Tocilizumab after a first-line with anti-TNF in rheumatoid arthritis: a cost-consequence analysis in the Italian setting

S. Iannazzo[1], M. Benucci[2], E.G. Favalli[3]

[1]SIHS Health Economics Consulting, Turin, Italy; [2]Rheumatology Unit, S. Giovanni di Dio Hospital, Florence, Italy; [3]Department of Rheumatology, Gaetano Pini Institute, Milan, Italy.

Abstract

Objective

Switching to a different mechanism of action in rheumatoid arthritis (RA) patients after a first anti-TNF-α has proved to be effective. The objective of this study was a health economic assessment in Italy.

Methods

The study was conducted using a pharmacoeconomic model with a 3-year time horizon. Effectiveness was measured as days gained in low disease activity (LDA; DAS28-ESR <3.2) or in remission (DAS28-ESR <2.6). The model simulated the response to treatments, based on the Rotation Or Change (ROC) trial, the probability of discontinuation and switch to a 3rd-line biologic, and the transition to death. Time on treatment curves for 2nd-line biologics were derived from published Italian real-word data. Costs were estimated based on published sources and Italian prices and tariffs.

Results

The switch to tocilizumab after the failure of a first anti-TNF-α was more effective than a second anti-TNF-α, in terms of days in remission (224 vs. 114 days) and of days in LDA (345 vs. 193 days). The cost-consequence ratio with tocilizumab iv was 174 euros/day in remission and 113 euros/day in LDA. With tocilizumab sc the ratio was 181 euros/day in remission and 117 euros/day in LDA. The same ratios for the anti-TNF-α treatments ranged from 233 to Euro 320 euros per day in remission and from 138 to 190 euros per day in LDA.

Conclusion

The switch to a different mechanism of action, namely tocilizumab, after the failure of a first anti-TNF-α agent seems a rational strategy for RA patients in the Italian setting.

Key words

rheumatoid arthritis, health economics, tocilizumab, anti-TNF-α

Iannazzo Sergio, MBA
Benucci Maurizio, MD
Favalli Ennio Giulio, MD

Please address correspondence to:
Dr Sergio Iannazzo,
Via Caboto, 45,
10129 Torino, Italy.
E-mail: sergio.iannazzo@icloud.com

Received on July 2, 2017; accepted in revised form on October 16, 2017.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2018.

Funding: the development of this study was supported by Roche Italia, through a service agreement with SIHS Health Economics Consulting. S. Iannazzo is an employee and owner of SIHS, and developed the HE model.
E.G. Favalli and M. Benucci received consulting fees from SIHS.

Introduction

About a third of patients with rheumatoid arthritis (RA) who are receiving a tumour necrosis factor α inhibitor (anti-TNF-α) as a first biologic treatment, presents persistent disease and/or insufficient response (1). Cycling to a second anti-TNF-α agent, after the failure of a first, may be a reasonable approach, as, in line of principle, the lack of efficacy of one anti-TNF-α drug does not preclude the potential efficacy of another (2, 3). However, some retrospective observational studies were published in the recent literature (4-7) and showed that the switch to a different mechanism of action after the failure of a first anti-TNF-α may be a more effective strategy. Recently, the Rotation or Change (ROC) trial added to this evidence base (8). The ROC trial was a 52-week pragmatic, multicentre, open-label, parallel-group, randomised clinical trial with a superiority design. Patients with insufficient response to an anti-TNF-α were randomly assigned in a 1:1 ratio to receive a non-TNF biologic or a second anti-TNF-α agent. The main endpoint was good or moderate EULAR response. Other outcomes were rates of low disease activity (LDA), defined as the 28 joints-erythrocyte sedimentation rate (DAS28-ESR) lower than 3.2, and remission, defined as DAS28-ESR <2.6.

The cost-effectiveness analysis is generally considered the gold standard to compare the clinical and economic profile of different treatment alternatives. In this analysis the benefits are normally measured as life-years or quality-adjusted life-years gained (QALY). To obtain such as measurements it is generally necessary to extend the analysis to a lifetime time horizon. A variant of the cost-effectiveness is one type of analysis that estimates the benefit of treatments in terms of more natural and disease-specific outcomes. This is often referred to as cost-consequence analysis. The cost-consequence analysis is not suitable to inform reimbursement decision, due to the non-transferability of the measured benefits across different therapeutic areas and the consequent impossibility to define acceptability thresholds. However, the cost-consequence analysis may be useful to explore the economic profiles of treatments being compared in a clinical trial. In this case the cost-consequence approach allows the direct use of the outcomes being measured in the trial, without the need to do the complex extrapolations over a longer time horizon that a full cost-effectiveness analysis would require.

Tocilizumab is a humanised antihuman monoclonal antibody directed against the α subunit of the receptor for interleukin-6. Tocilizumab was shown to be effective in the treatment of patients with RA either as monotherapy or in combination with methotrexate (9, 10).

The objective of this study was the cost-consequence analysis to compare the switch to tocilizumab after the failure of a first anti-TNF-α to a second anti-TNF-α in Italian RA patients, based on the results of the ROC study.

Methods

The study was conducted through a pharmacoeconomic simulation model in the perspective of the Italian healthcare system. The model was developed in MS Excel (Microsoft Corporation, Redmond, WA) as a Markov model with 6-month cycles and a 3-year time horizon.

Model design

The model allowed the simulation of the response to treatment, assessed with the DAS28-ESR score, of the possibility of interrupting the second biologic line of treatment and consequent switch to a third line, and of the mortality as a function of disease severity.

The outcomes of the analysis were the average number of days spent in LDA or remission status, within the time frame of the simulation, along with the total costs associated. The conceptual schema of the model is reported in Figure 1. The model was defined in 6 health states given by the combination of the disease activity (*i.e.* Remission, defined as DAS28-ESR <2.6; Low Disease Activity – LDA, defined as DAS28-ESR <3.2; Medium to High Disease Activity – MHDA, defined as DAS28-ESR ≥3.2) and of the line of treatment (*i.e.* 2nd or 3rd biologic line).

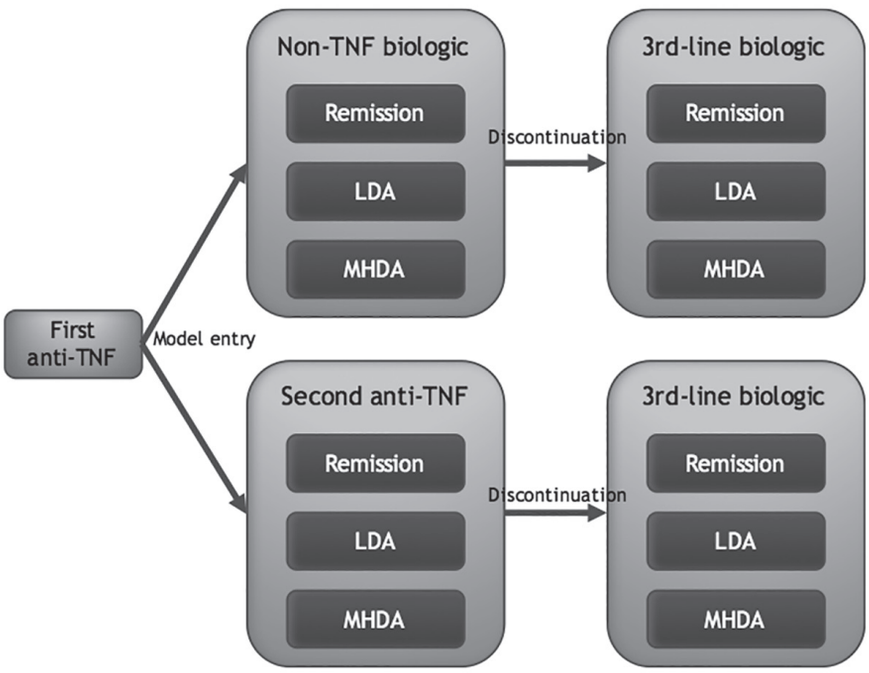

Fig. 1. Conceptual schema of the pharmacoeconomic model. The transition to death is possible from every state and is not represented. Remission is defined as DAS28-ESR <2.6; Low Disease Activity (LDA) is defined as DAS28-ESR <3.2; Moderate to High Disease Activity is defined as DAS28-ESR ≥3.2; DAS28-ESR: 28 joints-erythrocyte sedimentation rate.

Table I. Response rates at 6 and 12 months in the Rotation or Change (ROC) trial (8).

	Non-TNF-α group (n=146)		Second anti-TNF-α group (n=146)	
	n. assessed	n. in response (%)	n. assessed	n. in response (%)
Low Disease Activity (DAS28-ESR <3.2)				
6 months	139	62 (45%)	140	39 (28%)
12 months	130	53 (41%)	133	31 (23%)
Remission (DAS28-ESR <2.6)				
6 months	139	38 (27%)	140	26 (19%)
12 months	130	35 (27%)	133	18 (14%)

DAS28-ESR: 28 joints-erythrocyte sedimentation rate.

Additionally, the model included the dead state.

Clinical inputs

In the first two cycles of the simulation, corresponding to 6 and 12 months, we applied the rates of response, as resulting from the ROC trial (Table I). For subsequent cycles, we assumed that response rates reached at the end of month 12 were maintained until interruption of treatment, death or end of simulation, whatever came first. This assumption is directly based on the evidence of the substantial stability of the mean DAS28-ESR achieved in both arms of the ROC trial after 24 weeks.

We simulated the duration of treatment based on the findings of real-world evidences available in the literature. Several studies are available, reporting the duration of biologic treatments after the failure of a first anti-TNF-α (4, 5, 11-13). Among these we selected the study from Favalli *et al*. because it enrolled 201 Italian RA patients and followed them for 4 years (11). The Kaplan-Meier curves of survival on treatments for the non-TNF-α group and the second anti-TNF-α group were obtained from the original publication and digitised with the software Plot Digitizer. We applied a parametric survival analysis approach with 5 different models (Exponential, Weibull, Gompertz, Log-normal and Log-logistic), to estimate functions usable to extrapolate survival on treatment data within the model. This method is a standard approach in health economic modelling of survival data (14). After the estimation of the goodness of the fit and of the plausibility of the extrapolated portions of the different functions, the Gompertz model was chosen (Fig. 2).

We assumed that after the discontinuation of the 2nd line biologic the benefit (*i.e*. the response level reached) is lost and that all patients subsequently receive rituximab in association with methotrexate. Response rates for rituximab in 3rd line were based on the REFLEX study (*i.e*. Remission at 6 months 9%; LDA at 6 months 9%) (15).

We estimated the probability of death at each cycle of the simulation based on the mortality of the general Italian population by age and sex (16) and the standardised mortality ratio (SMR) characteristic of RA. This is derived from a large retrospective observational study which followed 1,015 RA patients from 2002 to 2009 in the US (17).

Cost inputs

For this analysis, we adopted the cost perspective of the Italian Healthcare System and consequently only direct medical costs were taken into account. More in detail we considered the following cost categories: acquisition of treatments, administration, co-medications, routine management costs as a function of disease activity. All costs were estimated as of March 2017.

We calculated acquisition costs of biologic drugs based on ex-manufacturer prices (18) and prescribed doses (as reported in their respective Summary of Product Characteristics – SPCs) (19-24) (Table II). The dose of tocilizumab iv was estimated considering the average body weight of 66 kg (25). For infliximab it was assumed an average dose of 3.57 mg/kg (26). For biosimilar products it was considered the same dosage of the originators. We based the estimation of the unit costs of an intravenous administration (Euro 11.62) on a previously published Italian cost analysis (27). In line with the same analysis we assumed no cost for a subcutaneous administration (27). Additionally, we considered monitoring costs associated with the administra-

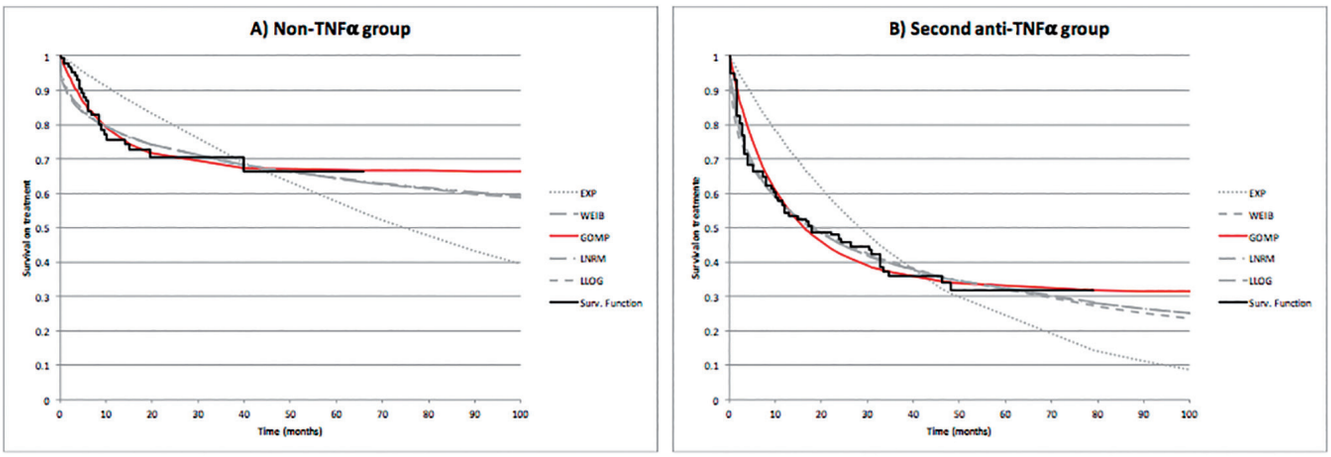

Fig. 2. Parametric survival analysis on the time on treatment data from Favalli *et al*. (11). The Gompertz model was selected based on the goodness of the fit and on the plausibility of the extrapolated portion of curves.

Table II. Per cycle (6-months) costs of the biologic drugs considered in the analysis.

Biologic	Dose	Admin frequency	Cost per cycle (Euro/6 months)	Sources
Tocilizumab ev	8 mg/kg	Once every 4 weeks	6,415.02	(18,19,25)
Tocilizumab sc	162 mg	Once a week	6,810.41	(18,19)
Adalimumab	40 mg	Once every 2 weeks	6,289.95	(18,19)
Certolizumab – 1st cycle	400mg first 3 injections;			
200 mg thereafter	Once every 2 weeks	7,384.95	(18,21)	
Certolizumab - cycles 2+	200mg	Once every 2 weeks	6,004.12	(18,21)
Etanercept	50mg	Once a week	6,007.25	(18,22)
Etanercept biosimilar	Same as the originator	Same as the originator	4,102.54	(18)
Golimumab	100mg	Once a month	6,265.14	(18,23)
Infliximab – 1st cycle	3.57 mg/kg	First infusions after 2 and 6 weeks; once every 7 weeks thereafter	5,163.24	(18,24-26)
Infliximab – cycles 2+	3.57 mg/kg	Once every 7 weeks	3,951.54	(18,24-26)
Infliximab biosimilar – 1st cycle	Same as the originator	Same as the originator	3,872.43	(18)
Infliximab biosimilar - cycles 2+	Same as the originator	Same as the originator	2,963.66	(18)

Table III. Healthcare resources consumption in RA patients by disease activity, derived from Beresniak *et al*. (34).

Resource	DAS28 remission	DAS28 LDA	DAS28 MHDA
Rheumatologist visits	1-6 in first 6-month; 1-3 in following 6-month periods	1-6 in first 6-month; 1-4 in following 6-month periods	1-6 every 6 months
Other specialist visits	60-70% 1 visit per year	60-70% 1 visit per year	60-70% 1-3 visit per year
Laboratory tests (blood)	1-6 in first 6-month; 1-3 in following 6-month periods	2-6 in first 6-month; 1-4 in following 6-month periods	2-6 every 6 months
Radiographs (hands and feet)	1-4 over 2 years	1-2 over 2 years in first 6-month; 1-4 in following 6-month periods	1-2 every 6 months
Radiographs (main joints)	-	-	1 per year
Hospitalisation	0-10% hospitalised over 6 months	0-15% hospitalised over 6 months	5-25% hospitalised over 6 months

tion of tocilizumab, with the frequencies recommended in its SPC (ALT and AST: every 4–8 weeks in the first 6 months, and every 12 weeks subsequently; neutrophils and platelet count: every 4–8 weeks; lipid parameters: every 4–8 weeks) (19). Unit costs of these exams were derived from off-patient reimbursement tariffs (28).

Several Italian studies in the literature analysed the cost of managing patients with RA, however, none of them stratified this cost by disease activity (27, 29-33). In absence of Italian data, we considered a French study, that assessed the average healthcare resources consumption by disease activity, based on clinical guidelines and the opinion of clinical experts (34). The healthcare resources consumption from Beresniak *et al*. is reported in Table III. In the base

case analysis we used the central value of the range for each resource. The lower and upper bounds of the ranges were used to inform the sensitivity analysis.

Analysis

In the base case analysis we compared the cost-consequence ratios, *i.e.* the cost per day in remission and the cost per day in LDA, obtained with each treatment alternative. The incremental analysis was also undertaken. More specifically we calculated the incremental cost-consequence ratio of tocilizumab as compared to the most convenient treatment in the anti-TNF-α group. This incremental ratio has no direct meaning, but we used it to measure the amplitude of the displacement from the base case result produced in the one-way sensitivity analysis (OWSA). In such a sensitivity analysis all the input parameters are varied one at a time within their uncertainty range, and the impact on the final result is recorded. We derived the information on the uncertainty range from the original literature sources, with the min-max range, the 95%CI or the standard error of the mean being used in most cases. In all the cases where this information was not available we adopted the working assumption of a standard error equaling to the 10% of the mean, from which the uncertainty range was derived.

Results

In the base case analysis tocilizumab was more effective than anti-TNF-α, both in terms of days in remission (224 days with tocilizumab *vs*. 114 days with anti-TNF-α) and of days in LDA (345 days with tocilizumab *vs*. 193 days with anti-TNF-α) (Table IV). Total costs in the two tocilizumab arms were higher than those resulting from the anti-TNF-α (Euro 38,948 and Euro 40,374 for tocilizumab iv and sc *vs*. Euro 26,621–36,565 for the anti-TNF-α). The cost increase, due to the higher acquisition cost, was only marginally displaced by the savings in co-medications and management of patients (Table V). The cost-consequence ratios of tocilizumab iv was Euro 174.3/day in remission and Euro 112.8/day in LDA. The same values were Euro 180.7/day in remission and Euro 116.9/day in LDA for tocilizumab sc. These ratios were lower than those related to anti-TNF-α comparators (Table IV). For the purpose of the OWSA we performed the incremental analysis comparing tocilizumab iv with the most convenient among the anti-TNF-α, *i.e.* infliximab biosimilar. We developed the OWSA for this specific case, to assess the general stability of the model and the reliability of the entire set of results produced. The incremental cost-consequence ratio of the comparison tocilizumab iv *versus* infliximab biosimilar was Euro 112.97/day in remission gained and Euro 80.78/day in LDA gained. The OWSA was run on the first of these two results to identify the parameters that were most influencing the results and to assess the displacement produced from the base case. Figure 3 shows the result of the OWSA in the form of a tornado diagram, where parameters are sorted in order of their impact. The parameters that most impacted on results were the cost of biologics and the response rates at 12 months. Overall the model showed a good stability, with relatively small displacements from the base case value of the incremental cost-consequence ratio.

Table IV. Base case results of the cos-effectiveness analysis.

	Days in remission	Days in LDA	Costs (Euro)	Cost/day in remission	Cost/day in LDA
Tocilizumab ev	223.5	345.3	38,948	174.3	112.8
Tocilizumab sc	223.5	345.3	40,374	180.7	116.9
Adalimumab	114.3	192.7	36,293	317.4	188.3
Certolizumab	114.3	192.7	36,565	319.8	189.7
Etanercept	114.3	192.7	35,394	309.5	183.6
Etanercept biosimilar	114.3	192.7	29,336	256.6	152.2
Golimumab	114.3	192.7	36,214	316.7	187.9
Infliximab	114.3	192.7	30,022	262.6	155.8
Infliximab biosimilar	114.3	192.7	26,621	232.8	138.1

Table V. Break-down of costs in the base case analysis.

	Biologics	Co-medications	Administration	Management	Total
Tocilizumab ev	35,617	804	371	2,155	38,948
Tocilizumab sc	37,382	804	32	2,155	40,374
Adalimumab	33,396	885	62	1,950	36,293
Certolizumab	33,668	885	62	1,950	36,565
Etanercept	32,497	885	62	1,950	35,394
Etanercept biosimilar	26,439	885	62	1,950	29,336
Golimumab	33,317	885	62	1,950	36,214
Infliximab	26,995	885	193	1,950	30,022
Infliximab biosimilar	23,594	885	193	1,950	26,621

Discussion and conclusions

The aim of this study was to explore the economic implications of different treatment strategies in rheumatoid arthritis patients who have failed a first line of biological treatment with an anti-TNF-α in the Italian setting. Several evidences are available in the literature, and among them, probably the most relevant published in the recent past was the ROC trial. Following the design of this study we assessed the cost-consequence ratios of a choice of possible second anti-TNF-α and compared it with a drug based on different mechanism of action, namely tocilizumab. The results of our study showed that the choice of tocilizumab may be rational from the pharmacoeconomic point of view.

The ROC trial was an important piece of evidence in the rheumatic clinical literature, however there are some critical points associated with its design. These critical points affect in turn our economic analysis. While we acknowledge this, we still believe that the ROC trial is the best evidence currently available. One of such elements is the clinical index used to define response to the treatments, namely the DAS28-

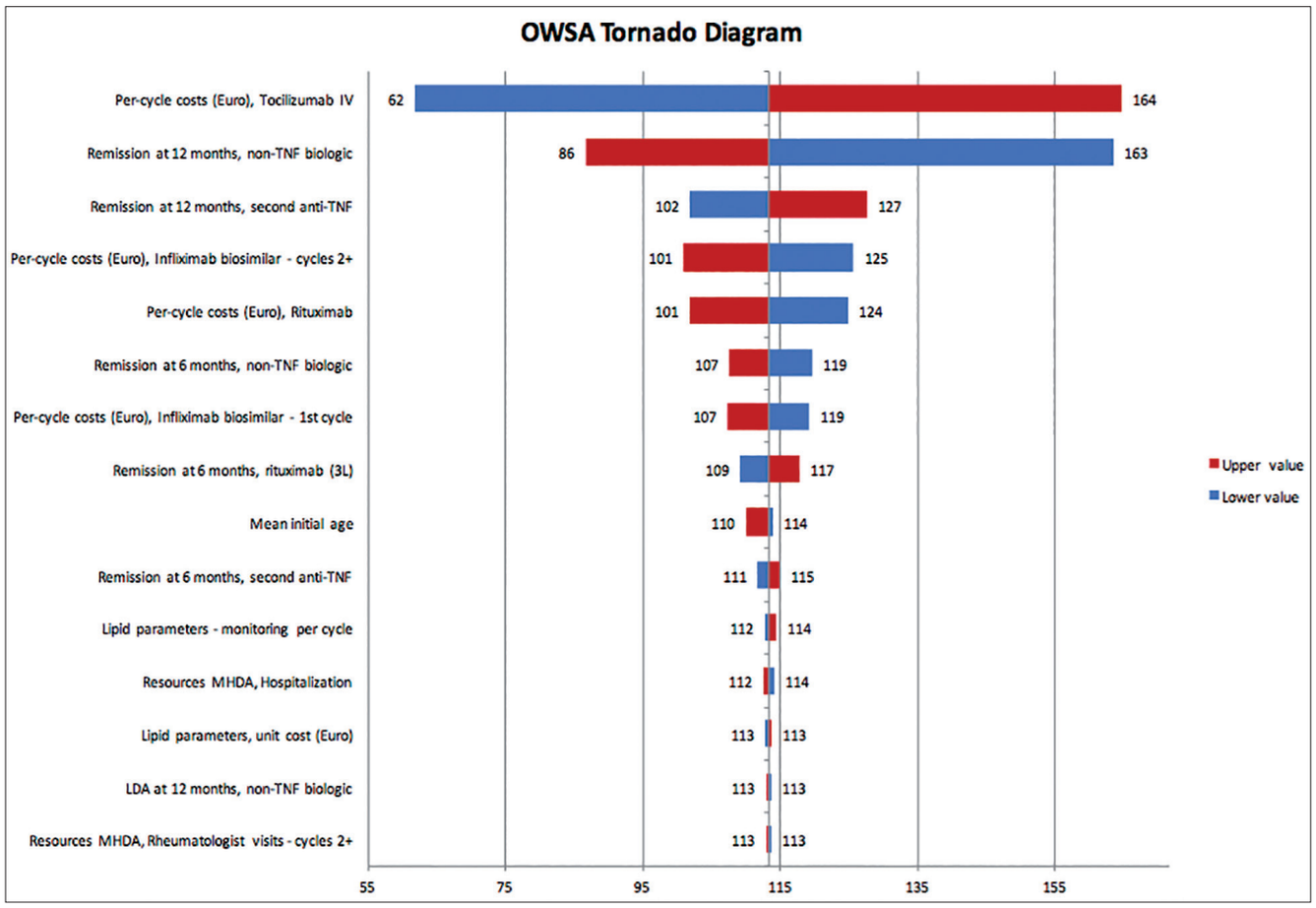

Fig. 3. Tornado diagram reporting the results of the one-way sensitivity analysis (OWSA). The input parameters are sorted by impact produced on the result of the analysis. The base case incremental cost-consequence ratio of the comparison tocilizumab iv *vs*. infliximab biosimilar was Euro 112.97/day in remission gained.

ESR score. We acknowledge the long-going debate on the use of this score in RA and the criticism that was raised in some instances. Moreover, the most recent clinical guidelines now recommend the use of composite indexes to measure responses such as, for instance the SDAI score. However, this type of scores was not used in the ROC trial. Another limit linked to the design of the ROC trial is the pooling of different treatments into the two trial's comparators, *i.e*. the second anti-TNF-α and the non-TNF-α groups. Patients in the first group received adalimumab (39%), certolizumab (16%), etanercept (36%) and infliximab (5%), while patients in the second group received abatacept (23%), rituximab (28%), and tocilizumab (48%). The implicit assumption in this design is that anti-TNF-α drugs and biologic drugs based on a different mechanism of action have the same efficacy profile, which is debated in the literature with the presence of conflicting evidences in favour or against this hypothesis. However, another randomised clinical study, *i.e*. the recent EXXELERATE head-to-head trial, which assessed the effectiveness of certolizumab pegol and adalimumab, seems to be in support of this assumption (35).

Another point of discussion is related to the estimation of costs, where we added monitoring and exams associated with the administration of tocilizumab (*i.e*. ALT and AST testing, blood exams and lipid parameters control). This should be regarded as a conservative assumption, because, in our experience these exams are routinely executed with all treatments, regardless the fact that they are explicitly recommended only in tocilizumab SPC. Another consideration is related to the choice of rituximab as a third biologic line. Rituximab response data were derived from the REFLEX study, which enrolled 2nd line as well as 3rd or more line patients (about 40% of the enrolled patients received two or more biologics before rituximab). Adopting this input data we thus implicitly assumed that with this drug response rates are similar across all lines of treatment. However, this assumption was necessary, because no data are available in 3rd line only. It should also be noted that the assumption of rituximab in third line is not introducing a bias in the analysis, as demonstrated by the OWSA where rituximab-related input parameters do not rank among those producing the highest impact. A final remark is to be done on the generalisability of the findings of this study to contexts different from the Italian setting. The analysis is based on clinical data that have a general validity. However the economic section of the analysis makes large use of unit costs that are specific of the

Italian setting. It is generally acknowledged that this is a general limit of all economic evaluations because of local unit costs and treatment patterns that can greatly vary from country to country. Thus we believe that the findings of our study are only limitedly transferrable to another setting.

In conclusion, our study is showing that, on the basis of the findings of the ROC trial and within the limits of the available evidence, the switch to a drug characterised by a different mechanism of action, namely tocilizumab, after the failure of a first anti-TNF-α may be considered an effective and cost-effective strategy in RA in Italy.

References

1. 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.
2. SMOLEN JS, KAY J, DOYLE MK *et al*.; GO-AFTER STUDY INVESTIGATORS: Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet* 2009; 374: 210-21.
3. SCHIFF MH, VON KEMPIS J, GOLDBLUM R, TESSER JR, MUELLER RB: Rheumatoid arthritis secondary non-responders to TNF can attain an efficacious and safe response by switching to certolizumab pegol: a phase IV, randomised, multicentre, double-blind, 12-week study, followed by a 12-week open-label phase. *Ann Rheum Dis* 2014; 73: 2174-7.
4. CHASTEK B, BECKER LK, CHEN CI, MAHAJAN P, CURTIS JR: Outcomes of tumor necrosis factor inhibitor cycling versus switching to a disease-modifying anti-rheumatic drug with a new mechanism of action among patients with rheumatoid arthritis. *J Med Econ* 2017; 20: 464-73.
5. PASCART T, PHILIPPE P, DRUMEZ E *et al*.: Comparative efficacy of tocilizumab, abatacept and rituximab after non-TNF inhibitor failure: results from a multicentre study. *Int J Rheum Dis* 2016; 19: 1093-102.
6. BACKHAUS M, KAUFMANN J, RICHTER C *et al*.: Comparison of tocilizumab and tumour necrosis factor inhibitors in rheumatoid arthritis: a retrospective analysis of 1603 patients managed in routine clinical practice. *Clin Rheumatol* 2015; 34: 673-81.
7. BERGMAN MJ, ELKIN EP, OGALE S, KAMATH T, HAMBURGER MI: Response to biologic disease-modifying anti-rheumatic drugs after discontinuation of anti-tumor necrosis factor alpha agents for rheumatoid arthritis. *Rheumatol Ther* 2014; 1: 21-30.
8. GOTTENBERG JE, BROCQ O, PERDRIGER A *et al*.: Non-TNF-targeted biologic vs a second anti-TNF drug to treat rheumatoid arthritis in patients with insufficient response to a first anti-TNF drug: a randomized clinical trial. *JAMA*. 2016; 316: 1172-80.
9. KREMER JM, BLANCO R, HALLAND AM *et al*.: Clinical efficacy and safety maintained up to 5 years in patients with rheumatoid arthritis treated with tocilizumab in a randomized trial. *Clin Exp Rheumatol* 2016; 34: 625-33.
10. HARAOUI B, CASADO G, CZIRJÁK L *et al*.: Patterns of tocilizumab use, effectiveness and safety in patients with rheumatoid arthritis: core data results from a set of multinational observational studies. *Clin Exp Rheumatol* 2017; 35: 899-906.
11. FAVALLI EG, BIGGIOGGERO M, MARCHESONI A, MERONI PL: Survival on treatment with second-line biologic therapy: a cohort study comparing cycling and swap strategies. *Rheumatology* (Oxford) 2014; 53: 1664-8.
12. ROTAR Z, HOČEVAR A, REBOLJ KODRE A, PRAPROTNIK S, TOMŠIČ M: Retention of the second-line biologic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis failing one tumor necrosis factor alpha inhibitor: data from the BioRx.si registry. *Clin Rheumatol* 2015; 34: 1787-93.
13. DU PAN SM, SCHERER A, GABAY C, FINCKH A: Differential drug retention between anti-TNF agents and alternative biological agents after inadequate response to an anti-TNF agent in rheumatoid arthritis patients. *Ann Rheum Dis* 2012; 71: 997-9.
14. LATIMER, N: NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011. Available from http://www.nicedsu.org.uk
15. COHEN SB, EMERY P, GREENWALD MW *et al*.; REFLEX TRIAL GROUP: 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.
16. ISTAT – Italian National Institute for Statistics. Mortality table of the general population – 2015 data. Available from http://demo.istat.it
17. MIKULS TR, FAY BT, MICHAUD K *et al*.: Associations of disease activity and treatments with mortality in men with rheumatoid arthritis: results from the VARA registry. *Rheumatology* (Oxford) 2011; 50: 101-9.
18. CODIFA L'Informatore Farmaceutico. EDRA publications. Available from http://www.codifa.it/default.asp
19. RoActemra Summary of Product Characteristics. Available from http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124&jsenabled=true
20. Humira Summary of Product Characteristics. Available from http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124&jsenabled=true
21. Cimzia Summary of Product Characteristics. Available from http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124&jsenabled=true
22. Enbrel Summary of Product Characteristics. Available from http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124&jsenabled=true
23. Simponi Summary of Product Characteristics. Available from http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124&jsenabled=true
24. Remicade Summary of Product Characteristics. Available from http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124&jsenabled=true
25. PUNZI *et al*.: Terapia evidence based 2008 www.wkhealth.it/teb/
26. 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.
27. BATTICCIOTTO A, RAVASIO R, RIVA M, SARZI-PUTTINI P: Efficacy and treatment costs of monotherapy with bDMARDs in the treatment of rheumatoid arthritis in patients intolerant to or inappropriate to continue treatment with methotrexate. *Adv Ther* 2016; 33: 1360-73.
28. Ministry of Health. Decree 18 october 2012 "Remunerazione prestazioni di assistenza ospedaliera per acuti, assistenza ospedaliera di riabilitazione e di lungodegenza post acuzie e di assistenza specialistica ambulatoriale". GU n.23 of 28-1-2013 - Suppl. Ordinario n. 8
29. ANMAR-SIR. RAPPORTO SOCIALE SULL' ARTRITE REUMATOIDE. Rome, October 2008. Available from http://www.reumatologia.it/cmsx.asp?IDPg=102
30. 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.
31. TURCHETTI G, BELLELLI S, MOSCA M: The social cost of rheumatoid arthritis in Italy: the results of an estimation exercise. *Reumatismo* 2013; 65: 271-7.
32. DELLA ROSSA A, NERI R, TALARICO R *et al*.: Diagnosis and referral of rheumatoid arthritis by primary care physician: results of a pilot study on the city of Pisa, Italy. *Clin Rheumatol* 2010; 29: 71-81.
33. CERRA C, RAVASIO R, POLCARO F: Il costo dell'Artrite Reumatoide: l'esperienza dell'ASL della Provincia di Pavia. *Giorn It Health Technol Assess* 2009; 2: 111-7.
34. BERESNIAK A, GOSSEC L, GOUPILLE P *et al*.: Direct cost-modeling of rheumatoid arthritis according to disease activity categories in France. *J Rheumatol* 2011; 38: 439-45.
35. SMOLEN JS, BURMESTER GR, COMBE B *et al*.: Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study. *Lancet* 2016; 388: 2763-74.