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The psoriatic arthritis cost evaluation study: a cost-of-illness study on tumour necrosis factor inhibitors in psoriatic arthritis patients with inadequate response to conventional therapy

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Objective. To evaluate costs, benefits and cost–effectiveness of anti-TNF agents in PsA patients with inadequate response to conventional treatment.

Methods. A total of 107 patients, from nine Italian rheumatology centres, with different forms of PsA were given anti-TNF treatment, mainly etanercept (87%). Information on resource use, health-related quality of life, disease activity, function and laboratory values were collected at baseline and through out the 12 months of therapy. Cost (expressed in euro 2007) and utility (measured by EuroQol) before and after anti-TNF therapy initiation were compared in order to estimate the incremental cost per quality-adjusted life year (QALY) gained, and cost–effectiveness acceptability curve was calculated.

Results. At the end of 12 months, there was a significant increase in direct cost due to an increase of drug cost caused by TNF inhibitors that was only partially offset by the decrease in indirect cost. In the last 6 months of therapy, the direct cost increased by €5052, the cost for the National Health System (NHS) by €5044 and the social cost by €4638. However, a gain of 0.12 QALY resulted in a cost per QALY gained of €40 876 for the NHS and of €37 591 for the society. The acceptability curve showed that there would be a 97% likelihood that anti-TNF therapy would be considered cost-effective at willingness-to-pay threshold of €60 000 per QALY gained.

Conclusion. Cost–effectiveness ratios are within the commonly accepted willingness-to-pay threshold. These results need to be confirmed in larger samples of patients.

Key words: Psoriatic arthritis, Anti-tumour necrosis factor, Cost–effectiveness, Quality-adjusted life year.

Introduction

PsA is an inflammatory arthropathy associated with psoriasis. It may affect the peripheral joints as well as the axial skeleton and the peripheral entheses and is classified among the SpAs. In the past, PsA was considered a rare and mild disease. Actually, 0.5–1% of the population may suffer from PsA since psoriasis affects about 2–3% of the general population and PsA occurs in one-third of the psoriatic patients [1, 2]. A frequency of 36% was found in an Italian dermatological series of consecutive and unselected patients with psoriasis [3]. In the last 20 yrs, evidence has been accumulated that PsA is erosive and deforming in 40–60% of the patients with joint damage appearing in the first year of disease onset [4–7]. It is estimated that almost 20% of the PsA patients develop a severe destructive disease [4–7]. Patients with PsA suffer from reduced quality of life (QoL) and impairment of functional status and are at greater risk of death compared with the general population [7–9]. Therapies for PsA have been unsatisfactory until some years ago [10]. NSAIDs are useful in relieving symptoms but have no effect on joint damage. Local corticosteroid injections may be of great benefit in patients with mono- or oligoarthritis but the use of systemic corticosteroids is not supported by any evidence. Traditional DMARDs are used in PsA to control the symptomatic manifestations but there is no evidence that they prevent or significantly decrease the progression rate of structural joint damage. The anti-TNF agents (etanercept, infliximab and adalimumab) have opened new horizons. These drugs reduce signs and symptoms of inflammation, improve QolL and functional status and inhibit the progression of structural damage in peripheral joints [11–13]. Axial disease was not assessed in these studies. However, TNF blockers are effective in primary AS in controlling symptoms and preventing the progression of the structural damage in the spine [14]. These results can plausibly be extrapolated to psoriatic spondylitis.

TNF inhibitors are very expensive and not easily available to all patients, either depending on a national health system or on private insurance. Illness costs in PsA were found high even without these drugs and not much more different from those in RA, SLE and AS [15]. Costs are also high for patients with psoriasis alone [16]. Two strategies have been adopted to be able to treat all PsA patients who may need anti-TNF agents. On the one hand, evidence-based guidelines for their use have been developed [10, 17]. On the other hand, pharmacoeconomic studies have been promoted with the aim of demonstrating their cost–effectiveness [18–21]. To date cost–effectiveness studies on TNF antagonists in PsA have only been performed using data from published international studies [19–21].

We have designed a cost evaluation study on PsA patients with inadequate response to traditional DMARDs to be treated with TNF blockers in clinical practice. The objective of the study was to evaluate costs, benefits and cost–effectiveness of the class of TNF inhibitors over 1 yr of follow-up.

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Methods

Techniques

To reach the objectives of the study, we conducted a cost-of-care analysis, a technique used to evaluate the economic burden of a disease [22]. Health-related Qol (HRQoL) or health state utility was also evaluated. Cost and utility before and after anti-TNF therapy initiation were then compared in order to estimate an incremental cost–effectiveness ratio (cost per QALY gained). As the measurement of costs depends on the point of view adopted for the analysis (e.g. a hospital admission may represent a cost to the National Health Service (NHS) or to an insurance company but not to the patient), the study was carried out from the point of view of the community, the largest entity that can have a point of view, and which included the Italian third-party payer (NHS), patients and their families.

Study cohort

Patients were consecutively enrolled during 2005 in nine Italian tertiary referral centres after obtaining their informed consent. Patients had to satisfy the following inclusion criteria: age older than 18 yrs, established diagnosis of PsA and failure or intolerance of conventional therapy.

Patients with predominant or exclusively peripheral arthritis had not to have responded to adequate therapeutic trials of at least two NSAIDs for at least 3 months (unless contraindicated or not tolerated), to at least two steroid injections (in cases of mono- or oligoarthritis) as well as to adequate therapeutic trials of at least one of the DMARDs most commonly used in PsA (MTX, cyclosporin, SSZ and LEF). Patients also had to have at least one swollen joint plus at least two of the following: patient global assessment $\geq$40 mm on a 100 mm visual analogue scale (VAS), $\geq$3 tender joints and ESR $\geq$28 mm/1st h or CRP $\geq$15 mg/l.

Patients with predominant or exclusively axial disease had to have met the modified New York criteria [23] for the diagnosis of AS, had to have active disease for $\geq$4 weeks with a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [24] $\geq$4 and had to have failed adequate trials of at least two NSAIDs for at least 3 months, unless contraindicated or not tolerated, in accordance with the ASAS (Assessment in Ankylosing Spondylitis) working group recommendations for the use of anti-TNF agents in patients with AS [25].

Patients with exclusive peripheral enthesitis or with exclusive dactylitis had not to have responded to adequate therapeutic trials of at least two NSAIDs for at least 3 months (unless contraindicated or not tolerated) and to at least two local corticosteroid injections. They also had to have a patient global assessment $\geq$40 mm on a 100 mm VAS and tender enthesitis of $\geq$2 on a 0–4 Likert scale.

The subjects's written consent was obtained according to the declaration of Helsinki and the protocol was approved by the institutional review boards of the participating centres. The study was monitored by a contract research organization and was sponsored by Wyeth Italy through an unrestricted research grant.

Observation period

Patients enrolled were studied globally for 18 months. They were asked to provide information on resource use and HRQoL in the preceding 6 months. In accordance with Gringeri *et al.* [26], 6 months seem to be a reasonable time period for a retrospective study on patients affected by chronic intensively treated disease such as PsA. We do not expect recall bias might impact our cost estimates since most of the information were collected from medical records.

Data collection. To evaluate the cost of care and the HRQoL, patients were interviewed by means of a specially designed structured electronic case report form (CRF; available on request from author), which was administered to them by a physician at each participating centre and filled in by the physician to make sure that data were of high quality.

At the time of the enrolment visit, information was obtained on demographic characteristics (date of birth, sex), clinical characteristics (year from diagnosis of PsA, concomitant diseases, allergies, complete physical examination including height and weight, vital signs as pulse rate and blood pressure), surgical procedures, physicians' visits, hospitalizations, number of working days lost by patients due to PsA, caregiver time (number of days lost) devoted to patients' assistance and, in general, all events leading to resource absorption of health care and non-health care resources during the 6 months before enrolment. This information was also collected prospectively during the follow-up period at 6 and 12 months.

Clinical data recorded at enrolment and during the follow-up visits included laboratory parameters (blood cell count, transaminases, creatininaemia, ESR mm/1st h, CRP mg/litre and RF), 68/66 tender/swollen joint count [27], number of digits with dactylitis, Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) [28], BASDAI [24], Bath Ankylosing Spondylitis Functional Index (BASFI) [29], occiput-to-wall distance, chest expansion, modified Schober's test [30], physician's and patient's global assessments of pain and overall disease activity (0–10 cm VAS), duration of morning stiffness, Psoriasis Area and Severity Index (PASI) [31], HAQ [32], EuroQol (EQ-5D) [33, 34] and Medical Outcome Survey Short Form-36 (SF-36) [35, 36]. At inclusion, data on previous and current treatment with DMARDs, analgesics, NSAIDs and corticosteroids were recorded. During follow-up, any modifications of these drugs and of anti TNF-α treatment were registered.

Cost-of-care analysis

Costs were quantified considering the societal perspective. Consistently, health care resources absorbed were quantified into monetary terms in the perspective of the third-party payer, the NHS, which in Italy is in charge of financing and providing health care services to patients with PsA. Direct medical costs financed by the NHS were calculated by multiplying resources absorbed by their unit cost. They included the cost of therapies, hospitalizations, laboratory and other diagnostic examinations, surgery, rehabilitation procedures, physicians' visits and any other possible cost. Diagnosis-related group (DRG) [37] charges were applied to estimate the cost of hospitalizations.

Cost of transport was quantified in the patients' perspective. Indirect costs absorbed for patients' assistance, and caregivers' and patients' absenteeism were quantified in the perspective of patients and their family, using the human capital approach. Indirect cost attributable to reduction in or cessation of working ability were not quantified because of the relatively short-term observation period and the nature itself of PsA.

We report costs as follows: (i) direct NHS costs as cost related to health care, which are financed by the NHS, i.e. all medical costs for this sample of individuals; (ii) direct costs that include direct NHS costs and cost of transportation; (iii) overall social cost that includes direct costs and indirect costs as defined above. All costs are expressed in euros from the year 2007 and are computed as euro per patient per 6 months.

Quality of life

To evaluate HRQoL and assess health status, the widely used self-administered questionnaire such as the EQ-5D [33, 34] and SF-36 [35, 36] were adopted.

EQ-5D is applicable to a wide range of medical conditions and treatments and generates a health profile (EQ profile) consisting of five domains (mobility, self-care, anxiety/depression, usual activities and pain/discomfort) and three levels ('no problem,'

'some or moderate problems,' 'extreme problems/impossible to do'). A VAS (EQ-VAS) scores the overall HRQoL from 0 (the worst imaginable health status) to 100 (the best imaginable health status) [32, 33]. EQ-5D has been used in PsA [38]. Sokoll and Helliwell [38] found similar scores in RA and PsA patients matched for disease duration although RA patients had significantly greater joint damage. The additional burden of skin disease in PsA [39] was thought to explain these results.

Designed for use in clinical practice and research, health policy evaluations and general population surveys, the SF-36 questionnaire is considered a standard instrument for patient-based health care outcome assessment [35, 36]. It has been recently validated in Italy and used in several studies ranging from epidemiological to clinical trials [40]. Applicable to adults and adolescents, SF-36 assesses eight dimensions of HRQOL that relate to the physical and mental components of health perception. Physical functioning, role-physical and bodily pain are more related to the physical component; social functioning, role-emotional and mental health are more related to the mental component; and energy/vitality and general health relate to both components [34, 35]. These eight dimensions can be grouped in two summary scores [physical component summary (PCS) and mental component summary (MCS)]. These global measures were estimated using standard US algorithms [41]. To test the internal consistency of SF-36, the Cronbach's-α was computed, with values >0.70 considered satisfactory [42]. SF-36 has been used in several PsA therapy trials [27].

Cost–effectiveness analysis

We used the approach described and applied by Kobelt *et al*. [43] for anti-TNF therapy in RA patients. An incremental cost per QALY gained was estimated by calculating the ratio between the incremental cost before and after anti-TNF therapy and the incremental utility. In order to estimate the incremental (6 months) cost, we computed the difference between the average cost(s) per patient in the 6 months period before anti-TNF therapy and in the last 6 months of observation. Our choice was motivated by the need to contrast costs and QoL data pertinent to equivalent time periods, considering that only data for the 6 months before enrolment were available. Our analysis was intentionally conservative; we considered data collected during the last 6 months of follow-up in order to ensure that all patients were being treated for at least 6 months. In order to estimate utility, results from the EQ profile were converted to utility score, suitable for economic evaluations, by means of an algorithm that uses population-based (social) values [44, 45]. Because specific conversion values for the Italian population are not available yet, to convert our EQ profile results in EQ utility index, the algorithm was implemented with values from the United Kingdom [46], using the method described by Gringeri *et al*. [26]. QALYs gained were estimated by computing the difference between the average per patient utility values at enrolment, i.e. before anti-TNF therapy and the average utility value at the end of observation, i.e. after anti-TNF therapy initiation. This difference was then multiplied by 0.5, as the reference unitary observation period was 0.5 yr (i.e. 6 months)

Uncertainty due to parameter estimation was demonstrated by calculation of the cost–effectiveness acceptability curve.

Statistical analysis

For cost-of-care analysis, we used means as central tendency parameters, generally expressed as mean cost per patient per month, because this parameter can be easily used to make projections on different populations and is of easy use for policy makers. Costs were stratified according to their category, i.e. direct health care and indirect costs. Descriptive statistics were applied also to define HRQOL and health status measurement variables.

We compared direct health care costs, indirect costs and HRQoL cost of the 6-month prior to enrolment in the study to those related to the 6 months before the end of the study, using paired *t*-test, Wilcoxon signed-rank test or Mc Nemar test depending on the shape and type of the distribution of the variable to be tested. *P*-values < 0.05 were considered statistically significant. All analyses were performed using SPSS versions 14.0 and 15.0 software (SPSS, Chicago, IL, USA).

Results

A total of 107 patients with PsA met the inclusion criteria in the enrolment period extending from January to December 2005. Ninety-three out of the 107 received etanercept, 15 infliximab and 8 adalimumab. During the follow-up period, 10 patients were switched from one to another TNF antagonist for diverse reasons. The reason for the repartition of our patients among the three available TNF inhibitors was due to the different times of their formal introduction in Italy. Etanercept was allowed for PsA in 2004 and the two antibodies during 2005. At the end of observation seven (6.5%) patients had stopped anti-TNF therapy for diverse reasons. In order to avoid bias in favour of anti-TNF therapy in the estimate of effectiveness and QALY, they were included in the analysis. The baseline characteristics of the patients are shown in Table 1. The majority of patients (87) had a predominant or exclusive peripheral arthritis, 19 had predominant or exclusively axial involvement and only 1 had exclusive peripheral enthesitis. Table 2 shows the cost per patient for the 6 months preceding the beginning of the observation period. The mean overall direct and indirect costs were €942.87 and €576.30, respectively, with the cost for drugs accounting for €630.85.

Social costs were €1519.17: 41.5% attributable to cost of drugs, 37.9% attributable to indirect cost and 11.0% attributable to hospitalization, while costs for the NHS were €883.09.

Table 3 shows the improvement of the most important clinical variables at the end of the 12 months of follow-up. There was a significant improvement of levels of pain and activity, numbers of swollen and tender joints, and MASES, BASDAI, BASFI, HAQ and PASI. The direct cost increased by €5052.34, the cost for the NHS by €5044.21 and the social cost by €4638.72 (value referring to 6 months) (Table 4). There was also a significant increase of direct cost, cost for the NHS and social cost caused by an increase of drug cost due to TNF inhibitors. This increase was partially offset by the decrease in overall indirect cost. At the end of the 12-month observation there was a significant increase by 19.4 points in the EQ-5D VAS with a gain in utility of 0.25.

The results of SF-36 are shown in Fig. 1. Low levels were detected at baseline in all domains with the lowest values in the physical-role and emotional-role domains and the highest in energy/vitality and mental health domains. The mean value of QoL measured by EQ-5D VAS was 47.12 with a utility of 0.38. Figure 2 shows the EQ-5D profile results. At baseline, two-thirds or more of patients reported 'some/moderate problems' in all five domains. The percentage of patients with 'extreme problems/impossible to do' ranged between 1% in the mobility domain and 26% in pain and discomfort domain. QoL improved as demonstrated by the significantly higher values in both SF-36 (Fig. 1) and EQ-5D profile (Fig. 2). In the first (Fig. 1), there was a significant improvement in all domains except in the energy/vitality and in mental health domains. In the second (Fig. 2), the proportion of patients with 'no problems' increased in all five domains.

In the last 6 months of follow-up, there were incremental costs compared with the 6 months preceding the beginning of the observation (Table 5). However, the utility gain of 0.25 gave a QALY gain of 0.12 resulting in a cost per QALY gained of €40 876.90 for the NHS and of €37 591.01 for the society. The cost–effectiveness acceptability curve (Fig. 3) suggests that if decision makers' willingness to pay per QALY was €45 000 then

TABLE 1. Baseline patient characteristics

	Mean or frequency	S.D.	95% CI Lower, Upper
Total number of patients	107	–	
Patients with predominant peripheral arthritis, *n* (%)	87 (81.3)	–	
Patients with predominant axial involvement, *n* (%)	19 (18.8)	–	
Patients with exclusive peripheral enthesitis, *n* (%)	1 (0.9)	–	
Male patients, *n* (%)	51 (47.7)	–	
Age (yrs)	49.68	11.7	47.47, 51.90
Years since diagnosis of PsA	7.32	7.4	2.89, 8.28
Patient's assessment of pain (0–100)	62.83	21.10	58.77, 66.90
Patient's assessment of disease activity (0–100)	63.51	17.25	60.18, 66.86
Physician's assessment of disease activity (0–100)	60.15	13.33	57.57, 62.73
Swollen joint count (0–66)	7.60	6.39	6.37, 8.82
Tender joint count (0–68)	16.97	11.8	14.71, 19.24
MASES index (0–13)	3.65	3.76	
BASDAI (0–10)			
All patients	5.95	1.82	5.60, 6.30
Patients with axial involvement	6.4	1.72	5.57, 7.24
Patients with peripheral involvement	5.86	1.84	5.48, 6.26
BASFI (0–100)			
All patients	43.37	24.49	38.68, 48.07
Patients with axial involvement	49.94	22.29	39.19, 60.69
Patients with peripheral involvement	41.87	24.96	36.55, 47.19
PASI (0–72)	5.04	7.29	3.64, 6.44
HAQ (0–3)	1.14	0.57	1.03, 1.25
Therapies in the 6 months before enrolment, *n* (%)			
LEF	12 (11.2)		
MTX	53 (49.5)		
SSZ	15 (14.0)		
Glucorticoids	46 (43.0)		
NSAIDs	42 (39.3)		
COXIBx	27 (25.2)		
No DMARDs	37 (34.6)		

TABLE 2. Cost of care of patients in the 6 months before the beginning of the study

	Mean	S.D.	95% CI Lower, Upper
Overall direct cost	942.87	1156.11	721.29, 1164.46
Cost of drugs	630.85	963.20	446.24, 815.47
Cost of hospitalization	167.50	627.389	47.25, 287.75
Cost to the NHS	883.09	1148.65	662.94, 1103.26
Indirect cost	576.30	1565.11	276.33, 876.28
Social cost	1519.17	1945.16	1146.36, 1891.99

TABLE 3. Changes (improvement or reduction) in patient clinical characteristics at the end of the study in comparison with baseline value

Variable	Mean (S.D.)	95% CI Lower, Upper	*t*-test	*P*-value
Patient's assessment of pain	31.18 (27.56)	25.88, 36.49	11.65	<0.0001
Physician's assessment of disease activity	33.83 (19.60)	30.04, 37.63	17.69	<0.0001
Patient's assessment of disease activity	31.18 (24.48)	26.44, 35.91	13.05	<0.0001
Swollen joint count	6.33 (5.94)	5.10, 7.47	11.04	<0.0001
Tender joint count	9.00 (11.16)	6.86, 11.13	8.34	<0.0001
MASES	1.486 (2.96)	0.918, 2.05	5.18	<0.0001
BASDAI	2.72 (2.39)	2.26, 3.18	11.81	<0.0001
BASFI	17.72 (27.89)	12.38, 23.07	6.57	<0.0001
HAQ	0.48 (0.66)	0.35, 0.62	7.19	<0.0001
PASI	3.75 (7.03)	2.40, 5.10	5.50	<0.0001

anti-TNF treatment would be cost effective in 82% of the cases and that this would be increased to 97% if the threshold for willingness to pay was raised to €60 000.

Discussion

To the best of our knowledge ours is the first pharmacoeconomic study on anti-TNF-α drugs in PsA in clinical practice. The previous published studies dealt with data from published international trials [19–21]. Over 10 yrs of treatment, Bansback *et al.* [19] found a cost of about £30 000 per QALY gained by using etanercept as compared with LEF or combination MTX and cyclosporin. Woolacott *et al.* [20] found an incremental cost per QALY gained of etanercept compared with no active therapy of £14 818–£49 374 in a systematic review and economic evaluation on etanercept and infliximab. Eandi and Salvarani [21] compared cost/effectiveness and cost/utility of etanercept, infliximab and adalimumab examining data obtained from three Phase III trials.

In our study in clinical practice, cost–effectiveness ratios between therapy with TNF blockers and traditional therapy for PsA were calculated based on the change of costs and utilities from baseline, rather than on a comparison among different treatments. This is not a customary technique in economic evaluation, but is similar to that used by Kobelt *et al.* [43] to evaluate cost–effectiveness of TNF inhibitors in the treatment of RA in clinical practice. We chose this strategy for two reasons. The first was the superiority of TNF antagonists to traditional DMARDs in controlling signs and symptoms and inhibiting the progression of structural damage of PsA [11–13]. Accordingly, we wanted to offer a more effective therapy to our patients. With this view, aimed to start this new therapy earlier in the course of disease, we enrolled patients with peripheral arthritis who had failed one DMARD and not two as in the recommendations of the Italian Society of Rheumatology for beginning TNF inhibitors in patients with predominant peripheral arthritis [17]. These recommendations, along with others for initiating these drugs in the rheumatic diseases in which they are allowed, are deeply conditioned by the high cost of anti-TNF treatment. The second reason was our interest in the current study of all forms of PsA and not on individual forms (axial, peripheral arthritis, peripheral enthesitis and dactylitis) separately. Today, there are different pharmacological options for peripheral arthritis. On the contrary, pharmacological therapy for psoriatic spondylitis, similarly to primary AS, is based on NSAIDs with DMARDs having no

TABLE 4. Difference in overall cost of care (€) and its components between baseline and the end of follow-up

Variable	Mean (S.D.)	95% CI Lower, Upper	*t*-test	*P*-value
Increase in overall direct cost	5052.34 (2716.61)	4531.66, 5573.02	19.238	<0.0001
Increase in cost of drugs	5189.97 (2686.59)	4675.04, 5704.89	19.983	<0.0001
Decrease in cost of hospitalization	142.63 (667.16)	14.76, 270.49	2.21	0.029
Increase in overall direct cost to NHS	5044.21 (2739.56)	4519.12, 5569.27	19.046	<0.0001
Decrease in overall indirect cost	413.34 (1574.09)	715.32, 111.92	2.71	0.007
Increase in overall social cost	4638.73 (3087.08)	4047.03, 5230.40	15.543	<0.0001
Increase in EQ-5D VAS	19.40 (25.00)	14.59, 24.22	7.99	<0.0001
Increase in EQ-5D utility	0.25 (0.31)	0.18, 0.30	8.06	<0.0001

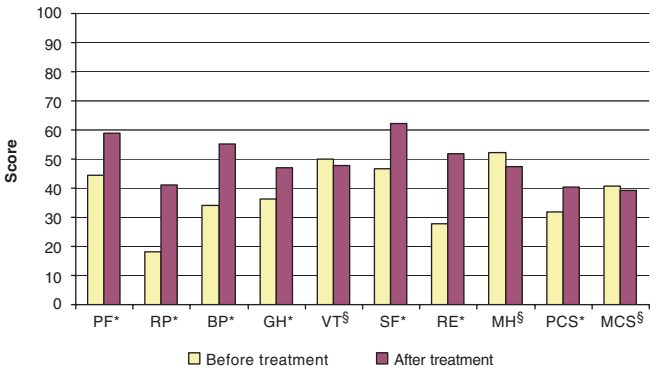

FIG. 1. SF-36 results before and after treatment. *Significant at the 0.0001 level; §non-significant; PF: physical functioning; RP: role-physical; BP: bodily pain; GH: general health; VT: energy/vitality; SF: social functioning; RE: role-emotional; MH: mental health; PCS: Physical Component Summary score; MCS: Mental Component Summary score.

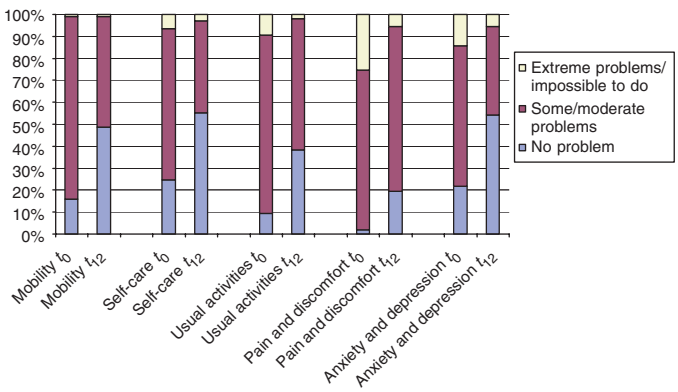

FIG. 2. EQ-5D items response frequencies before and after treatment. t_0: time of the enrolment; t_{12}: time of the second visits of follow-up.

evidence-based role. The ASAS/EULAR recommendations for the management of primary AS state that patients failing NSAID therapy should be treated with TNF blockers without trying or combining SSZ or MTX [25]. Therefore patients with predominant axial involvement did not have any other possible therapeutic option other than TNF inhibitors.

With the perspective of evaluating the entire clinical spectrum of the disease we chose unique principal instruments for measuring function and disease activity. BASFI and BASDAI, designed for measuring disease activity and function in primary AS, have been shown to have good internal consistency on both peripheral and axial PsA disease [47]. Similarly, both HAQ and its modified version for spondyloarthritides (HAQ-S) have been shown to be valid measures for function in PsA patients with peripheral and/or axial disease [48].

TABLE 5. Incremental cost–effectiveness ratios of anti-TNF-α therapy related to comparable periods before and after anti-TNF-α therapy (6 months before enrolment compared with the last 6 months of the study

Variable	Incremental cost (€) (6 months)	Utility gain (utility at final − utility at initial observations)	QALY gain (6 months)	Cost/QALY (€)
Direct cost	5052.34	0.25	0.12	40 942.78
NHS cost	5044.21	0.25	0.12	40 876.90
Social cost	4638.73	0.25	0.12	37 591.01

Data are rounded to two significant digits.

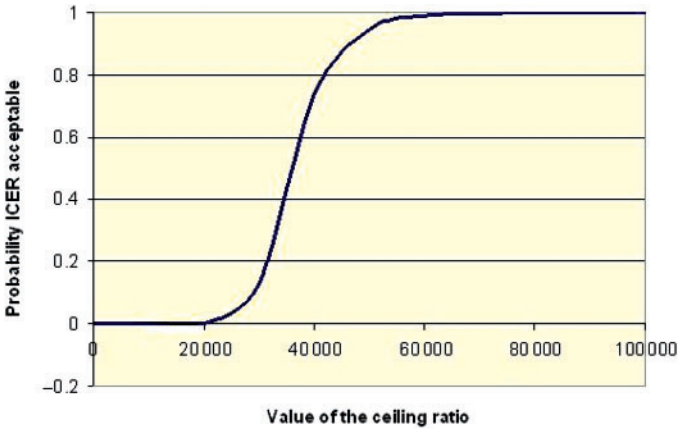

FIG. 3. Cost–effectiveness acceptability curve.

The patients of the present study had low EQ-5D and SF-36 scores at baseline. Utility values appeared to be lower than the ones that could have been expected from disease activity and function values. This probably reflects the negative effect of psoriasis on HRQoL [38] even if the baseline PASI score was only 5. Severe skin disease may cause problems with self-esteem and this may be reflect on the score of anxiety and depression subscale of the EuroQoL-5D. In addition, involvement of hands and genital areas may affect activities of self-care and hygiene.

The cost for the society of PsA treatment in the 6 months before the beginning of the study was €1519.17, different from that found by Huscher *et al.* [15] in German PsA patients. They found a total cost per year of €11 075 considering different types of costs, which is likely to explain the differences. Indeed, when comparable costs (i.e. direct health care costs) are considered, our estimate of pre-treatment cost of ~950 euros per 6 months is in line with the estimate of about 3100 euros per year, taking into account that our patients have shorter disease duration and higher functional status than those studied by Huscher *et al.*

At the end of 12 months of observation, there was a significant increase in the vast majority of SF-36 and EQ-5D domain scores resulting in a gain in EQ-5D utility of 0.25. This was due to the significant improvement of PsA disease activity, function status and psoriasis. The cost for the society and the NHS increased

significantly as a consequence of the high costs of TNF inhibitors. This increase was only partially offset by the reduction of the indirect costs. On considering the last 6 months of the study, social costs increased by €4638.73, cost for the NHS increased by 5044.21 and direct cost increased by €5052.34. However, the utility gain of 0.12 gave a cost for QALY gained of €37 591.01, €40 876.90 and €40 942.78, respectively. The magnitude of cost per QALY similar to that of our study has already been observed by Kobelt and colleagues [43] in RA patients. Similar to what has been observed in RA patients treated with anti-TNF agents, models that examined PsA treatment had previously estimated that biological therapy would become cost effective only in the long term [19].

The choice of comparing the 6 months period before enrolment and the last 6 months of observation was motivated by the need to contrast, within the same patient, periods of time in which the patient was exposed *vs* not exposed to biological therapy. The unexposed period was the one before enrolment whereas the last 6 month of observation (6–12 months) was the only period in which all the patients had been exposed to biological therapy at least once.

In fact, administrative barriers (high cost of drugs and limited pharmaceutical budget), may cause delays in the initiation of biological therapy even if this was indicated at enrolment. Consequently, some patients did not actually receive therapy for this reason therapy before the sixth month of follow-up. In turn, other patients had already stopped therapy (due to side-effects or lack of efficacy) by month 12.

Therefore, our costs and utilities estimates referring to the last 6 months actually, incorporate and factor in, real word events like therapeutic failure, induction periods, therapeutic switch, etc.

Our results with PsA are also consistent with the observation in an RA setting [43] that the anti-TNF therapy is cost effective even in the short term, and that this is mainly attributable to the dramatic improvement in functional status and, consequently in quality of life. The importance of this observation is related to the fact that public decisions makers are keen to have a short- or mid-term time horizon rather than a long-term one. In this view, anti-TNF therapy seems to generate its 'pay-offs' in term of effectiveness and cost–effectiveness rather soon after initiation, thus reducing the usual time gap between an investment in health care and its returns in terms of health. In particular, our results are mostly based on patients treated with etanercept accounting for 87% of the study population.

Anyway, it should be considered that cost–effectiveness ratios do not themselves provide information about whether the treatment is a cost effective use of resources. This decision depends on the perspective of the health care payer. One approach often used to assess the value of a treatment is to compare its cost–effectiveness ratio with ratios obtained with treatments in other fields. Whether a more effective yet more expensive treatment is cost-effective depends on the health payer's willingness to pay for additional benefits. The value of this threshold is difficult to quantify. In the United Kingdom, recent recommendations for the treatment by the National Institute of Clinical Excellence (NICE) seems to suggest a threshold of about £30 000 (€45 000) per QALY [49]. In the last few years, a threshold of €60 000 per QALY gained has been proposed for Italy [50]. Using these thresholds, anti-TNF treatment in our cohort appears acceptable already in the first year of treatment. In fact, taking €60 000 per QALY as the maximum acceptable cost–effectiveness ratio in Italy, which is broadly in line with decisions from the NICE [49], the probability of being cost-effective in 6 months is ~97%.

The quality of the collecting data is very important in all health economic studies. In observational and clinical practice-based studies such as ours, there is always the possibility of compliance problems. To avoid these, patients and physicians were particularly motivated and made conscious of the importance of collecting information and data were gathered by the physicians. However, this motivation should not have introduced significant bias in favour of the cost–effectiveness of anti-TNF by magnifying the utility benefits. We also used electronic tools to minimize missing data and to improve the precision of data collection. In addition, the study was monitored by a contract research organization to guarantee quality.

In conclusion, our study suggests that TNF antagonists provide 'value' and 'value for money' in the treatment of PsA in clinical practice. However, our results (mainly valid for etanercept) should be confirmed by studies in larger numbers of patients with different disease duration, severity and functional disability.

Rheumatology key message

- TNF antagonists provide 'value' and 'value for money' in the treatment of PsA in clinical practice.

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