Rheumatoid arthritis (RA) is a chronic inflammatory disorder that affects joints with swelling and progressive joint destruction. The pathology leads to a progressive disability with an impact on the quality of life of the patients. Strategies to reduce in-patient care costs could have a considerable impact on lowering the direct medical costs of RA in Italy. Abatacept, a selective T-cell costimulation modulator, is a valuable treatment option for patients with moderate-to-severe RA. A search using the keywords “cost-effectiveness analysis”, “budget impact model”, “abatacept”, and “rheumatoid arthritis” was carried out on PubMed. Abatacept in the first- and second-treatment lines has been evaluated in our research. We evaluated patients with inadequate MTX response, inadequate anti-TNF agents response, switch studies and real-world data. Furthermore, in our research, we evaluated the main head-to-head studies published.

**Keywords:** abatacept, budget impact model, cost-effectiveness analysis, rheumatoid arthritis

**Introduction**

Rheumatoid arthritis (RA) is an inflammatory, chronic disorder that affects the joints, with swelling and progressive destruction. The pathology determines disability and a progressive impact on the quality of life of patients. Patients receive sDMARD therapies often for life. The social burden of illness of RA is high, involving patients, families and society with direct, indirect and intangible costs. Direct health care costs alone represent approximately one-fourth of all costs and are largely represented by in-patient care costs. In Italy, the socioeconomic cost of RA was estimated as 1,600 million euros (1,210 million for indirect social costs and 380 million for direct medical costs). On the basis of prevalence data, the total social cost of RA was estimated as €3.5 billion in Italy per year. Direct medical costs accounted for 21% of the total costs (drugs, in-patients care and day hospital, visits, diagnostic examinations, rehabilitation), while the remaining 79% were non-medical costs (direct non-medical costs and indirect costs). Strategies to reduce in-patient care costs could have a considerable impact on lowering the direct medical costs of RA in Italy. Abatacept, a selective T-cell costimulation modulator, is a valuable treatment option for patients with moderate-to-severe RA. Given new clinical evidence, for the first time, recommendations from the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have included abatacept in the list of options for first-line biologic DMARD (bDMARD) use in patients with inadequate response to conventional DMARD monotherapy. These new guidelines place abatacept at the same line of treatment options as TNF-α inhibitors, which traditionally have been considered the first-line biologic therapy.
Main search
The main research was carried out in September 2018. We started from the keywords cost-effectiveness analysis, budget impact model, abatacept and rheumatoid arthritis. The research on PubMed subsequently selected the papers with the following topics: a) real-world data; b) patients with inadequate MTX response; c) patients with inadequate response to anti-TNF; d) head-to-head studies and pharmacoeconomic consequences; and e) persistence and costs of a switch.

The Institutional Review Board, the Health Director of San Giovanni di Dio Hospital in Florence, reviewed and approved this research, in the respect of Privacy Law, for clinical and scientific studies and publications.

Real-world data
A retrospective observational study based on an administrative database of three Local Health Units was assessed in the period from January 1, 2009, to December 31, 2011, based on the prescriptions of biological drugs approved for RA. Patients were followed one year before enrollment and for a period of 12 months after. The primary and secondary aim was to evaluate the escalation dose in bio-naive patients without switches. For all agents, dose escalation was 21.4% for infliximab, 11.5% for adalimumab, 5.6% for abatacept, 4% for tocilizumab and 3.8% for etanercept. The annual costs per treated patients were €12,803 for adalimumab, €11,924 for etanercept, €11,830 for tocilizumab, and €11,201 for infliximab and €10,943 for abatacept.8

Patients with inadequate MTX response
A simulation model evaluated patients with inadequate MTX response in patients with moderate or severe RA. The simulation evaluated the progression of disability assessed with HAQ. Patients were enrolled to receive MTX or MTX+abatacept. In the 10-year perspective, abatacept determined a gain of 1.2 quality-adjusted life years (QALYs) per patient (4.6 vs 3.4 MTX) with an additional cost of $51,426 ($103,601 vs $52,175, respectively); evaluation in a time frame of all life determined an improvement of 2.0 QALYS (6.8 vs 4.8) and an additional cost of $67,757 ($147,853 vs $80,096). Cost-effectiveness was $47,910 ($44,641, $52,136) per QALY gained over 10 years and $43,041 ($39,070, $46,725) per QALY gained over a lifetime.9

Patients with inadequate response to anti-TNF
In a simulation model, patients with RA with inadequate anti-TNF response were assessed in terms of disability with HAQ. Patients were placed on treatment with oral DMARDs alone or with the addition of abatacept. In a 10-year time frame, abatacept determined an increment of 1 QALYs (4 vs 3 for oral DMARDs) with an incremental cost of $45,497 (100,648 vs $55,151) respectively. In a lifetime space, the QALYs earned were of 1.6 (5.8 vs 4.2) and the incremental cost of $64,978 ($140,714 vs $82,489). Cost-effectiveness was $50,576 ($47,056, $54,944) per QALY gained over 10 years, and $45,979 ($42,678, $49,932) per QALY gained over the lifetime.10 Model simulation evaluated the response to 4 treatment sequences in patients with inadequate anti-TNF response over a 2-year time frame. Efficacy was assessed on the number of theoretical days (TEND) in remission or low disease activity (LDAS) assessed with the DAS28 (Disease Activity Score, evaluating 28 joints). Based on the LDAS after etanercept failure, patients treated with abatacept had a number of 102 days (TEND) in 2 years compared to those treated with rituximab 82 days (TEND) with re-treatment every 6 months over 2 years. Mean cost-effectiveness ratio showed significantly lower costs per TEND with abatacept as second biological agent (euros 278) compared with rituximab (euros 303).11

A Monte-Carlo simulation was performed by evaluating the LDAS with the DAS28 in patients with inadequate response to etanercept as the first biological treatment line. The study evaluated the use of 4 sequential treatment strategies with abatacept, rituximab, adalimumab and infliximab in a 2-year time frame. Cost-effectiveness ratio showed lower costs per day in LDAS with abatacept (427 €) compared to rituximab as second biological option (508 €).12 In another study, remission (RS), LDAS and moderate or high disease activity (MHDAS) were evaluated. The model evaluated the needed to reach days of remission (RS) and LDAS of 6 sequential treatment strategies over a 2-year time frame. Estimating mean costs per day in RS and LDAS, respectively, as €829 and €428 for the biologic sequence composed of ADA-ABA-ETA, €1292 and €517 for the sequence ADA-RTX-ETA, €829 and €429 for the sequence ETA-ABA-ADA, €1292 and €517 for the sequence ETA-RTX-ADA, €840 and €434 for the sequence INF-ABA-ETA and €1309 and €523 for the sequence INF-RTX-ETA.13 In another model, abatacept as a second line of treatment in patients with inadequate response to an anti-TNF resulted in a better response in LDAS (17.1% vs 10.2%) and remission (7.4% vs 3.9%) terms and is cost-effectiveness compared to a
second sequential biological line with anti-TNF agents.\textsuperscript{14} A large observational study performed in Germany evaluated the absence or presence of remission (RS/no RS) or low disease activity (LDAS/no LDAS). In a 2-year time frame, abatacept after an inadequate response to anti-TNF agents appeared cost-effectiveness with respect to the sequence of two anti-TNF (€633 vs €1,067/day in LDAS and €1,222 vs €3,592/day in remission), and compared to treatment with rituximab after TNF antibody failure (€633 vs €728/day in LDAS and €1,222 vs €1,812/day in remission).\textsuperscript{15} A simulation model included a switch after six months of treatment with a first biological line with anti-TNF agents. Abatacept or sequences that etanercept, infliximab, adalimumab or rituximab were predicted in the model. The sequence with abatacept was better in terms of remission and LDASafter failure of a first anti-TNF (102 days in LDAS) compared to the sequence with rituximab (82 days in LDAS). In addition, treatment with abatacept (63 days in LDAS) was better than an anti-TNF (32 days in LDAS) even after the failure of two anti-TNF. Mean cost-effectiveness ratios showed significantly lower costs per day in LDAS with abatacept used after one anti-TNF agent (€376) compared to rituximab (€456).\textsuperscript{16} In the double-blind controlled ATTEST study, patients with inadequate MTX response could be randomized to either abatacept or infliximab. Data on drug costs, days of LDAS or remission (RS) and serious adverse events (SAE) were assessed for one year and subsequently in the open-label phase. The data were, respectively, in favor of abatacept compared to infliximab for both days of remission (€5,321/€2,819) and days of LDAS(€7,189/€3,916).\textsuperscript{17} In another paper, patients with inadequate response to anti-TNF agents were assessed in terms of disability assessed with HAQ-DI. The incremental cost–utility ratio relative compared to methotrexate was $47,191 (95% CI $44,810–$49,920) per QALY gained for abatacept/methotrexate and $54,891 (95% CI $52,274–$58,073) per QALY gained for rituximab/methotrexate.\textsuperscript{18} 

**Head-to-head studies and pharmacoeconomic consequences**

Cost-consequences data reported in an Italian cost scenario have been evaluated starting from the AMPLE study.\textsuperscript{19} The data have shown efficacy in favor of abatacept compared to adalimumab. The data in favor of abatacept were due to a difference with lower costs for adverse events (-€237,246 or -€237 per patient).\textsuperscript{20} Data from the AMPLE study were also evaluated in a scenario in Germany, Spain, Italy, United States and Canada. Patients were classified by the presence or absence of anti-citrullinated protein antibodies (ACPA) and their response to abatacept or adalimumab. The cost per response in ACPA-positive patients was in favor of abatacept compared to adalimumab for ACR20, ACR90 and HAQ-DI. The costs for remission (DAS28) were in favor of abatacept in ACPA-negative patients and for Clinical Disease Activity Index and Simplified Disease Activity Index in ACPA-positive patients.\textsuperscript{21} In another study, patients starting treatment with abatacept or adalimumab plus methotrexate were evaluated after 6 months. The continuation or the discontinuation of the therapy was evaluated with European League Against Rheumatism treatment response; the progression of the disease and disability was evaluated with Health Assessment Questionnaire Disability Index score. QALYs and incremental cost per QALY gained were calculated by baseline ACPA groups (Q1, 28–234 AU/mL; Q2, 235–609 AU/mL; Q3, 613–1045 AU/mL and Q4, 1060–4994 AU/mL). Incremental cost per QALY for abatacept (vs adalimumab) was the lowest in the high ACPA titer group (Q4, £6,200/ QALY), followed by the next lowest titer group (Q3, £26,272/QALY).\textsuperscript{22} In another study, the response as the first biological line of treatment was evaluated in patients with inadequate MTX response in a German scenario. The response in terms of remission was evaluated with DAS28<2.6. The study also considered the direct costs and costs of the drug. The response to abatacept or adalimumab was evaluated in terms of cost-effectiveness analysis as a function of the presence of ACPA in patients. Treatment sequences starting with abatacept resulted in lower costs per day in remission (mean 330 €/day, range 328–333 €/day) compared to sequences starting with adalimumab (mean 384 €/day, range 378–390 €/day).\textsuperscript{23} 

**Persistence and costs of a switch**

The cost of a treatment seems to be influenced by its persistence, the switch rate and its consumption. A switch was defined as the presence of a biological therapy other than that administered at the index date during the last 3 months of the follow-up period.\textsuperscript{24} A retrospective longitudinal analysis was conducted in patients with RA using IMS PharMetrics Plus database from 1/1/2004 to 3/31/2010. The first line of patients started abatacept or an anti-TNF agent adalimumab, etanercept or infliximab and was followed up for 12 months. The second line of treatment included patients initiating a bDMARD with evidence of a different bDMARD within the previous 2 years and with 12 months of continuous follow-up. Switching was defined when a
therapy was changed in a 200% gap in day compared to previous biological therapy. In the first treatment line, the switch ratio was 2.1% for abatacept, 9.5% for adalimumab, 9% for etanercept and 5.5% for infliximab. In the second treatment line, the switch ratio was 8% for abatacept, 16.7% for adalimumab, 14.4% for etanercept and 14.3% for infliximab.25

**Perspectives with competitors and in the biosimilars scenario**

Recent research has evaluated the cost-effectiveness analysis in 122 patients who had failed a first-line therapy with TNF agent+MTX. Patients were randomized to an alternative anti-TNF group, rituximab or abatacept. Cost-effectiveness analysis was in favor of rituximab with an ICER of £332.02 £ for QALY. The value was unfavorable to abatacept considering the NICE £20,000 threshold, but the same authors concluded that this could be due to the small sample of patients considered.26 Data on biosimilars in the literature currently refer to budget impact model studies where biosimilars for low cost allow more patients to be treated over time.27 The incremental cost-effectiveness/quality-adjusted life year (ICER)/QALY of etanercept ranges from €15,315.00 when we consider direct and indirect costs and up to €38,639.00 for direct costs only. Yisaipu, another biosimilar of etanercept, in a model based on the PRESERVE study, had an estimated ICER of between $18,324 and $40,333 with the best strategy model based on the PRESERVE study, had an estimated ICER of between $18,324 and $40,333 with the best strategy and $2,39 million, respectively.

Finally, recent data on non-medical switches NMS between originator and biosimilar show that NMS rate to 25% and 50% increased payer’s total switching costs to $1,19 and $2,39 million, respectively.29 Further studies that consider the cost-effectiveness analysis of biosimilars as a function of retention rate and interruptions due to ineffectiveness or adverse events must be published to clarify.

**Conclusions**

RA is a condition that has an economic burden due to direct and indirect costs related to disability. Cost-effectiveness analysis studies can address treatment choices based on the scarce economic resources of our healthcare system. Choices can be made according to the budgets of individual hospitals, individual healthcare companies or at regional level. The personalization of medicine has shown that abatacept proves to be cost-effectiveness in patients with inadequate response to DMARDs, anti-TNF and in a subgroup of patients with ACPA positivity.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**


