

Rituximab in the treatment of rheumatoid arthritis patients in Italy: a budget impact analysis

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Abstract

Objectives

The objective of this Budget Impact Analysis is to evaluate the financial implications of a rituximab-based sequencing strategy in the treatment of rheumatoid arthritis in the perspective of the Italian National Health Service.

Methods

Yearly patients who were eligible for a second-line biological DMARD in Italy were entered into a 5-year model. A Markov chain reproduced the course of this cohort under a number of alternative strategies, including anti-TNF- α cycling and rituximab or abatacept as second and third line agents. The dynamic of the simulation was given by first biological drug failure data, mortality rates, and survival-on-treatment data from published literature. Drug acquisition, administration and monitoring costs were assessed.

Results

Italian patients refractory to a first anti-TNF- α therapy resulted to be about 650 per year, giving a cumulative number of treated patients in five years of 3,240. The anti-TNF- α cycling had a total direct cost which rose from €8.2 million in the first year to €33.8 million in the fifth. The cost per patient of rituximab was lower than the average cost of the anti-TNF- α therapies; the annual difference was around € 4,300. The savings gained from lower individual costs with rituximab were partially offset by the increasing number of patients receiving active medication, resulting in a substantial cost equivalence between third line rituximab and anti-TNF- α cycling scenarios; rituximab, as a second line therapy, produced a savings in total costs of -31.8%. Strategies including abatacept shared the same dynamics, but with higher costs.

Conclusion

The introduction of rituximab in clinical practice could allow an increase in the number of patients receiving an active rheumatoid arthritis treatment without inflating therapy costs.

Key words

Rituximab, rheumatoid arthritis, budget impact analysis, Italy.

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Introduction

Rheumatoid arthritis (RA) is an inflammatory disease of the synovial joints which predominantly affects young women.

Despite the relatively low prevalence rate, the highly detrimental character of the disease induces important management costs. The socioeconomic burden of RA in Italy was estimated to be €1,600 million in 2002, of which €380 million was attributable to direct medical costs (1).

Several disease-modifying anti-rheumatic drugs (DMARDs) for pharmaceutical treatment of RA, such as methotrexate (MTX), have been available for many years. Biological DMARDs have emerged more recently, like the anti-TNF- α agents, etanercept (ETN), adalimumab (ADA) and infliximab (IFX). In recent years, two newer biological drugs for RA have been marketed in Italy, rituximab (RTX) and abatacept (ABA). RTX is a genetically engineered monoclonal antibody that depletes the B-cell population by targeting cells that express the CD20 marker. Its use is recommended in combination with MTX as an option for the treatment of adults with severe active RA who have had an inadequate response (or showed intolerance) to other DMARDs, including at least one TNF- α inhibitor (2). The efficacy and safety of RTX in the treatment of RA has been demonstrated in several studies (3-5).

In clinical practice the choice of the best sequencing strategy for RA patients with inadequate response or intolerance to a first anti-TNF- α is under particular debate. In fact, there is no randomised, prospective, head-to-head trial comparing the strategies of switching to an alternative TNF- α inhibitor (anti-TNF- α cycling) to using an agent with a different mechanism (10). Anti-TNF- α cycling has become an established approach, largely because of physicians' familiarity with the efficacy and safety profile of these drugs, and of the robust body of evidence supporting their use (11). Some observational studies demonstrated an improvement in disease activity in patients who were switched to another TNF- α inhibitor after an inadequate response to a prior one (12).

However, results from other large studies indicated that response and survival rates in therapies with a second-line TNF- α inhibitor are less satisfactory than in naïve patients (12-15). This, as well as the common recurrence of class adverse events after a switch to another TNF- α inhibitor, represents the rational basis for switching to a drug with a different mode of action.

An observational study, conducted within the Swiss Clinical Quality Management program for RA (SCQM-RA), compared the effectiveness of using alternative anti-TNF- α agents or RTX in RA patients with an inadequate response to at least one anti-TNF- α agent. The effect on disease activity was more favourable in the RTX group and no significant difference in tolerance was noted (16). These findings were confirmed in the extended analysis of more than 300 patients from the same cohort (17). Overall, these results suggested that RTX should be considered sooner as a therapeutic alternative after inadequate response to a first or second anti-TNF- α agent, rather than trying all alternative anti-TNF- α agents. Another important aspect to consider is that RTX is the only biological treatment for RA for which there is a good evidence of prognostic factors of response (18). Given the high purchasing price of biological drugs, their rational use, intended as prescription choices based on the evaluation of expected pharmacoeconomic performance, appears unavoidable (10). Moreover, variables other than purchasing price should be part of the decision. For example, differences in administration routes can account for a large part of the cost difference between strategies. These considerations provide the scope for a pharmacoeconomic analysis. In recent years, Budget Impact (BI) analyses have become an essential part of the economic evaluation of health-care interventions. Its purpose is to estimate the financial consequences of the adoption and diffusion of new technology within a specific context. The use of mathematical models to perform this prediction and the best methodology to select economical and epidemiological data for modelling are well established (19).

Conflict of interest: Drs Benucci and Sabadini cooperated with AdRes for the development of the model through a consultancy agreement; Dr Iannazzo is an employee and owner of AdRes srl.; Dr Zaniolo is an employee and owner of AdRes srl. Roche SpA supported the development of the model through a service contract with AdRes.

The aim of the present paper is to present the results of a Budget Impact (BI) model developed to estimate the impact on the Italian National Health Service (INHS) expenditure of the treatment with RTX *vs.* other available strategies in severe RA patients who already failed a first line biological treatment.

Materials and methods

The BI model was developed with MS Excel over a 5-year simulation time horizon. The model was based on a Markov chain and, consistent with the financial perspective of the budget impact analysis, no discount rate has been applied to estimated costs and health benefits. All mathematical and technical details have been published elsewhere (20). In brief, the model considered several alternative treatment strategies for severe RA patients who had already failed to show results in first line biological treatment. All the considered strategies were assumed to be composed of a sequence of a second biological therapy, followed by a third (Table I). When the third line therapy was also interrupted, because of a lack of efficacy or tolerance, the MTX monotherapy was adopted as a prosecution therapy, with palliative purpose. This last assumption is surely an oversimplification of the actual clinical practice but it is, in fact, non-influential with respect to the economic evaluation as it generates no differential cost between the compared strategies.

The reference strategy for the analysis was anti-TNF- α cycling, the most common clinical choice before the introduction of RTX and ABA. Figure 1 shows patient flow into the model according to the considered strategies.

The dynamic of the simulation was given by mortality rate and transition rate from one therapy to the next. These last data were based on the survival-on-treatment parameter specific to each drug which was taken from published literature. Limited evidence of the duration of biological therapies was available for Italian RA patients because, unlike in many other countries, a centralised register does not exist. The only data partially published (21) were related to 711 patients treated with anti-TNF- α who were enrolled in

Table I. - Strategies recommended after the failure of a first anti-TNF- α considered in the BI model.

Strategy	Description
aTNF	Anti-TNF- α cycling: after the first failure, a second anti-TNF- α is adopted and, subsequently, a third.
RTX 3	RTX as third biological line: an anti-TNF- α drug is adopted as second line and, when this second drug fails, RTX is started.
ABA 3	ABA as third biological line: like the previous strategy, with ABA instead of RTX.
RTX 2	RTX as second biological line: RTX is adopted as second line and, when this fails, another anti-TNF- α is started.
ABA 2	ABA as second biological line: like the previous strategy, with ABA instead of RTX.

RTX: rituximab; ABA: abatacept.

a multicentre observational study. In order to obtain the survival-on-treatment parameters for the anti-TNF- α therapies in the model, we combined these data with those from the Spanish register for patients with chronic rheumatism treated with biological drugs (BIOBADASER) (14). For RTX and ABA no observed survival-on-treatment statistics were available, therefore for these drugs we applied the average values for anti-TNF- α drugs when used as a first biological line. Mortality was established by applying a disease-specific relative risk ($RR=2.03$) (22) to the mortality of the general Italian population (23).

The simulated cohort was given by the yearly number of Italian severe RA (24-26) patients who interrupt a first biological treatment (14).

Costs were computed from the INHS perspective, and, therefore, only direct medical costs were considered (drug acquisition, administration, premedication and monitoring costs).

Drug acquisition costs were computed considering the least costly package, or, in case of multiple identical alternatives, the package consistent with the recommended dosage. Ex-factory price was applied to all drugs (because of exclusive hospital use) except MTX (distributed in territorial pharmacies), for which the public price was considered. Prices were updated to February 2009 (27). Dosing schemes were derived from the Summaries of Product Characteristics (SPCs) of the considered drugs, from Italian guideline recommendations (28) or from the literature (6, 29). Biological drugs were always considered to be associated with MTX.

Administration costs of intravenous drugs in the hospital environment (RTX, ABA and IFX) included the cost of medical supplies and health personnel work (25). For drugs administered subcutaneously (ETN and ADA), a domiciliary visit was considered for

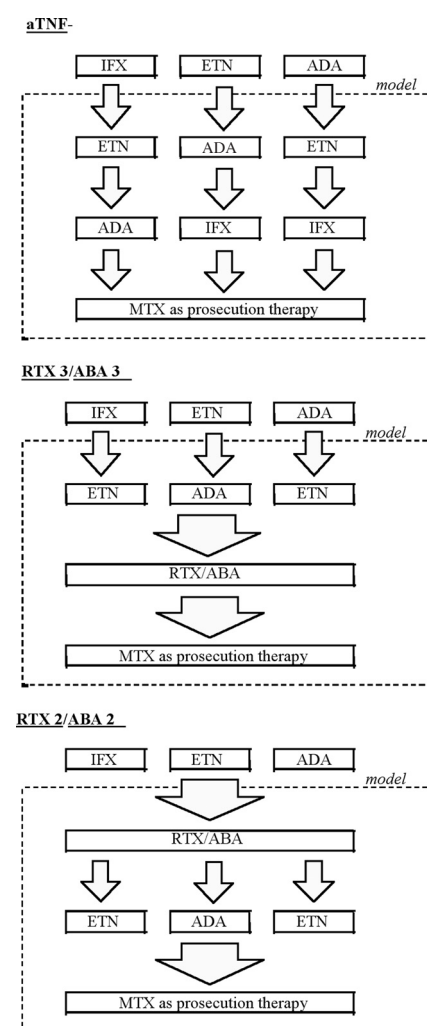


Fig. 1. Patient flow into the model according to the considered strategies

15% of treated patients (30). RTX was the only treatment requiring pre-medication to reduce adverse effects, therefore the cost of one dose of prednisolone 100 mg per RTX infusion was added. Annual costs for each treatment are shown in Table II.

Results

Based on the epidemiological data considered in the model the number of Italian subjects affected by RA was evaluated to be 227,560, of which 7,000 received a first anti-TNF- α agent. From these, 648 patients interrupted a first line biological therapy each year. These patients entered the model each year and spread through the lines of treatment according to the different sequencing strategies.

There was no difference in the number of deaths in each category; this is because no effect on mortality has been modeled. In RTX- and ABA-based strategies the number of patients in active treatment (*i.e.* not in prosecution therapy with MTX with a palliative purpose) increased.

Figure 2 illustrates total expense forecasts for the management of Italian RA patients who failed a first-line biological treatment divided by year of treatment and analysed strategies.

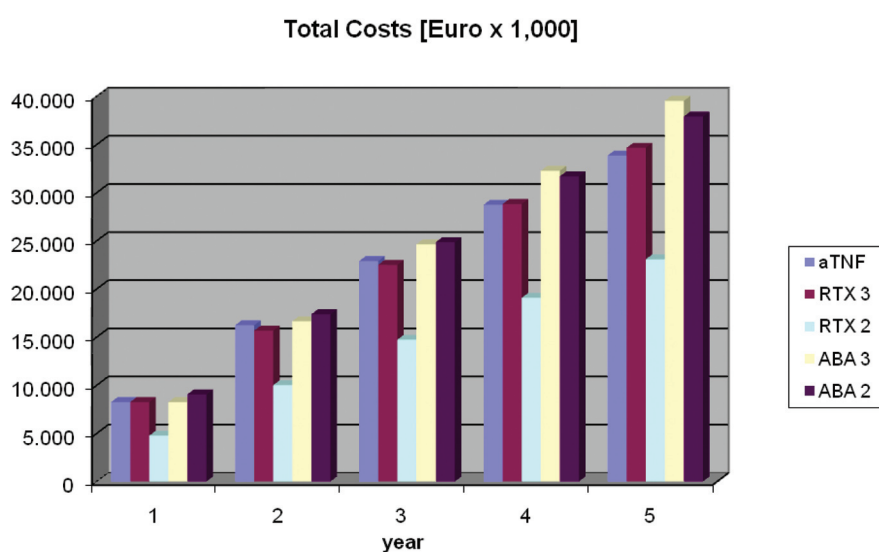
The overall cost rose with time, since the number of patients increased year on year. The anti-TNF- α cycling strategy had an overall direct cost which rose from € 8.243 million in the first year to €33.839 million in the fifth year.

In general, the introduction of RTX in therapeutic schemes for RA produced a reduction in total therapy costs. This is mainly due to the fact that its purchasing price is lower than that of the other biological drugs. However, the increase in the number of patients kept in active treatment, related to the use of RTX, caused a cost increase in the following years. This produced a substantial equivalence in total costs between the strategy based on RTX as a third line and the strategy based on anti-TNF- α cycling (€34.644 million, +2.4% *vs.* aTNFs in the 5th year) (Fig. 3). On the other hand, the strategy which implied the use of RTX as a second line, anticipating the use of this more economic

Table II. Yearly costs of treatment.

Drug		Drug Cost (€/year)	Administration Cost (€/year)	Monitoring Cost (€/year)	Total Cost (€/year)
RTX+MTX		7,102.13	80.53	154.98	7,337.64
ABA+MTX	First year				
	Subsequent years	13,530.68 12,568.65	264.77 245.85	154.98	13,950.43 12,969.49
IFX+MTX	First year	10,462.86	252.40	182.78	10,898.03
	Subsequent years	8,134.37	195.89		8,513.04
ETN+MTX		12,510.48	201.24	174.23	12,885.95
ADA+MTX		12,175.42	50.31	172.09	12,397.82
MTX		62.28	–	154.98	217.26

RTX: rituximab; ABA: abatacept; IFX: infliximab; ETN: etanercept; ADA: adalimumab; MTX: methotrexate.



RTX: rituximab, ABA: abatacept.

Fig. 2. 5-year total expense forecasts for the management of all severe Italian RA patients (648 patients per year; 3240 cumulative patients treated at the fifth year) who have failed a first-line biological treatment: comparison between analysed strategies

drug and giving it to a higher number of patients, maximised the total cost saving (€23.067 million, -31.8% *vs.* aTNFs in the 5th year).

The strategies based on ABA as third and second lines reproduced the same dynamics of the RTX-based ones, but the higher acquisition and administration costs caused a rise in total costs (€39.525 million, +16.8% and €37.898 million, +12.0% *vs.* aTNFs, respectively, in the 5th year).

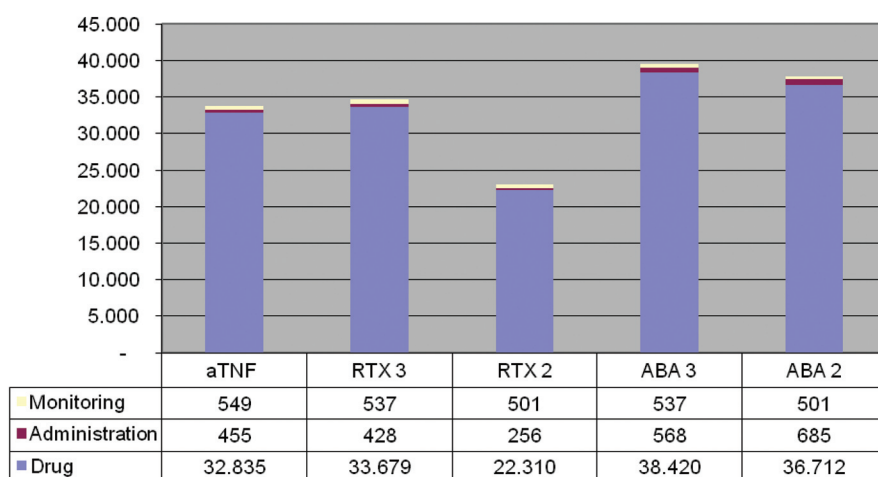
The estimation of the number of patients kept in active treatment with a specific amount of economic resources is useful in the evaluation of the relative efficiency of the compared strategies. With €100,000 spent in direct

medical costs for the anti-TNF- α cycling strategy, it is possible to maintain about 8 patients in active treatment for one year (Fig. 4). This figure could be improved by 54.8% (12.5 pts in the 5th year) and by 9.6% (8.8 pts in the 5th year) by adopting the strategy based on RTX as a second and third line, respectively.

Discussion

In order to estimate the financial impact and, consequently, the affordability of RTX in RA treatment, a 5 years prevalence-based BI model has been implemented. The costs of different sequences, including anti-TNF- α cycling, RTX as a second and third line,

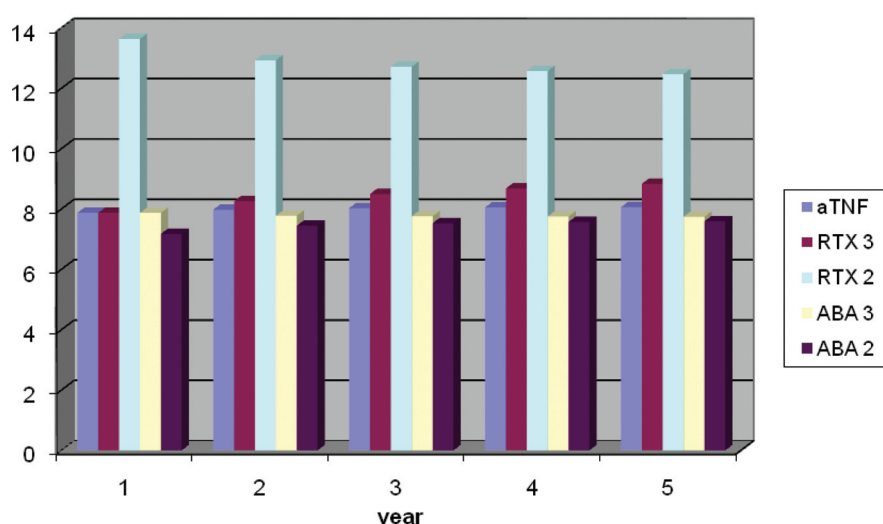
Costs in the 5th year [Euro x 1,000]



RTX: rituximab, ABA: abatacept.

Fig. 3. Costs at the 5th year of the simulation for the cumulative 3,240 patients treated in each of the considered strategies.

Patients in active treatment [pts / 100,000 Euro]



RTX: rituximab, ABA: abatacept.

Fig. 4. Number of patients who could be kept in active treatment for one year with € 100,000.

and ABA under the same conditions of RTX, were compared.

Per-patient annual cost was lower for RTX (€7,338 vs. €11,663 on average for anti-TNF agents), mainly due to minor acquisition and administration costs. These results are quite consistent with those in a BI analysis conducted in the context of the French health care system (31). A Markov model reproduced the course of patients treated either by IFX, ETN, ADA or RTX, after the failure of one or more anti-TNF- α therapies.

The model showed that when RTX was not used, mean annual cost was about € 16,555, including €13,206 for drug acquisition. When RTX was given to all patients who failed a first anti-TNF, these costs decreased to €11,444 and €7,469 respectively.

As compared with the present model, the RTX acquisition costs in France and Italy (€7,102 in Italy) were similar, while anti-TNF agents costs were lower (€ 11,328 on average); administration costs were also higher than

those estimated by the present model. This is especially true for RTX treatment which, according to French data, caused an increase in hospitalisation costs for its administration compared with anti-TNF- α .

Despite different cost structures, both the French and Italian models estimated a net saving in the cost per patient with the use of RTX compared to anti-TNF- α cycling (€5,000 per patient per year in the French context and €4,300 in Italy).

Also, in another study on costs and outcomes of biological RA treatments (only ETN and IFX available in Sweden in 1999-2002) the administration costs were higher than those in the present study. These discrepancies may be partially explained by national specificities (32).

Within the specific RA framework, it is worth pointing out the economical impact of different sequencing strategies. The RTX-related per patient saving would lead to a net total saving under the hypothesis of a close cohort. However, the dynamic structure chosen for this model includes the fact that the introduction of a further active biological therapy delays the switch to prosecution therapy (palliative care); thus, in time, a higher number of patients are kept in active therapy compared to the situation before RTX (or ABA) introduction. This results in a total budget impact which is similar for anti-TNF- α cycling and RTX as a third line therapy. The use of RTX as a second line leads to a higher number of patients receiving the less expensive therapy during the simulated 5 years, producing a 30% reduction in total cost.

To better understand this dynamic, it may be useful to analyse how the number of patients under active treatment can vary according to the chosen strategy. With the anti-TNF- α cycling strategy the INHS could treat about 8 patients for one year with an expenditure of € 100,000. The introduction of RTX as a third line makes it possible to treat one further patient with the same amount. The use of this drug as a second line improves this figure to 12.5 patients.

In conclusion, the clinical efficacy and safety of RTX have been well demon-

strated through pre-marketing trials and subsequent observational studies. From a clinical perspective point of view, the best sequencing-strategy remains to be further clarified. From an economical point of view, this analysis suggests that sequences which include RTX induce a lower cost per patient with an efficacy which is at least similar to its competitors, allowing the freeing of resources which would be used for the treatment of patients otherwise eligible for palliative care only.

References

1. LEARDINI G, SALAFFI F, MONTANELLI R, GERZELI S, CANESI B: A multicenter cost-of-illness study on rheumatoid arthritis in Italy. *Clin Exp Rheumatol* 2002; 20: 505-15.
2. Rituximab for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 126. August 2007.
3. EDWARDS JCW, SZCZEPANSKI L, SZECHINSKI J *et al.*: Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004; 350: 2572-81.
4. EDWARDS JC, CAMBRIDGE G: Sustained improvement in rheumatoid arthritis following a protocol designed to deplete B lymphocytes. *Rheumatology* (Oxford) 2001; 40: 205-11.
5. EMERY P, FLEISCHMANN R, FILIPOWICZ-SOSNOWSKA *et al.*: The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum* 2006; 54: 1390-400.
6. COHEN SB, EMERY P, GREENWALD MW *et al.*: Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum* 2006; 54: 2793-806.
7. YAZICI Y, MCMORRIS BJ, DARKOWT, ROSENBLATT LC: Patient and physician perception of the infusion process of the biologic agents abatacept, infliximab, and rituximab for the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2009; 27: 907-13.
8. BRAUN J, KALDEN JR: Biologics in the treatment of rheumatoid arthritis and ankylosing spondylitis. *Clin Exp Rheumatol* 2009 Jul-Aug; 27 (Suppl. 55): S164-7.
9. WALSH CA, FEARON U, FITZGERALD O, VEALE DJ, BRESNIHAN B: Decreased CD20 expression in rheumatoid arthritis synovium following 8 weeks of rituximab therapy. *Clin Exp Rheumatol* 2008; 26: 656-8.
10. THE NATIONAL COLLABORATING CENTRE FOR CHRONIC CONDITIONS: Funded to produce guidelines for the NHS by NICE. RHEUMATOID ARTHRITIS. National clinical guideline for management and treatment in adults. <http://www.nice.org.uk/nicemedia/pdf/CG79FullGuideline.pdf>. Last accessed September 2009.
11. RADSTAKE TR, SVENSON M, EIJSBOUTS AM *et al.*: Formation of antibodies against infliximab and adalimumab strongly correlates with functional drug levels and clinical responses in rheumatoid arthritis. *Ann Rheum Dis* 2009; 68: 1739-45.
12. RUBBERT-ROTH A, FINCKH A: Treatment options in patients with rheumatoid arthritis failing initial TNF inhibitor therapy: a critical review. *Arthritis Res Ther* 2009; 11 (Suppl. 1): S1.
13. KARLSSON JA, KRISTENSEN LE, KAPETANOVIC MC, GÜLFÉ A, SAXNE T, GEBOREK P: Treatment response to a second or third TNF inhibitor in RA: results from the South Swedish Arthritis Treatment Group Register. *Rheumatology* (Oxford). 2008; 47: 507-13.
14. GOMEZ-REINO JJ, CARMONA L: Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a four-year period. *Arthritis Res Ther* 2006; 8: R29.
15. KISHIMOTO M, GREENBERG J, ABRAMSON SB *et al.*: Drug survival time on anti-TNF agents: does prior anti-TNF use influence RA outcomes?. *Arthritis Rheum* 2005; 52: 347.
16. FINCKH A, CIUREA A, BRULHART L *et al.*: B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents. *Arthritis Rheum* 2007; 56: 1417-23.
17. FINCKH A, CIUREA A, BRULHART L *et al.*: Which subgroup of rheumatoid arthritis patients benefit most from switching to rituximab versus alternative anti-TNF agents after previous failure to anti-TNF agents?. *Ann Rheum Dis* 2009. Epub ahead of print.
18. QUARTUCCIO L, FABRIS M, SALVIN S *et al.*: Rheumatoid factor positivity rather than anti-CCP positivity, a lower disability and a lower number of anti-TNF agents failed are associated with response to rituximab in rheumatoid arthritis. *Rheumatology* (Oxford) 2009; 48:1557-9
19. MAUSKOPF J, SULLIVAN S, ANNEMANS L *et al.*: Principles of Good Practice for Budget Impact Analysis: Report of the ISPOR Task Force on Good Research Practices-Budget Impact Analysis. *Value Health* 2007; 10: 336-47.
20. BENUCCI M, IANNAZZO S, SABADINI L: Analisi di budget impact dell'utilizzo di rituximab nel trattamento dell'artrite reumatoide in Italia. *Farmeconomia e Percorsi Terapeutici* 2009; 10: 19-31.
21. PUNZI L, CANTINI F, MATUCCI-CERINIC M *et al.*: Discontinuation rate of the 1st and 2nd anti-tumor necrosis factor therapies in patients with rheumatoid arthritis in Italy. ISPOR 11th Annual European Congress. 2008. Athens.
22. BJÖRNÅDAL L, BAECKLUND E, YIN L, GRANATH F, KLARESKOG L, EKBOM A: Decreasing mortality in patients with rheumatoid arthritis: results from a large population based cohort in Sweden, 1964-95. *J Rheumatol* 2002; 29: 906-12.
23. ISTAT - Italian National Institute of Statistics. Mortality tables. Table II.16. 2004.
24. MAROTTO D, NIEDDU ME, COSSU A, CACCASI A: Prevalence of rheumatoid arthritis in North Sardinia: the Tempio Pausania's study. *Reumatismo* 2005; 57: 273-6.
25. ISTAT - Italian National Institute of Statistics. Population as of 1st January 2008.
26. SALAFFI F, DE ANGELIS R, GRASSI W: Prevalence of musculoskeletal conditions in an Italian population sample: results of a regional community-based study. I. The MAP-PING study. *Clin Exp Rheumatol* 2005; 23: 819-28.
27. ITALIAN DRUG FORMULARY: Informatore Farmaceutico, 69a edizione. Elsevier Masson, 2009.
28. ATZENI F, SARZI-PUTTINI P: Early rheumatoid arthritis. *Reumatismo* 2007; 59: 100-17.
29. 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.
30. RUBIO-TERRÉS C, ORDOVÁS BAINES JP, PLÁ POBLADOR R: Use and cost of biological disease-modifying anti-rheumatic drugs in Spain (PRAXIS study). *Farm Hosp* 2007; 31: 78-92.
31. LAUNOIS R, PAYET S, SAIDENBERG-KERMANAC'H N, FRANCESCONI C, FRANÇA LR, BOISSIER M: Budget impact model of rituximab after failure of one or more TNF-alpha inhibitor therapies in the treatment of rheumatoid arthritis. *Joint Bone Spine* 2008; 75: 688-95.
32. KOBELT G, EBERHARDT K, GEBOREK P: TNF inhibitors in the treatment of rheumatoid arthritis in clinical practice: costs and outcomes in a follow up study of patients with RA treated with etanercept or infliximab in southern Sweden. *Ann Rheum Dis* 2004; 63: 4-10.