

Cost-Effectiveness of Tocilizumab Compared to Standard Treatment Sequences for the Treatment of Moderate/Severe Rheumatoid Arthritis Patients in Portugal

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Introduction

Rheumatoid Arthritis (RA) is a chronic, progressive, autoimmune disease characterized by joint inflammation. RA is responsible for high morbidity rates that, in the long term, significantly interfere with the patients' quality of life. RA significantly affects patients' physical functioning and ability to work requiring greater use of health care and causing significant economic impact to society^{1,2}.

The initial therapeutic approach for RA consists of using classic Disease Modifying Anti-Rheumatic Drugs (DMARDs) such as methotrexate, leflunomide, sulphasalazine and hydroxychloroquine. After Inadequate Response (IR) to these drugs patients may change to a biological agent (bDMARD).

Tocilizumab (TCZ) is a monoclonal antibody with an innovative mechanism of action that has shown to reduce significantly RA signs and symptoms thus presenting as an important therapeutic alternative for RA patients.

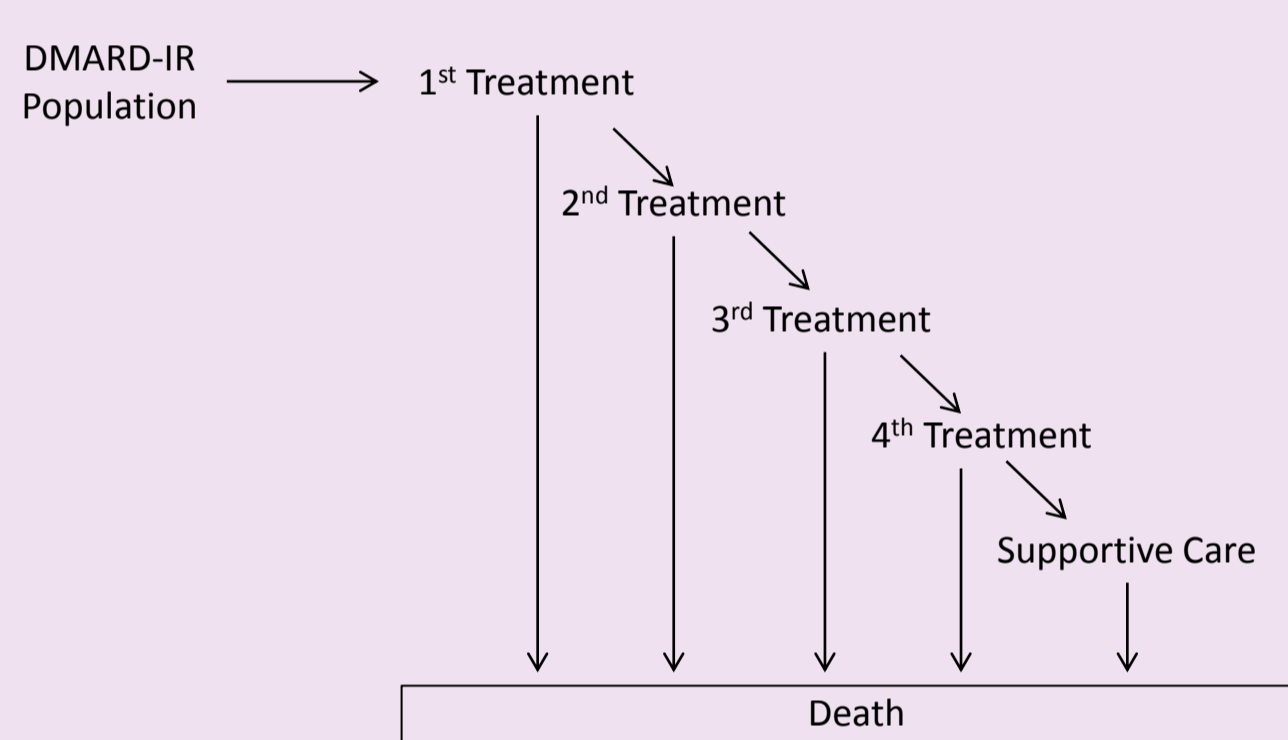
This study intends to evaluate the cost-effectiveness and cost-utility of treatment with therapeutic sequences initialized with tocilizumab (RoActemra®) versus similar therapeutic sequences commonly used in clinical practice initialized with an anti-TNF for the treatment of moderate to severe RA patients with inadequate response to previous DMARD therapy (DMARD-IR) in Portugal.

Methodology

A cost-utility and a cost-effectiveness analysis were carried out from the Portuguese National Health Service (NHS) and societal perspectives.

A Markov model, population-based, considering an hypothetical cohort of 10,000 patients diagnosed with moderate / severe RA and DMARD-IR was used. Projection of costs, Life Years Gained (LYG) and Quality-Adjusted Life Year (QALYs) until the end of life was performed.

Figure 1 – Schematic representation of the model



The analysis compares DMARD-IR patient outcomes in three different scenarios (Table 1): a treatment sequence initialized with tocilizumab followed by a TNF inhibitor, rituximab, abatacept and supportive care versus the same sequence initialized with a TNF inhibitor. Patients switched from one treatment to the following according to the ACR response rates for biologic treatments obtained from a mixed treatment comparison analysis³.

Table 1 – Therapeutic alternatives considered in the analysis for each of the three scenarios

	Scenario 1		Scenario 2		Scenario 3	
1 st treatment	Tocilizumab	Etanercept	Tocilizumab	Adalimumab	Tocilizumab	Etanercept
2 nd treatment	Adalimumab	Adalimumab	Etanercept	Etanercept	Infliximab	Infliximab
3 rd treatment	Rituximab	Rituximab	Rituximab	Rituximab	Rituximab	Rituximab
4 th treatment	Abatacept	Abatacept	Abatacept	Abatacept	Abatacept	Abatacept
Supportive care	60% MTX; 10% Leflunomide; 20% MTX+Leflunomide; 5% MTX+Cyclosporin; 5% MTX+Hydroxychloroquine					

Patients demographics - age, HAQ-DI score and gender - were based on data from a pooled analysis of three Phase III clinical trials⁴⁻⁶.

The modeling of the relationship between the HAQ-DI scores and EuroQol (EQ-5D) utilities was based on data from these clinical trials.

Resource use was estimated based on national clinical practice obtained in the framework of an expert panel of Portuguese rheumatologists.

The analysis considered treatment costs – i.e. drugs, administration and monitoring costs - as well as costs resulted from work incapacity / HAQ score (indirect costs)^{7,8} and hospitalization days. Unitary costs were obtained from official sources⁹⁻¹³. Costs and consequences were discounted at a rate of 5% per year.

Table 2 – Annual treatment costs

Alternative	Drugs (€)	Administration (€)	Monitoring (€)	Total (€)
Tocilizumab	10,573.98	201.50	583.84	11,359.32
Abatacept	13,485.26	201.50	542.34	14,229.10
Adalimumab	12,296.93	-	490.59	12,787.52
Etanercept	11,421.72	-	490.59	11,912.31
Infliximab	8,913.32	123.13	582.80	9,619.25
Rituximab	10,409.26	51.27	662.90	11,123.43
Supportive care	290.67	-	557.41	848.08
MTX	134.07	-	438.88	572.95

Table 3 – Annual costs of hospitalization and indirect costs

Score HAQ	Hospitalization (€)	Indirect Costs (€)	Total (€)
0.0 to 0.5	152.77	0.00	152.77
0.6 to 1.0	76.38	1,593.95	1,670.34
1.1 to 1.5	299.66	3,442.44	3,742.10
1.6 to 2.0	423.04	5,773.02	6,196.06
2.1 to 2.5	1,092.86	5,864.67	6,957.53
2.6 to 3.0	2,444.25	6,482.00	8,926.25

Results

Base case

The model estimated that all treatment sequences initialized with tocilizumab resulted in gains in terms of QALYs and LYG (0.22 and 0.043 respectively) and lower direct, indirect and total costs versus comparator sequences initialized with anti-TNFs, presenting themselves as dominant options against their comparators in all three scenarios.

Table 4 – Results of base case scenario

	Scenario 1		Scenario 2		Scenario 3	
	TCZ	Comparator	TCZ	Comparator	TCZ	Comparator
QALYs	8.11	7.88	8.11	7.88	8.11	7.88
Years of Life	25.51	25.36	25.51	25.36	25.51	25.36
Indirect Costs (€)	111,913	112,983	109,776	113,438	104,176	105,224
Direct Costs (€)	17,803	18,640	17,803	18,640	17,803	18,640
Total Costs (€)	129,715	131,623	127,578	132,077	121,978	123,863
QALYs incremental	0.22		0.22		0.22	
Total incremental Costs (€)	-1,908		-4,499		-1,885	
ICUR (Total Costs)	DOMINANT		DOMINANT		DOMINANT	
ICUR (Direct Costs)	DOMINANT		DOMINANT		DOMINANT	
ICER (Total Costs)	DOMINANT		DOMINANT		DOMINANT	

Legend: QALY – quality-adjusted life year; ICUR – Incremental Cost Utility Ratio, ICER – Incremental Cost-Effectiveness Analysis Ratio

Deterministic Sensitivity Analysis

One-way deterministic sensitivity analyses were performed with variables identified as having greater potential to bias namely:

- Biological drugs cost ($\pm 15\%$);
- Discount rate (0%);
- Rituximab dosage (re-treatment 6/6 months or 12/12 months);
- Patient weight (pooled population data from phase III clinical trials: 72.8 kg);
- Monitoring associated with tocilizumab and abatacept (12 appointments/year);
- Unadjusted response rate.

The sequences initialized with tocilizumab remained dominant in the sensitivity analyses for all the tested parameters, except when all biological drugs - except tocilizumab - costs were reduced by 15% and when patients weight was 72.8 kg.

Probabilistic Sensitivity Analysis (PSA)

The probabilistic sensitivity analysis (10,000 patients, 2,000 samples) carried out demonstrated the robustness of the results:

- Scenario 1 - The sequence initialized with tocilizumab was cost-effective under the threshold of €30,000/QALY in 98.5% and a dominant alternative in 72.0% of the samples.
- Scenario 2 - The sequence initialized with tocilizumab was cost-effective under the threshold of €30,000/QALY in 100% and a dominant alternative in 96.0% of the samples.
- Scenario 3 - The sequence initialized with tocilizumab was cost-effective under the threshold of €30,000/QALY in 95.0% and a dominant alternative in 69.0% of the samples.

Figure 2 - PSA Scenario 1

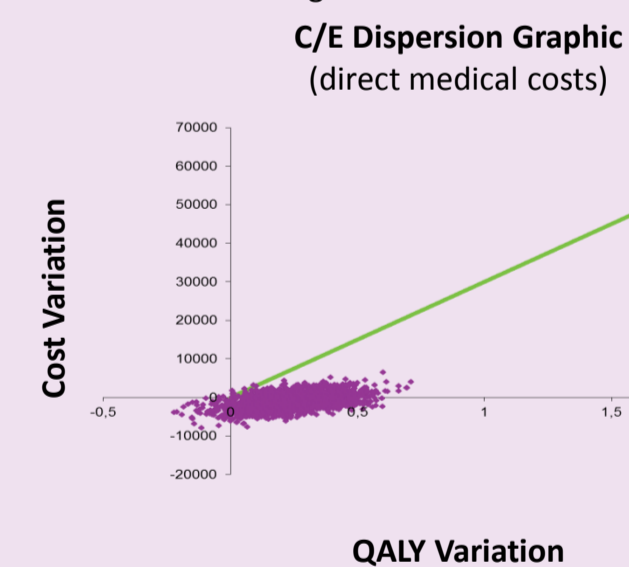


Figure 3 - PSA Scenario 2

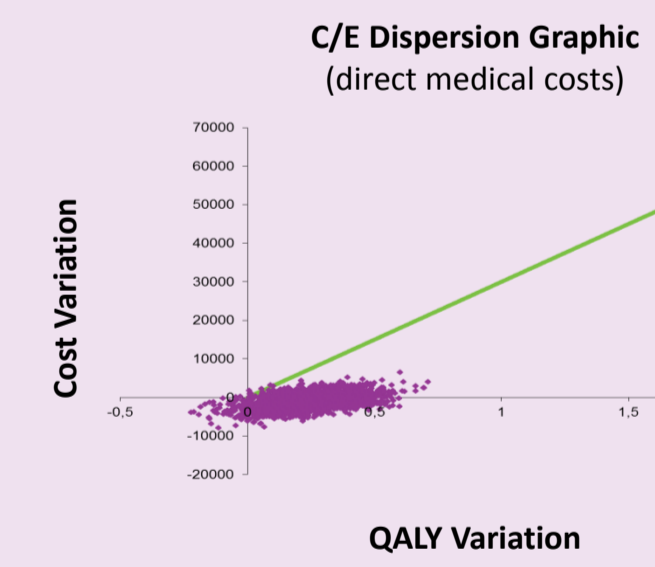
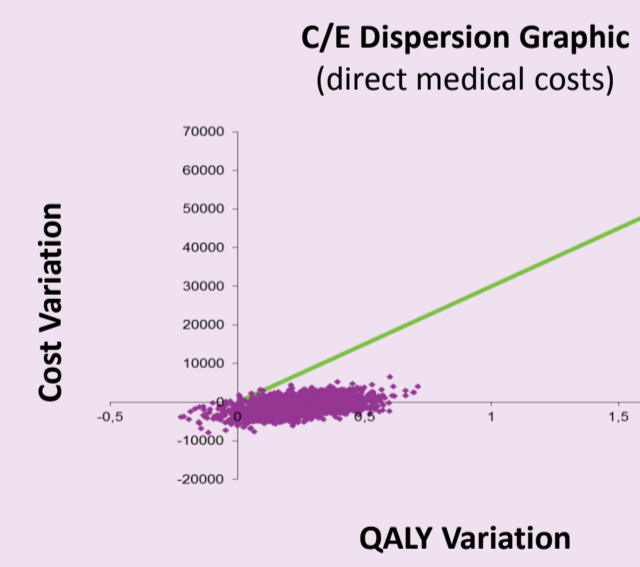


Figure 4 - PSA Scenario 3



Conclusions

- The model consistently predicts that treatment initialized with tocilizumab in DMARD-IR patients with moderate to severe RA is a dominant alternative compared to similar treatment sequences initialized with a TNF-inhibitor in Portugal.
- Tocilizumab therefore allows important gains in health and significant cost savings for society.

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