based on long-term outcomes of usual clinical care, independent of influence of pharmaceutical companies, are needed to clarify cost effectiveness of anti-TNF-α agents in PsA.

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