

Efficacy, safety and cost per responder of biologics in the treatment of non-radiographic axial spondyloarthritis

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ABSTRACT

Anti-tumour necrosis factor (TNF) agents are recommended as second-line therapy for patients with axial spondyloarthropathies. This analysis reviewed data on studies investigating the efficacy and tolerability of anti-TNF agents in patients with non-radiographic axial spondyloarthritis (nr-axSpA) who had failed first-line non-steroidal anti-inflammatory (NSAID) treatment. Efficacy data from RCTs were used to calculate the number needed to treat (NNT) for individual anti-TNFs and then the cost per responder was determined to provide an indication of the value of each therapy. A systematic literature review and analysis of search results over the period January 2008 to September 2014 identified four randomised placebo-controlled trials that were included in the analysis. Adalimumab, etanercept and certolizumab pegol were all effective and well tolerated in patients with nr-axSpA. A patient was more likely to reach ASAS20 or ASAS40 when treated with etanercept or adalimumab, the NNT was lowest for adalimumab, and the risk of adverse events was higher with certolizumab pegol 200 mg every 2 weeks. The cost per responder (NNT) was lowest for adalimumab, followed closely by certolizumab 400 mg every 4 weeks, intermediate for certolizumab 200 mg every 2 weeks and highest for etanercept. Although all anti-TNF agents were associated with clinical improvement in patients with nr-axSpA, adalimumab presented a better cost per responder than etanercept and certolizumab pegol.

Introduction

Axial spondyloarthritis (axSpA) is a rheumatic disease that predominately affects the spinal column and/or the sacroiliac joints. It is associated with a significant clinical and symptomatic

impact, characterised by pain, rigidity and functional impairment (1, 2). Literature describing the epidemiology of axial spondyloarthritis is scarce; a recent US study reported an axSpA prevalence rate of 0.7% (95% confidence interval [CI] 0.38–1.1%) (3).

The Assessment of SpondyloArthritis International Society (ASAS) has proposed and approved new classification criteria (4, 5), based on which axSpA can be divided into two distinct diseases: ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA) (6). AS is characterised by anatomic damage to the bone, detectable with conventional radiography whereas this is absent in nr-axSpA. Magnetic resonance imaging (MRI) is therefore required to detect joint inflammation in nr-axSpA. The prevalence of nr-axSpA has been estimated to be 0.35% (95% CI 0.18–0.554%) (3). The two forms of axial spondyloarthritis are associated with the same degree of disability and the same negative impact on patient quality of life (7). In some cases, nr-axSpA can evolve into AS over time. Clinical studies have shown that up to 45% of patients progress from nr-axSpA to AS within 9 years (8, 9).

There is an average delay of 6 years from the early symptoms until a diagnosis of axSpA is made (10), and diagnostic delay is even more of an issue in nr-axSpA (2, 7) where this is primarily due to underestimation of symptoms [11]. The recent ASAS classification enables the early identification of patients with nr-axSpA, reducing the risk of a missed or delayed diagnosis and facilitating prompt treatment with the goal of limiting disease progression and permanent damage (1, 11, 12).

In accordance with the ASAS/EULAR recommendations, first-line treatment for patients with SpA (AS and nr-ax-

SpA) consists of non-steroidal anti-inflammatory drugs (NSAIDs) (13). If this is not effective, anti-tumour necrosis factor (TNF) agents are recommended as second-line therapy. Unlike traditional disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate or sulfasalazine, anti-TNF agents have been shown to be efficacious and safe in the treatment of AS and nr-axSpA (14-18).

This literature review assessed the efficacy and safety of anti-TNF agents in patients with nr-axSpA who have failed treatment with NSAIDs. Cost sustainability and, in particular, efficient resource allocation are important planning objectives, and it is therefore relevant to assess the economic impact of different treatment options in addition to their clinical usefulness. As far as costs are concerned, we have evaluated cost in relation to efficacy, *i.e.* cost per responder in addition to the acquisition cost value. As a result this review utilised existing efficacy data to calculate the number needed to treat (NNT). NNT can be interpreted as the number of patients who need to be treated with a particular drug in order to achieve one additional positive outcome (*i.e.* response, remission) (19). By relating NNT to the cost of treatment, the actual cost that the Italian National Health System (NHS) would need to pay per responder can be calculated (cost per responder).

Methods

Study selection and search strategy

A systematic literature review was performed using the PubMed databases in order to identify published, placebo-controlled, randomised, controlled clinical trials (RCTs) of biologic therapies for the treatment of nr-axSpA from January 2008 to September 2014. The search terms used were: non-radiographic axial spondyloarthritis, ankylosing spondylitis, spondyloarthritis, biological agents, anti-TNF agent, adalimumab, certolizumab, etanercept, infliximab, golimumab. The language of the publications was limited to English. Abstracts from national and international conferences (not available as full papers) and unpublished data were excluded.

Eligibility criteria

Studies were included if they met the following criteria: adult patients with nr-axSpA; randomised allocation to treatment with an anti-TNF agent or placebo, and reported at least one relevant clinical outcome. In selecting the literature, the title and abstract were first screened to see whether they met the inclusion criteria, then the full manuscript of studies that needed further examination was assessed.

Data extraction

Two authors independently extracted all relevant data and entered it into a specially-designed data form. Disagreements were resolved by discussion. For each trial, the following data were recorded: (i) author, year of publication, study design and identification of each trial; (ii) demographic characteristics of the participants; (iii) intervention characteristics, such as the anti-TNF dose, study visits and trial endpoints; (iv) the results; (v) information regarding the authors' conclusions. If necessary, data on outcomes were extrapolated from graphs.

Outcome measures

The primary outcome for the review reflected the primary endpoint of the included studies. This was usually ASAS40 response, but ASAS20 was used if ASAS40 was not available. Data from 12- and 24-week follow-up visits were collected. Safety, including any adverse events (AEs), was a secondary endpoint.

Statistical analysis

In order to compare the efficacy and safety of the different anti-TNF agents, risk ratio (RR) values and their 95% confidence intervals (CI) were calculated. The NNT per additional responder/remitter associated with each biologic drug was estimated using the point estimate of relative efficacy. Treatment costs were estimated by considering the purchase price of the drugs net of the deductions laid down by the law and the mandatory negotiated discounts that must be applied to supplies sold to the public facilities of the NHS. Costs per additional responder were estimated as

the NNT multiplied by the projected drug cost per patient. To use a standardised time horizon for all anti-TNF agents, costs per additional responder/remitter were recalculated using a 52-week time frame, with the assumption that shorter-term response rates (12 weeks) were maintained to year-end (11).

Results

Overview of the clinical studies

Six RCTs met all criteria for inclusion in the review (2,11,14, 20-22). Two of these (both using infliximab, a drug not currently indicated for nr-axSpA) were excluded from the review because ASAS40 was a secondary endpoint (14), or specific efficacy data for the subgroup of patients with nr-axSpA could not be extracted (22).

Table I shows the main characteristics of the remaining four RCTs that were assessed (2, 11, 20, 21). One trial included patients with any axSpA and divided them into two subgroups; data from the subgroup of patients with nr-axSpA were included in this review.

Adalimumab

The first adalimumab study investigated the efficacy and safety of this agent in patients with nr-axSpA without radiologically-defined sacroiliitis who were resistant to conventional treatment (NSAIDs) (11). Patients with active SpA were randomised to receive adalimumab 40 mg every other weeks (n=22) or placebo (n=24) for 12 weeks. The primary endpoint was ASAS40. All patients completed 12 weeks' observation and 38 were assessed up to 52 weeks. At 12 weeks, 54.5% of adalimumab recipients and 12.5% of those treated with placebo achieved an ASAS40 response ($p=0.004$). Response was maintained up to 52 weeks in the patients who continued adalimumab therapy, and placebo recipients who were switched to adalimumab at 12 weeks went on to achieve a similar ASAS40 response rate at 52 weeks.

In the other trial investigating adalimumab, efficacy and safety were determined in patients with nr-axSpA (2). Study participants met the ASAS criteria for SpA, had a Bath Ankylos-

Table I. Key characteristics of highlighted clinical trials.

Parameters	Sieper <i>et al.</i> (2)		Haibel <i>et al.</i> (11)		Dougados <i>et al.</i> (20)		Landewé <i>et al.</i> (21)		
	Placebo (n=24)	Adalimumab (n=22)	Placebo (n=24)	Adalimumab (n=22)	Placebo (n=109)	Etanercept (n=106)	Placebo (n=107)	Certolizumab 200 mg q2w (n=111)	Certolizumab 400 mg q4w (n=107)
Year of publication	2013		2008		2014		2014		
Country	Europe, USA, Australia		Germany		Europe, Asia, South America		Europe, North America, Latin America		
Patients	nr-axSpA		nr-axSpA		nr-axSpA		axSpA (AS + nr-axSpA)		
Anti-TNF agent	Adalimumab		Adalimumab		Etanercept		Certolizumab pegol		
Comparator	Placebo		Placebo		Placebo		Placebo		
Primary endpoint	ASAS40		ASAS40		ASAS40		ASAS20		
Age, years	38.4±10.4	37.6±11.3	37 (25-64)	38 (25-64)	38 (25-64)	31.9±7.8	39.9±12.4	39.1±11.9	39.8±11.3
Female, %	57	52	50	59	47	35.9	39.3	39.6	36.4
Symptom duration, years	10.1±8.8	10.1±9.0	8 (1-24)	7 (2-16)	2.5±1.8	2.4±1.9	7.7 (0.3-50.9)	6.9 (0.3-34.2)	7.9 (0.3-44.8)
BASDAI score	6.5±1.6	6.4±1.5	6.3 (4.2-8.9)	6.7(4.2-7.9)	6±1.9	6±1.8	6.4±1.7	6.5±1.6	6.4±1.5

Values are mean ± standard deviation, or mean (range).

AS: ankylosing spondylitis; ASAS: Ankylosing Spondylitis Response Criteria; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; nr-axSpA: non-radiographic axial spondyloarthritis; q2w: every 2 weeks; q4w: every 4 weeks; TNF: tumour necrosis factor.

Table II. Characteristics of the subpopulation in the trial by Landewé *et al.* (21).

	Total axSpA (n=325)	AS (n=178)	nr-axSpA (n=147)
Age, years	39.6 ± 11.9	41.5 ± 11.6	37.4 ± 11.8
Female, %	38.5	27.5	51.7
Symptom duration, years	7.7 (0.3-50.9)	9.1 (0.3-50.9)	5.5 (0.3-41.5)
BASDAI score	6.4 ± 1.6	6.4 ± 1.6	6.5 ± 1.5

Values are mean ± standard deviation, or mean (range).

AS: ankylosing spondylitis; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; nr-axSpA: non-radiographic axial spondyloarthritis.

ing Spondylitis Disease Activity Index (BASDAI) of ≥ 4 , a total back pain score ≥ 4 on a 10-cm visual analogue scale (VAS) and an inadequate response, intolerance or contraindication to NSAID treatment; patients who satisfied the New York criteria for the diagnosis of AS were excluded. A total of 185 enrolled patients were randomised to receive adalimumab (40 mg every other weeks; n=91) or placebo (n=94). The primary endpoint was the proportion of patients achieving ASAS40 response week 12, which was significantly high-

er in adalimumab (36%) versus placebo (15%) recipients ($p < 0.001$). The proportion of patients with AEs was similar in the adalimumab and placebo groups (57.9% vs. 58.8%, respectively). The most common AEs were nausea (8.2%) and diarrhoea (7.2%).

Etanercept

This randomised clinical trial assessed the efficacy of etanercept in patients with nr-axSpA resistant to NSAID treatment (20). Patients were randomised to receive etanercept 50

mg every week (n=106) or placebo (n=109) for 12 weeks, both added to background NSAID therapy. MRI of the sacroiliac joints and spinal column was performed at baseline and at 12 weeks. The primary study endpoint was ASAS30 at 12 weeks. At 12 weeks, the percentage of patients achieving ASAS40 was significantly higher in the etanercept group compared with placebo (32% vs. 16%; $p = 0.006$). During the 12-week study, AEs were reported in 57% of patients treated with etanercept and in 45% of placebo recipients; there was no significant difference between groups in the rate of grade 3 or 4 AEs.

Certolizumab pegol

This phase III clinical trial assessed the efficacy and safety of certolizumab pegol in patients with SpA, including subpopulations with AS (n=178) or nr-axSpA (n=147) (21). Patient demographic and clinical characteristics at baseline are shown in Table II. Randomised treatments were placebo,

Table III. Efficacy of anti-tumour necrosis factor agents in patients with non-radiographic axial spondyloarthritis.

Agent	Study	Endpoint	Patients (n)	Treatment response (%)	Placebo response (%)	ARR* (%)	NNT
Adalimumab	Sieper <i>et al.</i> (2)	ASAS 40	185	36	15	21	4.7
	Haibel <i>et al.</i> (11)	ASAS 40	46	55	13	42	2.4
	Pooled analysis		231	40	14	25	3.9
Etanercept	Dougados <i>et al.</i> (20)	ASAS 40	213	32	16	17	6.0
Certolizumab 200 mg q2w	Landewé <i>et al.</i> (21)	ASAS 20	96	59	40	19	5.4
Certolizumab 400 mg q4w	Landewé <i>et al.</i> (21)	ASAS 20	91	63	40	23	4.4

ARR: absolute risk reduction; NNT: number needed to treat; q2w: every 2 weeks; q4w: every 4 weeks.

certolizumab pegol 200 mg every two weeks or certolizumab pegol 400 mg every four weeks, and the primary study endpoint was ASAS20 at 12 weeks. Patients were randomised 1:1:1 to the three treatment arms. In the subgroup of patients with nr-axSpA, 58.7%, 62.7% and 40% of patients treated with certolizumab pegol 200 mg, certolizumab pegol 400 mg and placebo, respectively, achieved ASAS20. The overall rate of AEs during treatment was similar in certolizumab pegol and placebo recipients (mild AEs: 56.2% vs. 48.6%, respectively; moderate AEs: 36.1% vs. 33.6%, respectively). The most common AEs were nasopharyngitis (8.8% certolizumab pegol vs. 6.5% placebo) and upper respiratory tract infections (4.0% certolizumab pegol vs. 2.8% placebo).

Pooled analysis: efficacy and safety

On the basis of the efficacy and safety data from the reported trials, the NNT with the anti-TNF agent compared with placebo was calculated (Table III & IV). For adalimumab, NNT values are shown for the individual studies and as a pooled analysis of combined data, and for certolizumab pegol results are divided by used dosage. A patient was more likely to reach the treatment target (ASAS20 or ASAS40) when receiving adalimumab compared with etanercept or certolizumab (Fig. 1). The NNT also favoured adalimumab. Using pooled data, an average of nearly four patients need to be treated with adalimumab for one to reach the treatment target, with higher NNT values for certolizumab and, in particular, etanercept (Table III). In terms of safety, adalimumab, etanercept and certolizumab pegol 400 mg every 4 weeks had similar tolerability profiles to placebo, whereas the risk of AEs was slightly higher with certolizumab pegol 200 mg every 2 weeks (Table IV).

Cost per responder

The cost per responder was lowest for adalimumab, followed closely by certolizumab 400 mg every 4 weeks, intermediate for certolizumab 200 mg every 2 weeks and highest for etanercept (Table V).

Table IV. Safety of anti-tumour necrosis factor agents in patients with non-radiographic axial spondyloarthritis.

Agent	Clinical trial	Duration (weeks)	All the AE	
			RR	95% CI
Adalimumab*	Sieper <i>et al.</i> (2)	12	0.99	0.78–1.25
	Haibel <i>et al.</i> 2008 (11)	12	0.98	0.79–1.24
Etanercept	Dougados <i>et al.</i> (20)	12	1.27	0.97–1.63
Certolizumab 200 mg q2w	Landewé <i>et al.</i> (21)	24	1.22	1.02–1.46
Certolizumab 400 mg q4w		24	1.19	0.99–1.43

*Pooled analysis data for the entire population with axial SpA showed an RR of 0.98 (95% CI 0.81–1.19). AE: adverse events; CI: confidence interval; q2w: every 2 weeks; q4w: every 4 weeks; RR: risk ratio between patients on anti-TNF agents and those on placebo.

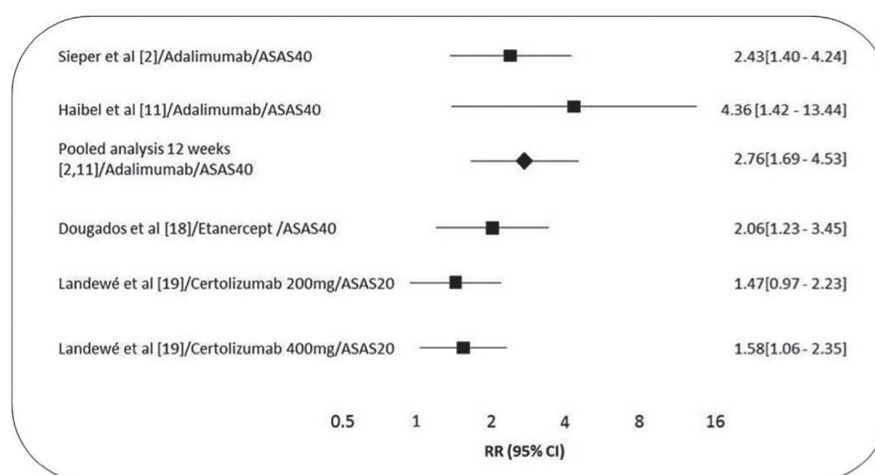


Fig. 1. Efficacy of anti-tumour necrosis factor agents in patients with non-radiographic axial spondyloarthritis.

RR: risk ratio; CI: confidence interval.

Discussion

The results of this review of clinical studies in patients with nr-axSpA show that adalimumab appears to be the most effective anti-TNF agent, with adalimumab recipients having a higher probability of achieving a clinical response during treatment compared with etanercept and certolizumab pegol (200 mg every 2 weeks or 400 mg every 4 weeks). The comparison with certolizumab was less robust because studies of this agent used the less stringent ASAS20 criteria as the primary endpoint compared with ASAS40 in the other studies. It has been conservatively assumed that the same difference between certolizumab pegol (200 mg or 400 mg) and placebo, expressed in terms of percentage points using the ASAS20 criterion, may remain unchanged when ASAS40 is used and that the RR value may not vary markedly. A number of factors are contributing to

increase in expenditure on drugs and healthcare. These include the ageing population demographic, the availability of new molecules, and higher health expectations from the general population. As a result, the economic analysis included in this review is particularly relevant and the cost per responder data provide another factor to decision-makers, in addition to efficacy and safety, on which to base healthcare resource allocation decisions. In this analysis, adalimumab had a lower cost per responder than etanercept (-36.8%) and certolizumab pegol (200 mg: -18.9%; 400 mg: -0.5%).

Interpretation of these results needs to take into account a number of factors. The first is the assumption that response rates reported in individual RCTs at 12 weeks would remain constant over 52 weeks of treatment. This seems appropriate in light of data from the open-label extension of one of the

Table V. Cost for responder for different anti-tumour necrosis factor agents.

Administration schedule	Adalimumab 40 mg q2w	Etanercept 50 mg qw	Certolizumab 200 mg q2w 400 mg in weeks 0, 2, 4 then 200 mg q2w	Certolizumab 400 mg q4w 400 mg in weeks 0, 2, 4 then 400 mg q4w
Administration method	1 prefilled syringe/prefilled pen (40 mg) SC	1 prefilled syringe/prefilled pen (50 mg) SC	1 prefilled syringe (200 mg) SC	1 prefilled syringe (200 mg) SC
Cost per dosage unit* (€)	442.59	227.42	341.52	341.52
No. of administrations	26	52	30	15
Cost of therapy for 52 weeks (€)	11,507	11,826	10,246	10,246
NNT	3.9	6.0	5.4	4.4
Cost per responder (€)	44,877	70,956	55,328	45,082
Cost per responder difference vs. adalimumab (€)	-	+26,079	+10,451	+205

*Drug costs were considered net of the deductions laid down by the law and the mandatory negotiated discounts that must be applied on the supplies sold to the public facilities of the National Health Service.

NNT: number needed to treat; q2w: every 2 weeks; q4w: every 4 weeks; qw: every week; SC: subcutaneous.

adalimumab studies suggesting that this does occur (11). The second is the use of ASAS20 versus ASAS40 for determining the efficacy of certolizumab pegol, on which the calculation of the NNT is based. As mentioned above, the use of a less stringent efficacy criterion might have favoured certolizumab pegol in the estimate of the NNT and the subsequent cost per responder. Finally, drug reimbursement needs to be considered. At the moment, the only drug reimbursed in Italy for the treatment of nr-axSpA is adalimumab, which is covered for all nr-axSpA patients who are non-responders at the first clinical reassessment. For this indication, the regulatory Italian Medicines Agency (AIFA) has an agreement with the manufacturer to share the risk (payment by results). As a result, the actual cost per responder to the Italian NHS for adalimumab is even lower than calculated in this review. In fact, irrespective of the expected efficacy data (and respective NNT), the Italian NHS will only be charged for patients who experience benefit from the treatment. In this way it is possible to avoid spending precious healthcare euros on an ineffective treatment, and there is the possibility of allocating these resources to treat additional patients.

The payment by results for the adalimumab treatment in nr-axSpA, is associated also to monitoring register in order to assess the efficacy of therapy in everyday clinical practice. This registry was activated by AIFA and the prescriber centers must complete enrolment and follow-up sheets for every

patient deemed eligible for treatment. With this type of approach (payment by results and registration), an attempt has been made to give all patients the right to access innovative treatments, while also ensuring that agents are prescribed appropriately and to the right patients, and that there is sustainability for the Italian NHS.

In conclusion, this review and analysis of studies investigating the treatment of nr-axSpA with anti-TNF agents indicates that all are effective at providing clinical improvement for patients and are well tolerated. Of course, the low number of studies evaluated represents a limitation of the study. Of the three agents included in the analysis, adalimumab had the highest efficacy and the lowest cost per responder.

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