Abatacept or infliximab for patients with rheumatoid arthritis and inadequate response to methotrexate: an Italian trial-based and real-life cost-consequence analysis

M. Benucci[1], W.B. Stam[2], I. Gilloteau[3], K. Sennfält[3], A. Leclerc[3], A. Maetzel[4], C. Lucioni[5]

[1]Rheumatology Unit, Department of Internal Medicine, Hospital S. Giovanni di Dio, Azienda Sanitaria di Firenze, Florence, Italy; [2]Stam-Consulting, Houten, the Netherlands; [3]Bristol-Myers Squibb, Rueil Malmaison, France; [4]Department of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada; [5]Springer Healthcare, Italy.

Abstract

Objectives

In the 1-year, double-blind, placebo-controlled ATTEST trial, efficacy of abatacept or infliximab versus placebo was reported in patients with rheumatoid arthritis (RA) and an inadequate response to methotrexate (MTX). The current study estimated trial-based and real-life costs of abatacept and infliximab for achieving pre-defined remission or low disease activity state (LDAS).

Methods

Quantity of drug, serious adverse event (SAE) rates and time (months) in remission or LDAS were taken from ATTEST for the trial-based calculation to derive a cost per remitting/LDAS patient and a cost per patient-month in remission/LDAS. Trial-based and real-life scenarios were performed.

Results

The annual trial-based costs per remitting/LDAS patient were €70.238/€37.208 for abatacept and €85.565/€46.602 for infliximab. In the first 6 months of the ATTEST trial, costs per patient-month in remission/LDAS were higher for abatacept (€11.024 and €6.018, respectively), relative to infliximab (€8.347 and €4.174, respectively). Over the full 12-month trial period cost per month in remission/LDAS estimates were only slightly in favour of infliximab (€6.959/€3.625) relative to abatacept (€7.297/€3.909). Assuming extension of treatment under real life conditions the cost per month in remission/LDAS turned substantially in favour of abatacept (€5.321/€2.819), as compared to infliximab (€7.189/€3.916). The higher initiation cost for abatacept to achieve remission/LDAS would be offset after a total 14.6 and 16.1 months of treatment, respectively, if treatment extended beyond 6 months under real-life conditions. These results proved to be robust when it was assumed that the (i) sharing of vials across patients completely averted infliximab wastage, (ii) AE risks were similar and (iii) onset of response was slower for abatacept.

Conclusion

Our findings suggest a lower cost-consequence for abatacept during real-life treatment.

Key words

abatacept, infliximab, economics, rheumatoid arthritis, Italy

Maurizio Benucci, MD
Wiro B. Stam, PhD
Isabelle Gilloteau, MSc
Karin Sennfält, PhD
Adriana Leclerc, MD
Andreas Maetzel, MD, PhD
Carlo Lucioni, MSc

Please address correspondence to:
Wiro B. Stam, PhD,
Lupine-oord 53,
3991VH Houten, the Netherlands.
E-mail: wiro.stam@stam-consulting.com

Received on July 3, 2012; accepted in revised form on February 5, 2013.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2013.

Competing interests:
W. Stam and A. Maetzel have collaborated on this project as part of a consulting agreement with BMS Europe;
I. Gilloteau is employed by BMS;
A. Leclerc and K. Sennfält were employees of BMS at the time of the study;
the other co-authors have declared no competing interests.

Introduction

A growing body of evidence indicates that treatment of rheumatoid arthritis (RA) should aim to control inflammation and should start immediately upon diagnosis, as this leads to improved long-term clinical outcomes and a reduced disease burden (1). Accordingly, the recent European League Against Rheumatism (EULAR) recommendations and consensus group formulated a "treatment to target strategy" that is focused on obtaining remission or at least a low disease activity state (LDAS) preferably within 3 months of initiating an RA treatment regimen (1, 2). In order to reach this goal, frequent treatment adjustments are recommended as necessary. This paradigm shift in the treatment of RA from a focus on reducing symptoms to disease remission has argued for intensive treatment and timely consideration of combination therapy.

Based on EULAR recommendations, methotrexate (MTX) is recommended as the initial disease-modifying antirheumatic drug (DMARD) drug of choice and is considered as the anchor drug for combination therapy (2). Abatacept is approved for use as first line biologic in patients with an inadequate response to one or more conventional DMARDs including MTX or a TNF-alpha inhibitor. This approval offers rheumatologists an additional treatment option after MTX failure with a mode of action different from TNF-alpha inhibitors.

Given that biological agents are considered expensive drugs, any final decisions on which agent to use after MTX failure will most likely consider the associated costs in addition to relative differences in efficacy and safety. Recently, two head-to-head studies have been reported comparing either subcutaneously administered abatacept (AMPLE trial [3]) or tocilizumab (ADACTA trial [4]) with adalimumab. For other biologicals, however, direct comparisons are lacking, which complicates a thorough assessment of the relative value of the multiple therapies available for RA. Although not designed as a head-to-head comparison, the ATTEST (Abatacept or infliximab *versus* placebo, a Trial for Tolerability, Efficacy and Safety in Treating RA) trial is a randomised, double blind, double dummy, placebo- and active comparator (infliximab)-controlled, 12-month global trial in patients with an inadequate response (IR) to MTX (5). This study demonstrated that after 6 months of treatment both biologics performed better than placebo, to a similar extent, in terms of patients reaching LDAS and remission. However, a more durable response for abatacept was observed upon prolonged treatment for another 6 months resulting in a numerically higher proportion of patients achieving LDAS and remission than on infliximab. Furthermore, abatacept displayed lower rates of serious adverse events (SAEs) and infections and lower discontinuation rates due to AEs and SAEs. Modest differences in outcomes may translate into favourable economic consequences for one biologic *vs*. another which is even more critical for higher priced drugs like biological DMARDs. A cost-consequence analysis between abatacept and infliximab has been performed based on the ATTEST trial to assess respective cost per responder and cost per month in LDAS/remission from the perspective of the Italian payer.

Methods

Structure

The ATTEST trial evaluated abatacept and infliximab, each in combination with MTX, in patients with active RA who had an inadequate response to MTX. The objective of this trial was to evaluate the efficacy of abatacept and infliximab *versus* placebo; ATTEST was a randomised active and placebo controlled trial, where placebo treatment was limited to days 1–197 to provide internal validity to the trial design and the clinical response rates of the two active treatment groups. In ATTEST, abatacept was administered by intravenous (IV) infusion 10 mg/kg on days 1, 15, and 29, then every 28 days, or a stable dose of infliximab 3 mg/kg on days 1, 15, 43, and 85, then every 56 days, according to the US/EU label at the time of the study, or matching placebo. After 6 months, placebo treated patients were reallocated to abatacept, though these patients were excluded from the analysis at 1 year.

The trial analyses allowed an evaluation of the patients' disease status according to DAS28 based on erythrocyte sedimentation rates (DAS28-ESR) and ACR response rates at 6 and 12 months of patients that were treated with abatacept or infliximab from trial start. At 6 months, the outcomes for abatacept and infliximab were compared to placebo. Both periods are characterised by a different infusion frequency: 8 and 5 times in the first 6-month period and 6 and 3 times in the last 6 months for abatacept and infliximab, respectively (Table I).

Where available and applicable, trial data are used in the cost/consequence analysis. These data are complemented with local registry data (mainly for real-life dose regimen) or data from additional sources (mainly for adverse events and costs) where applicable. This allowed simulation of a 'real-life' extrapolation scenario. For the benefits, the time in remission and in LDAS was considered. The current analysis assumes that the decision to prescribe a biologic has been taken and consequently it does not focus on the opportunity cost of allocating resources to alternative therapy choices, but solely on the cost per consequence for each possible alternative. For this analysis only direct medical costs are accounted for and expressed in association with the efficacy and safety benefits.

Scenarios

The current analysis differentiates 3 main scenarios corresponding to 3 different analysis periods (Fig. 1): a) a scenario based on the first 6 months of the ATTEST trial, b) a full ATTEST trial scenario based on the 12-month ATTEST period, and c) a 'real life' scenario which could start after either the 6- or 12-month ATTEST period and which applies real-life data on the use of infliximab and abatacept.

Additional sub-scenarios were defined to evaluate the impact of assumptions that were more conservative for abatacept: i) a "zero wastage" scenario where vial optimisation for infliximab was assumed to result in no wastage of infliximab, *i.e.* dose was not rounded up to the next vial; ii) a scenario which assumed similar AE rates for abatacept and infliximab, and iii) a scenario to evaluate the effect of a response onset during the first 6-month ATTEST period that was assumed to be slower for abatacept relative to infliximab.

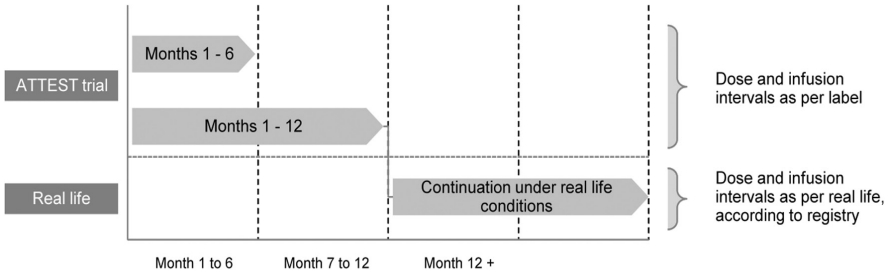

Fig. 1. Presentation of the different scenarios considered in the cost-consequence analysis.

Source data for the analysis

– Efficacy outcomes

Percentages of responders in either LDAS or remission were obtained from the ATTEST trial (Table I). In ATTEST, disease activity was assessed by DAS28-ESR, which is a recognised and validated score (1, 2). LDAS and remission were defined as DAS28 (ESR) ≤3.2 and DAS28 (ESR) <2.6, respectively. From these efficacy data the time in remission or LDAS was calculated by multiplying time (either 6 or 12 months) with the responder percentage (Table I). For the base case, it was assumed that the effects became established immediately after treatment start. Since the onset of action of biological agents with a cell-based mode of action such as abatacept has been suggested to be slower as compared to infliximab (6, 7), an additional scenario was evaluated which assumed a slower onset of action for abatacept. This scenario assumed a delay in response onset for abatacept of 1 month after that of infliximab. This delay of 1 month was based on the difference observed for ACR data before day 85 of the ATTEST trial after which response levels of abatacept and infliximab were similar (5). Since DAS scores were not reported (5), it was assumed that the difference in response kinetics was reflected by the reported ACR responder rates.

– Dose regimen

The dose regimens of abatacept and infliximab were defined by the dose and the frequency of dosing. For the first 12 months of treatment, the dose and infusion frequency of the biologics were in accordance with the label and as applied in the ATTEST trial. During the first 6 months of the ATTEST trial, patients either received 6 infusions of infliximab at a dose of 3 mg/kg or 8 infusions of abatacept. In ATTEST, abatacept was administered a dose of either 500 mg or 750 mg depending on body weight (5). In the trial, 25% of patients weighed less than 60 kg and were administered 500 mg abatacept, whereas the other 75% weighed >60 kg and received a dose of 750 mg (5, 8). Hence, the average dose of 687.5 mg required on average 2.75 vials of abatacept. It is worth noticing that for abatacept only complete vials are administered. Infliximab was administered on days 1, 15, and 43 and every following 56 days at a dose of 3 mg/kg (5). Based on an average body weight of 72.6 kg in ATTEST, this corresponded with an average dose of 218 mg. For the model it was assumed that 50% of patients required 2 vials of 100 mg infusion, whereas the remaining 50% required 3 vials resulting in an average of 2.5 vials per infusion to be used in the economic calculation. This can be considered a conservative assumption, since the median body weight in the ATTEST trail was 71 kg indicating that a greater proportion of patients required 3 vials of infliximab as compared to 2 vials (5, 8).

It is well established that clinical efficacy of infliximab declines upon prolonged use and dose escalation is commonly applied (9-11), either through an increase in dose, a reduction of the interval between infusions or a combination of both. For Italy, Favalli *et al.* (12) demonstrated that in clinical practice the interval between infusions was reduced to 50 days and the

Table I. Source data for the analysis.

			Abatacept	Infliximab	Source
Outcomes	Remission	Responders at month 6, %	11.3%	12.8%	ATTEST (5)
		Responders at month 12, %	18.7%	12.2%	
			Δ (95%CI): 6.5% (-2.2–15.2)*		
		Time (months) 1st 6 months	0.68	0.77	Calculated
		Total time months (1 year)	1.8	1.5	
	LDAS	Responders at month 6, %	20.7%	25.6%	ATTEST (5)
		Responders at month 12, %	35.3%	22.4%	
			Δ (95%CI): 12.9% (2.1–23.7)*		
		Time (months) 1st 6 months	1.24	1.54	Calculated
		Total time months (1 year)	3.36	2.88	
Dose regimen	Trial-based scenario	Dose per infusion (mg)	687.5	218	ATTEST (5, 8)
		Vials per infusion, n	2.75	2.5	Calculated
		Infusion frequency months 1–6	8	5	ATTEST (5)
		Infusion frequency months 7–12	6	3	ATTEST (5)
	Real-life scenario	Vials per infusion, n	2.7	2.8	Abatacept (14), infliximab (12)
		Infusion frequency	6.5	3.7	Abatacept (5), infliximab (12)
Adverse events	Trial-based scenario	Serious infections	1.9%	8.5%	ATTEST (5)
		SAE's (other than serious infections)	7.7%	9.7%	
	Real-life scenario	Serious infections (annual)	1.5%	3.7%	Cochrane meta-analysis (15)
		SAE's (other than serious infections) (annual)	6.4%	10.9%	
Costs	Drug	Cost per vial	€378.00	€570.68	List prices**
	Administration	i.v. infusion	€18.91	€26.37	(16, 17)
	SAE	Hospitalisation: serious infections	€5.908	€5.908	DRG 079: respiratory inflammation with complications (18)
		Hospitalisation: SAE (other than infection)	€4.183	€4.183	DRG 240: connective tissue disease with complications (18)

*ATTEST was not designed to demonstrate non-inferiority or superiority abatacept *versus* infliximab.
**In the analysis net prices (including all government measures and mandatory discounts to NHS) were considered.
i.v.: intravenous.

average infliximab dose was increased up to 3.57 mg/kg. These figures correspond to 2.8 vials of infliximab per infusion and 3.7 infusions on average per 6 months. The dose escalation of infliximab taken from these Italian registry data (12) was applied in the 'real-life' scenario. In contrast to infliximab and as suggested in US real-life data, the average dose of abatacept as well as the time interval between infusions is consistent over time in accordance with label (13). Consequently, in the absence of Italian real-life data, the applied dosing regimen of abatacept was chosen according to label for the real-life scenario. For abatacept the average number of vials per infusion (2.7) for the real-life scenario was according to the weight distribution of RA patients included in an observational Italian study (14) which was almost similar to the trial-based analysis.

– Adverse events

Adverse events (AEs) that involved hospitalisation were incorporated in the analysis. Hospitalisations due to serious infections were considered separate from other serious adverse events (SAEs), since both are believed to incur different costs. The 1-year probabilities for serious infections as reported in the trial (5) were incorporated in the ATTEST based scenarios. Furthermore, the risk for SAEs other than serious infections was calculated by subtracting the serious infection rate from the SAE risk, as reported in the ATTEST trial (Table I).

For the real-life scenario, the risks for serious infections and SAEs other than serious infections were obtained from a Cochrane network meta-analysis (Table I) (15). The calculation to discriminate the risks for serious infections and SAEs other than serious infections was similar as to that applied for the ATTEST based scenarios described above. Although most data on adverse events come from pooled relative short-term trials on the use of biologics across different indications, this can be considered as the best evidence available. The Cochrane review group synthesised available evidence in a network meta-analysis and calculated a SAE rate of 79 per 1.000 (95%CI 53–118) for abatacept compared to 118 per 1.000 in the control group. For serious infections, the calculated rates were 15 per 1.000 (95%CI 8–28) (abatacept) *vs*. 26 per 1.000 (control). For infliximab, SAEs rates were 146 per 1.000 (95%CI 116–185) *vs*. 118 per 1.000 in the control group, and the rates of serious infections were 37 per 1.000 (95%CI 26–54) *vs*. 26 per 1.000 in the control group (15). Of all biologics evaluated, abatacept and anakinra were associated with a significantly lower

risk of serious adverse events compared to most other biologics.

– Costs

Both biological DMARDs are commercialised in vials (100mg vial for infliximab, 250 mg vial for abatacept). The drug acquisition costs for abatacept and infliximab represent the ex-factory drug price costs for the hospital including all government measures and mandatory discounts to Italian NHS. Administration costs for the infusion of infliximab and abatacept were obtained from reports by Iannazzo *et al*. (16) and Benucci *et al*. (17), respectively. AE costs were obtained from the national 2010 DRG (18). Since most observed serious infections in trials were respiratory tract infections (5), the DRG 079 tariff of respiratory inflammation with complications was applied as a proxy for the average costs incurred by the healthcare system for treating serious infections. For SAE other than serious infections, the DRG 240 tariff for connective tissue disease with complications was applied to reflect the average costs to the healthcare system. Annual costs of AEs were obtained by multiplying annual probabilities with DRG tariffs. Also for the ATTEST trial we used annual probabilities and did not discriminate between AE rates for the first 6 months and the second 6 months. It was assumed that the annual costs for AEs were equally distributed per 6 months.

Results

With respect to the cost-consequence results (Table II), there were several differences across the scenarios.

Month 1 to 6 of the ATTEST trial

Drug acquisition costs were the main driver of the total costs during this period: 96% and 91% of the total costs for abatacept and infliximab treated patients, respectively. Total costs during the first 6 months were higher for abatacept (€7.474) relative to infliximab (€6.411) due to the higher acquisition cost. Since the proportion of LDAS/remission patients after 6 months of treatment was relatively similar for infliximab and abatacept (Table I), the cost-consequence expressed as the cost per month in remission/LDAS were therefore higher for abatacept (€11.024/€6.018), as compared to infliximab (€8.347/€4.174).

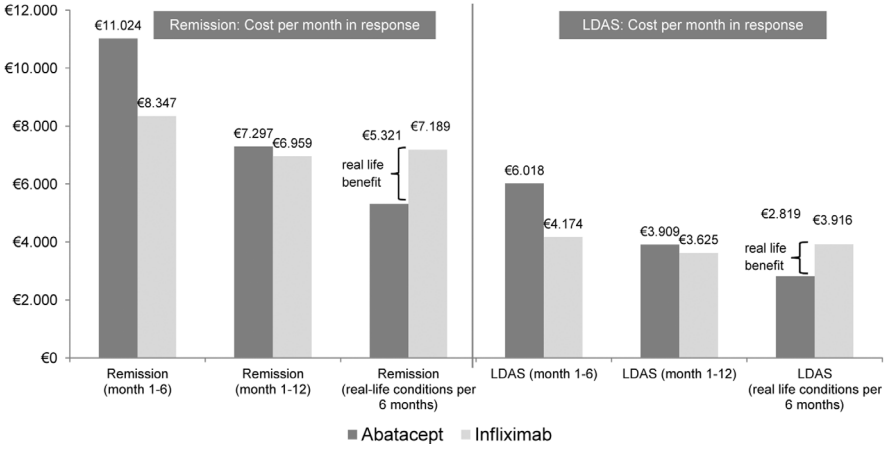

Fig. 2. Cost consequence results upon prolonged use of abatacept and infliximab under real-life conditions.

Full ATTEST trial: month 1 to 12

Inclusion of month 7–12 of the ATTEST trial period by an analysis of the full 12-month trial period yielded cost per month in remission/LDAS estimates that were only slightly in favour of infliximab (€6.959/€3.625) as compared to abatacept (€7.297/€3.909). However, this results in a larger reduction of the cost per month in remission/LDAS for abatacept (by 34%/35%) than for infliximab (only 17%/13%) relative to the first 6 months of treatment scenario. For the full ATTEST period the 12-month cost per remitting patient/LDAS responder was lower for abatacept (€70.238/€37.208) relative to infliximab (€85.565/€46.602).

Scenario first 6 months: slower time of onset of abatacept relative to infliximab

Importantly, this scenario did not affect total costs of the 6 and 12 months ATTEST scenarios, but mainly increased the initial costs per month in remission/LDAS for abatacept for the first 6 months of the ATTEST period (€13.229/€7.222) and to a lesser extent the costs per month in remission/LDAS for the full 12-month trial period (€7.786/€4.166), when compared to the base case scenario, which assumed no difference in the time of onset for both agents (Table II).

Real-life extrapolation scenarios

Real-life extrapolation scenarios took into account dose escalation for infliximab. Three different scenarios were evaluated: a) real-life base case – no vial sharing across patients as a base case – b) vial sharing across patients, and c) assuming similar SAE probabilities for both agents.

a) Real-life base case scenario (per 6 months treatment continuation) with individual dosing and no vial sharing across patients

In this scenario, each patient on infliximab was assumed to use a whole vial package. So, for example, a patient requiring a dose of 250 mg infliximab would require 3 vials of 100 mg corresponding with wastage of 50 mg infliximab. The average number of vials used was based on the weight distribution of people in the ATTEST trial. For each 6 months of treatment continuation under real-life conditions, the cost consequence results per month in remission/LDAS were substantially in favour of abatacept (€5.321/€2.819, respectively), as compared to infliximab (€7.189/€3.916) (Fig. 2). The higher initiation costs for abatacept to achieve remission/LDAS would be offset rapidly, *i.e*. after a total of 14.6/16.1 months of treatment if treatment after 6 months would be prolonged under real-life conditions.

For the scenario that assumed a delay in the onset of the abatacept response, treatment prolongation up to a total 21.7/22.7 months under real-life condi-

Table II. Overall costs and cost consequence results for different scenarios.

Category	Item	Abatacept			Infliximab				
		ATTEST		Real life	ATTEST		Real life (extrapolation)		
		ATTEST 1st 6 months	Full ATTEST (12 months)	(per 6 months)	ATTEST 1st 6 months	Full ATTEST (12 months)	Base case: individual dosing (per 6 months)	'Zero wastage' (per 6 months)	Individual dosing and similar AE risk (per 6 months)
Costs	Drug costs	€ 7.106	€12.436	€5.669	€5.825	€9.320	€4.828	€4.483	€4.828
	Admin. costs	€151	€265	€123	€132	€211	€98	€98	€98
	AE costs	€217	€ 434	€178	€454	€908	€337	€337	€178
	Total costs	€7.474	€13.135	€5.970	€6.411	€10.439	€5.263	€4.918	€5.103
Cost consequence	Per month Remission	€11.024 (€13.299)*	€7.297 (€7.786)*	€5.321	€8.347	€6.959	€7.189	€6.718	€6.972
	Per month In LDAS	€6.018 (€7.222)*	€3.909 (€4.166)*	€2.819	€4.174	€3.625	€3.916	€3.659	€3.797

*Assuming response onset for abatacept 1 month after treatment initiation.

tions was required to offset the higher 6-month initiation cost for abatacept for achieving remission/LDAS.

b) Real-life scenario with vial sharing across patients

In contrast to abatacept, where only complete vials are used for infusion, infliximab is dosed on a mg/kg basis and supplied in 100 mg vials, which can lead to considerable wastage. For example, for a person weighing 75 kg dosed at 3.57 mg/kg a total amount of 268 mg infliximab per infusion would need 3 vials and potentially waste 32 mg infliximab per infusion. In Italian clinical practice, several patients are often scheduled for infusion at the same time in order to optimise vial usage and reduce wastage (12). To account for such vial optimisation, an additional theoretical scenario was defined that assumed zero wastage of infliximab. This scenario can be considered "theoretical", as zero wastage is unlikely in clinical practice, but supports testing the robustness of the real-life findings. For this scenario, the infliximab dose administered was based on the average body weight of patients in the ATTEST trial while assuming zero wastage. Hence, based on the average body weight of 72.6 kg and a real-life dose of 3.57 mg/kg, this would equal 259 mg corresponding to 2.6 vials of infliximab per infusion. As a consequence, this scenario lowered the drug costs for infliximab to €4.483 per 6 months and improved the cost per month in remission/LDAS for infliximab (€6.718/€3.659). Even in this scenario, abatacept performed better with cost per month in remission/LDAS for abatacept of €5.321/€2.819. This scenario confirms the robustness of the cost-consequence benefits of abatacept relative to infliximab in real-life clinical practice.

c) Real-life scenario assuming no difference in adverse events risks between infliximab and abatacept

The majority of the studies incorporated in the network meta-analysis of Singh *et al*. (15) were of a relative short duration (median duration of 6 months). A recent updated Cochrane analysis produced slightly different SAE rates still favouring abatacept relative to infliximab, but results no longer reached significance (19). Since there is a general lack of comparative long-term data regarding the safety of biologics, differences in SAE risk during prolonged use can be considered uncertain. To evaluate the impact of AE risk, a scenario was defined where the SAE risk for infliximab was assumed to be similar to that of abatacept: serious infections 1.5% and other SAE 6.4%. Table II demonstrates that even with similar SAE risk for infliximab and abatacept, the cost-consequence expressed as cost per month in remission/LDAS (€6.972/€3.797 *vs.* €5.321/€2.819) remained strongly in favour of abatacept under real-life conditions.

Discussion

The current cost-consequence analysis modelled the cost per month in LDAS and cost per month in remission achieved with abatacept or infliximab. The clinical results from the ATTEST trial were used to derive the expected time in remission or LDAS during the initial 6 months of treatment and during a full 12-month period of treatment. The ATTEST trial evaluated efficacy and safety of two biological agents in a randomised setting. Furthermore, dose information from an Italian registry study for infliximab was used to calculate the expected real-life costs for infliximab from an Italian healthcare system perspective. In the absence of head-to-head comparative long-term safety data, Cochrane network meta-analysis data on AEs across biologics were used as providing the best available data for real-life extrapolation analyses.

The costs per month in remission or LDAS were higher for abatacept during the first 6 months of treatment compared to infliximab. However, these cost differences were reduced over the subsequent 6 months in the trial-based scenario. The cost per month in remission/LDAS turned in favour of abatacept when applying a real-life scenario where the infliximab dose is escalated.

Accordingly, if treatment after 6 months is prolonged under real-life conditions, the higher initial (first 6 months of treatment) costs for abatacept per month in LDAS and remission will be offset after a total 16.1 and 14.6 months of treatment, respectively. Although the cost differences between abatacept and infliximab for the real-life scenario decline when vial optimisation was assumed, a conservative "no wastage" scenario still favoured abatacept for long-term use: cost per month in remission/LDAS for infliximab (€6.718/€3.659) *versus* €5.321/€2.819 for abatacept. The more durable efficacy of abatacept over time as observed in the ATTEST trial resulted in cost consequence benefits, which were higher when patients continued on abatacept *vs*. infliximab. Therefore, based on the trial data, abatacept is likely to be an economically attractive alternative for prolonged treatment of RA.

Despite a comprehensive and transparent presentation of the costs and consequences of both interventions, it is not possible to provide an incremental assessment of the value for money of abatacept when using such a cost consequence approach (20). Accordingly, it has been argued that the disaggregated presentation of cost and consequences bears a potential risk for non-transparent decision making. This allows for a decision maker to select the outcomes and consequences which are most relevant for his or her individual perspective, but which are not necessarily aligned with the optimal decision from a societal perspective. However, the consequences considered in the current analysis, time in LDAS and remission, are well aligned with the treatment to target strategy as formulated by EULAR and therefore individual bias is unlikely to affect decision making.

As for any model analysis, underlying assumptions and simplifications were made, which should be acknowledged as these might caution any conclusions. The current analyses do not incorporate any uncertainty in the estimates as derived from the ATTEST trial and the Cochrane meta-analysis and therefore the analysis calculated expected values only. In this perspective it should be noted that the confidence interval of the difference in the proportion of patients reaching remission at 12 months in the ATTEST trial included the point of no difference (Table I), and therefore it cannot be excluded that the difference in efficacy was a random observation. However, the observation that a significantly higher proportion of patients in the abatacept group as compared to infliximab arm shift from LDAS to a state of remission during month 7 to 12 of the ATTEST trial (21) makes this unlikely. Still, decisions based on the cost/month in remission would have been less certain than those based on month in LDAS had this been a probabilistic model.

In order to provide useful results, the outcomes provided by any cost consequence model will need to be trustworthy, given the uncertainties in the data used as well as around the use of both biologicals in real-life clinical practice. Therefore, the robustness of the model outcomes was evaluated for scenarios that incorporated different data sources and real life use patterns of both infliximab and abatacept. For the main scenario, it was assumed that the onset of response was immediately upon treatment start for both abatacept and infliximab. Although this assumption is unrealistic and overestimates the treatment effect expressed as months in remission/LDAS for the first 6 months, it does so for both treatments; therefore, this assumption was unlikely to impact the results. However, it has been argued that abatacept displays a slower onset of the response compared to infliximab (6, 7). Consequently, it could be argued that an immediate onset of the response for both agents would bias in favour of abatacept. Therefore, a scenario was defined where abatacept's onset of response was delayed by 1 month relative to that for infliximab. Since the ATTEST trial (21) did not report the proportion of patients reaching LDAS/remission on other time points than 6 and 12 months after treatment initiation, the reported ACR rates were used as a proxy to assess the response delay. According to the ACR20 figures presented in the ATTEST trial (21), the 1-month delay is believed to represent the maximum response delay for abatacept. Although abatacept has been suggested to display a slower response onset compared to anti-TNF inhibitors, this is challenged by recent head-to-head data, where subcutaneously administered abatacept was compared to the TNF inhibitor, adalimumab (3). In this trial there was only a slight, statistically insignificant advantage for adalimumab in ACR20 response rates and DAS28 scores at 2 weeks after treatment initiation. Since subcutaneous and intravenous administered abatacept display similar ACR response kinetics (22), a response delay of 1 month for abatacept *versus* infliximab can be considered conservative. The slower response onset for abatacept did not affect the total treatment costs, but increased the cost per month in remission/LDAS for abatacept during the ATTEST period. However, these higher initiation costs were still offset by prolonged treatment under real-life conditions.

The 12-month efficacy data from ATTEST were assumed to also reflect the efficacy of infliximab and abatacept for the real-life scenario. Therefore, the real-life scenario implicitly assumes that a dose escalation of infliximab is not associated with increased efficacy. This assumption might bias against infliximab if dose escalation would be associated with improved efficacy. Although dose increases are common in patients treated with infliximab and observational studies (9) suggested that a dose increase of infliximab was associated with improved clinical efficacy this was refuted by randomised trial by Pavelka *et al*. (23). They demonstrated that a dose increase in RA patients with an inadequate response to prolonged use of infliximab did not lead to a greater proportion of patients reaching remission as defined by DAS28 score. Furthermore, the dose of infliximab (3.57 mg/kg) as reported in the Italian registry (12) and applied for the real life scenario represented a 19% increase in dose compared to the ATTEST trial and can be considered to be conservative estimate of real-world dosing in light of other evidence. An analysis of multiple observational studies (9) demonstrated that dose escalation of infliximab of at least 25% was common. Therefore, the

19% dose increase of infliximab applied in the real-life scenario can be considered conservative and is more likely to bias in favour of infliximab. Furthermore, the robustness of the analysis is underscored by the observed beneficial cost consequence results for abatacept under real-life conditions where vial sharing optimised cost efficient use of infliximab.

In contrast to abatacept, infliximab is considered to increase the risk for serious infections and for that reason received a black box warning from the FDA (19). Recently, a large Italian registry study has demonstrated that long-term anti-TNF treatment, and especially infliximab, was associated with a higher risk for serious infections (24). On the other hand, a large observational study has recently confirmed abatacept's favourable profile regarding serious infections relative to infliximab (25). In this study, however, the median exposure time was only 7 months (25). Similarly, the AE rates applied for the real-life scenario as reported by the Cochrane network meta-analysis (15) were mainly based on trials with a relatively short duration (median 6 months) and included trials outside the RA indication. Therefore, due the lack of long-term comparative data, the incidence of SAEs within the RA indication upon prolonged use of biologicals remains uncertain from either observational or from controlled trials. Also a recent alternative Cochrane analysis has produced slightly different SAE rates, which still favoured abatacept relative to infliximab, but to a lesser extent, and results were non-significant (19). To account for the uncertainty around a difference in adverse event rates upon prolonged use of abatacept and infliximab an additional 'real-life' scenario assuming no difference was explored. This scenario demonstrated that the cost consequence results were insensitive to changes in SAE rates in accordance with the drug acquisition costs being the main driver of the overall costs and durability of response as the main driver for cost offsets.

The current cost consequence analysis was based on the ATTEST trial where abatacept was administered through intravenous infusion. Future analysis should determine whether the current cost consequence outcomes would also apply for subcutaneously administered abatacept for which 1 year data of a direct comparison against adalimumab have been recently reported (3). Once the full 24-month data of this AMPLE study (3) are available, it will be of interest to evaluate the cost consequences of subcutaneously administered abatacept against adalimumab. Also differences in adherence to therapy, which was shown to be under 50% for infliximab in the Italian setting (26), might affect the cost-consequence results once these data become available for abatacept.

Conclusions

The results of these analyses demonstrated that relative to infliximab, abatacept is a favourable treatment for patients failing MTX, both from a clinical and economic perspective, in the Italian healthcare setting. Our findings suggest a lower cost-consequence for abatacept during real-life treatment. Future long-term comparative data might be used to confirm the validity of extrapolation of the ATTEST results and also establish whether similar findings will be obtained for subcutaneously administered abatacept.

References

1. SMOLEN JS, ALETAHA D, BIJLSMA JW *et al*.: Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010; 69: 631-7.
2. SMOLEN JS, LANDEWÉ R, BREEDVELD FC *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010; 69: 964-75.
3. WEINBLATT ME, SCHIFF M, VALENTE R *et al*.: Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. *Arthritis Rheum* 2013;65: 28-38.
4. GABAY C, EMERY P, VAN VOLLENHOVEN R *et al*.: Tocilizumab (TCZ) monotherapy is superior to adalimumab (ADA) monotherapy in reducing disease activity in patients with rheumatoid arthritis (RA): 24-week data from the phase 4 ADACTA trial. 2012 p. 172.
5. SCHIFF M, KEISERMAN M, CODDING C *et al*.: Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis* 2008; 67: 1096-103.
6. RUBBERT-ROTH A, BURMESTER GR: Clinical trials: how to cope with medical needs, ethics and timelines. *Ann Rheum Dis* 2010; 69: 1-3.
7. KIELY PD, DEIGHTON C, DIXEY J, OSTOR AJ: Biologic agents for rheumatoid arthritis--negotiating the NICE technology appraisals. *Rheumatology* (Oxford) 2012; 51: 24-31.
8. CLINICAL STUDY REPORT ATTEST TRIAL: Trial registration number NCT00095147. 2007.
9. ARIZA-ARIZA R, NAVARRO-SARABIA F, HERNANDEZ-CRUZ B, RODRIGUEZ-ARBOLEYA L, NAVARRO-COMPAN V, TOYOS J: Dose escalation of the anti-TNF-alpha agents in patients with rheumatoid arthritis. A systematic review. *Rheumatology* (Oxford) 2007; 46: 529-32.
10. AGARWAL SK, MAIER AL, CHIBNIK LB *et al*.: Pattern of infliximab utilization in rheumatoid arthritis patients at an academic medical center. *Arthritis Rheum* 2005; 53: 872-8.
11. BLOM M, KIEVIT W, KUPER HH *et al*.: Frequency and effectiveness of dose increase of adalimumab, etanercept, and infliximab in daily clinical practice. *Arthritis Care Res* (Hoboken) 2010; 62: 1335-41.
12. FAVALLI EG, MARCHESONI A, COLOMBO GL, SINIGAGLIA L: Pattern of use, economic burden and vial optimization of infliximab for rheumatoid arthritis in Italy. *Clin Exp Rheumatol* 2008; 26: 45-51.
13. SIMONS W, TRIVEDI DN, ROSENBLATT LC: Real World Treatment patterns of patients with rheumatoid arthrits receiving two infusable biologics: abatacept and infliximab. EULAR 2009. SAT0120. 2009.
14. PUNZI L, MATUCCI CM, CANTINI F *et al*.: Treatment patterns of anti-TNF agents in Italy: an observational study. *Reumatismo* 2011; 63: 18-28.
15. SINGH JA, WELLS GA, CHRISTENSEN R *et al*.: Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev* 2011; (2): CD008794.
16. IANNAZZO S, ZANIOLO O, D'ARPINO D: Un modello di Budget Impact per la valutazione economica di tocilizumab come prima linea biologica nei pazienti con artrite reumatoide di grado moderato o servero. *Italian Journal of Public Health* 2010; 7 (Suppl. 2): S44-S53.
17. BENUCCI M, LI GF, SABADINI L, SAVIOLA G, BAIARDI P, MANFREDI M: The economic burden of biological therapy in rheumatoid arthritis in clinical practice: cost-effectiveness analysis of sub-cutaneous anti-TNF-alpha treatment in Italian patients. *Int J Immunopathol Pharmacol* 2009; 22: 1147-52.
18. Tariffa Unica Conventionale 2010. 2011.
19. SINGH JA, WELLS GA, CHRISTENSEN R *et al*.: Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev* 2012; (3): CD008794.
20. COAST J: Is economic evaluation in touch with society's health values? *BMJ* 2004; 329: 1233-6.
21. SCHIFF M, SCHMIDELY N, LAFOSSE C, LE BM, DOUGADOS M: Abatacept provides an

increasing magnitude of response over time in measures of rheumatoid arthritis disease activity: results from the ATTEST trial. *Ann Rheum Dis* 2008; 67: 337.

22. GENOVESE MC, COVARRUBIAS A, LEON G *et al*.: Subcutaneous abatacept versus intravenous abatacept: a phase IIIb noninferiority study in patients with an inadequate response to methotrexate. *Arthritis Rheum* 2011; 63: 2854-64.
23. PAVELKA K, JAROSOVA K, SUCHY D *et al*.: Increasing the infliximab dose in rheumatoid arthritis patients: a randomised, double blind study failed to confirm its efficacy. *Ann Rheum Dis* 2009; 68: 1285-9.
24. ATZENI F, SARZI-PUTTINI P, BOTSIOS C *et al*.: Long-term anti-TNF therapy and the risk of serious infections in a cohort of patients with rheumatoid arthritis: comparison of adalimumab, etanercept and infliximab in the GISEA registry. *Autoimmun Rev* 2012; 12: 225-9.
25. CURTIS JR, XIE F, CHEN L *et al*.: The comparative risk of serious infections among rheumatoid arthritis patients starting or switching biological agents. *Ann Rheum Dis* 2011; 70: 1401-6.
26. IANNONE F, GREMESE E, ATZENI F *et al*.: Longterm retention of tumor necrosis factor-alpha inhibitor therapy in a large italian cohort of patients with rheumatoid arthritis from the GISEA registry: an appraisal of predictors. *J Rheumatol* 2012; 39: 1179-84.