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Original article

Budget impact model of rituximab after failure of one or more TNFα inhibitor therapies in the treatment of rheumatoid arthritis

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Abstract

Objectives: To estimate the budget impact implied by the introduction of rituximab after failure of one or more anti-TNFα therapies in the perspective of the French health care system.
Methods: A Markov model reproduced the course, over 4 years, of patients treated either by infliximab, etanercept, adalimumab or RTX, after failure of one or more anti-TNFα therapies, in a multicentric study. A sensitivity analysis was developed to account for patients in 3rd and subsequent lines of treatment who are expected to consume more healthcare resources.
Results: When RTX is not used, total annual medical cost is €16,555 per patient, €13,206 of which are dedicated to drug acquisition. When RTX is the only treatment in use, these costs decrease respectively to €11,444 and €7469. Total savings per patient and per year is €5000. Over 4 years, total savings for the targeted population reach €118 M. In the sensitivity analysis, the difference between H2 and H2-coeff 2 (20%) reaches €5,400,000 in total direct costs during the first year of simulation. This difference decreases along the period, to reach €2,400,000 the fourth year of simulation, and is due to the fact that rituximab acquisition costs are independent from the treatment line.
Conclusion: If TNFα inhibitors were the only treatment available, the annual global cost of treatment would be €16,555 per patient versus €11,444 for patients treated exclusively with rituximab. RTX is expected to produce important savings (−31%) if used after failure of one or more TNFα therapies. This is mainly due to its lower drug acquisition cost. These savings could increase with the development of rituximab in earlier stages of treatment.

Keywords: Rheumatoid arthritis; Costs; Rituximab; TNFα inhibitors; Budget impact

1. Introduction

Rheumatoid arthritis (RA) is the most common inflammatory rheumatism in France. Its prevalence is about 4-fold higher in women than in men and increases with age. Its prevalence is between 0.3 and 1% of the population. The peak incidence is between 25 and 55 years old, with a global annual incidence of 20 cases/100,000 [1]. RA is a chronic disease, mainly characterized by a synovium inflammation. In the absence of treatment, it can lead to long-term joint damage, resulting in fatigue, chronic pain, functional loss and disability.

Current treatments have to be distinguished between those focusing on relieving pain and reducing inflammation (non-steroidal anti-inflammatory drugs, analgesic drugs, glucocorticoids) and those focusing on stopping or slowing joint damage (disease modifying anti-rheumatic drugs: DMARDs). DMARDs, particularly methotrexate, have been the standard for treating RA. However, responses obtained are very unstable and adverse effects may be important. When DMARDs fail, biologic treatments are used. They directly modify the immune

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system by inhibiting proteins, which contribute to inflammation. Three tumor necrosis factor (TNFα) inhibitors are currently marketed in Europe – infliximab, etanercept, and adalimumab – as well as one interleukin-1 inhibitor, anakinra.

New biologic treatments have demonstrated their efficacy in rheumatic diseases, among others: abatacept [2], tocilizumab [3] and rituximab [4,5]. Until recently, there was no specific marketing authorization for patients who failed a first TNFα inhibitor treatment. Therefore, the treatment of those patients was empirically based on the replacement of a TNFα inhibitor by another. Rituximab, an anti-B cell antibody, received in July 2006 a European marketing authorization in association to methotrexate for adult patients with severe active RA who have had an inadequate response or intolerance to other DMARDs including one or more TNFα inhibitors [6,7]. All the biologics are expansive treatments in comparison to the classic [8–10].

The present study was designed in order to estimate the budget impact implied by the introduction of rituximab after failure of one or more TNFα inhibitor therapies, a budget impact model was developed.

2. Methods

For a new agent to be reimbursed, it must first successfully clear the clinical-effectiveness hurdles of safety, efficacy, and quality. To clear the fourth hurdle, the new agent must have a favorable economic profile compared with existing treatments. And finally, the new agent must be affordable. Often an agent can clear the first four, but get disqualification on the fifth hurdle. National regulatory agencies such as the National Institute for Clinical Excellence (NICE) in England and Wales and the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia, as well as managed care organizations (MCOs) in the USA, now require that companies submit estimates of the cost effectiveness of a new drug and the likely impact of the new drug on the national or health plan budgets.

In 2006, few data were available in France on the specific population of RA patients in 2nd and subsequent lines of biotherapy treatment as no drug was specifically indicated for this population. Consequently, a retrospective observational study has been conducted in order to gather the health care resources consumptions (TC2 study). These consumptions were to be included in a Markov model, in order to estimate the budget impact of treating patients in 2nd and subsequent lines, with rituximab.

Decision makers may sometimes not consider cost effectiveness analysis useful because it does not provide direct information on the impact of a new intervention on a healthcare budget each year after its introduction. A budget impact model does since it takes the simple approach of estimating the costs of the patients with RA diagnoses group before the introduction of rituximab and the costs of patients with RA diagnoses after the introduction of rituximab

2.1. Markov model

The Markov model was designed to reproduce accurately the course of patients with severe active RA who have had an inadequate response or intolerance to one or more TNFα therapies. The budget impact model was run by having the current patient cohort progress through the model, accompanied each 6 month by the cohort of the newly diagnosed cohort. This prevalence approach has to be opposed to the incidence approach classically used in the cost effectiveness analysis; the prevalence approach estimates the impact of a new drug on healthcare budgets. The modeled period extends over 4 years (2006–2009) with cycle length of 6 months. The model comprises four states corresponding to the four treatment strategies (infliximab, etanercept, adalimumab and rituximab), and one additional entry/exit state (''switch'' state) (Fig. 1).

Etanercept and adalimumab could be given alone or in combination with methotrexate, while infliximab and rituximab were compulsorily given in combination with methotrexate. Treatment line was specified as it could influence the level of resource consumptions. During the first 6 months of treatment, patients could discontinue their treatment because of lack of efficacy. For TNFα inhibitor therapies, lack of efficacy was determined after 12 weeks of treatment, compared to 16 weeks for rituximab. At the end of each Markov cycle a patient could either continue with the original treatment if ACR20 criterion was fulfilled, or switch to a new biologic treatment, or exit the model (switch to a non-biologic strategy or die). New patients in second line treatment were also generated from the ''switch'' state to exactly compensate for patients exiting the model. In other words, we assumed that the target population was constant over time

2.2. Hypotheses

Three different hypotheses were tested for rituximab penetration into the market. Hypothesis H1 represents the situation where rituximab is not marketed with constant market shares as follows: infliximab 16%, etanercept 38% and adalimumab 46%. Hypothesis H2 assumes that rituximab penetrates progressively the market. Previous market shares were used for the first cycle. Then, each patient who failed a TNFα inhibitor therapy switched to rituximab and each new patient in 2nd line biologic treatment began with rituximab. Hypothesis (H3) represents the situation, where rituximab is the only treatment used in the indication for the whole modeled period.

Based on French Transparency Commission evaluations [11], we assumed the number of patients with RA who are eligible for rituximab would be up to 5700 patients. Posology and administration patterns are extracted from the summary of product characteristics (SmPC) of each drug. Patients received two 500 mg infusions of rituximab per hospitalization; time to next injections required by reemergence of symptoms is 9 months (median). The length of the Markov cycle is equal to 6 months. Therefore four hospitalizations are required in 18 months and the number of hospitalizations per Markov cycle is equal to 1.33 [(4/18)*6] and the number of infusion per cycle is equal to 2.66 [(8/18)*6].

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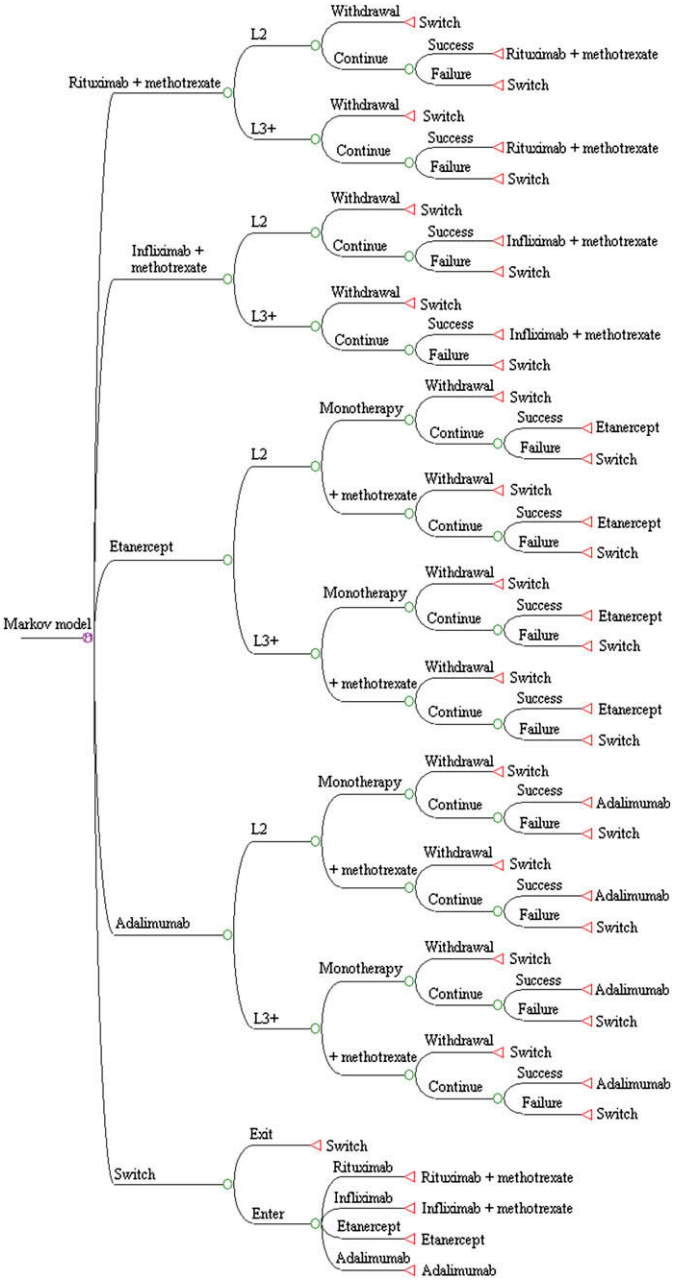

Fig. 1. Design of the Markov model that was used.

Hospital administration costs are considered identical to infliximab's. Other hospitalization costs, outpatient costs and medical visits are set to be the average of TNFα inhibitors costs except for nurses' visits for which infliximab costs are applied.

2.3. Efficacy and safety data

The model requires relative efficacy data between treatments in order to estimate transitions and/or treatment continuation. For each strategy, the percentage of patients stopping treatment because of a lack of efficacy, the percentage of patients achieving ACR20 and the percentage of patients experiencing a serious adverse event were obtained from the literature. The Bayesian mixed treatment comparisons (MTC) methodology was used to synthesize information about the four strategies of interest, as they had not been compared into a single head-to-head trial [12]. Efficacy data were extracted from 16 published clinical trials [4,13–26]. The combination methotrexate + placebo was defined as the reference comparator. Among the 16 studies, heterogeneity was observed in terms of time horizon (mostly 24 weeks but ranges from 12 to 52 weeks) and of populations. Thanks to the MTC method, these discrepancies were taken into account. Percentage of early discontinuations, defined as discontinuations for non-efficacy, have also been extracted from published clinical trials [13–23,27–30]. Adverse events levels leading to treatment discontinuation have been gathered out of the same sample of clinical trials [13–23].

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The MTC method gives the level of ACR20 responders between the different treatments (Table 1). The most efficient strategy is the combination of adalimumab + methotrexate. However, rituximab + methotrexate is not significantly different from this later (OR = 1.39; CI 95% = [0.44; 4.79]). Early discontinuation seems more frequent when biological treatments are administered as monotherapies, however no difference can be considered as significant (Table 2). Patients treated with placebo are most likely to discontinue treatment for lack of efficacy (60.8%), followed by patients treated with methotrexate + placebo (29.5%). In terms of treatment discontinuation, patients treated with adalimumab are the most likely to discontinue their treatment due to adverse events (Table 3).

2.4. Resources utilization data

A retrospective study has been conducted to provide healthcare resources for our model. A multicenter observational study was conducted between the 15th of April and the 13th of July 2006, recruiting patients treated since at least 4 months, with a 2nd line TNFα inhibitor therapies for severe RA. Inpatient and outpatient consumption in the preceding 4 months were collected retrospectively by 67 rheumatologists through a dedicated resources utilization questionnaire. The following costs categories were assessed: treatment administration, hospitalizations, outpatient visits, concomitant treatments, imaging and tests, hospital-home transport. Fifty nine centers participated in the study: 55 public hospitals and four non for profit hospitals. For profit hospitals were not recruited. An adjustment method was used to reduce the selection bias between the three treatment groups using the propensity score (PS) method. A total of 293 patients were included over 4 months.

Population characteristics: patients were treated at the hospital, in rheumatology or internal medicine departments. Inclusion criteria were as follows: adult patient, patient suffering from rheumatoid arthritis as defined by the American College of Rheumatology, treated since at least 4 months with a TNFα inhibitor, after failure to a previous one, not in 3rd or subsequent lines of TNFα inhibitor therapy. The sample representativeness was acceptable with a high correlation level between the regional activity in anti-TNFα prescriptions and the number of patients included per region ($r = 0.88$; $p < 0.0001$). Out of the 293 patients, 16 patients were excluded: one patient was in 3rd line of treatment, 11 patients were treated with rituximab (early access program), and four patients were treated for less than 4 months. On average, the population was 54.5 years old with a high proportion of women (79.1%). Most of the patients presented an active and erosive RA with a median duration of 13.2 years. Mean DAS28 was 5.4. Respectively 82.9% and 77.5% of the patients were rheumatoid factor and anti-CPP positives (Table 4). At the time of the study, mean TNFα inhibitor treatment duration was 19 months.

Table 1
Results of the MTC model in terms of ACR20 responders

Treatment	Median (%)	Percentile 2.5% (%)	Percentile 97.5% (%)
MTX + RTX_{1000}	62.5	42.9	78.3
MTX + ETA_{25}	61.1	39.2	79.6
ETA_{25}	44.0	18.5	72.3
MTX + ADA_{40}	69.8	49.3	85.0
ADA_{40}	38.1	12.8	70.5
MTX + $INF_{3/8}$	44.2	28.1	62.7

MTX, methotrexate; RTX, rituximab; ETA, etanercept; ADA, adalimumab; INF, infliximab.

Table 2
Results of the MTC model in terms of early discontinuation

Treatment	Median (%)	Percentile 2.5% (%)	Percentile 97.5% (%)
MTX + RTX_{1000}	3.5	0.5	11.9
MTX + ETA_{25}	1.5	0.0	22.7
ETA_{25}	6.8	0.3	76.9
MTX + ADA_{40}	4.4	0.4	33.6
ADA_{40}	7.2	0.0	90.3
MTX + $INF_{3/8}$	5.5	1.3	13.5

Healthcare consumptions: according to the consumptions observed in the TC2 study, number of administration per cycle (6 months) was calculated for each strategy. The first cycle of infliximab comprises 5.25 infusions, whereas for the following cycles it decreases to 3.6 infusions. Patients treated with etanercept receive in average 26.5 injections of 25 mg and 9.5 injections of 50 mg. For adalimumab, it reaches 13.9 injections per cycle.

The following intensive administration patterns were observed: 4.7% of patients treated with infliximab received more administrations than stated in the label, while 18.6% had a higher dosage; 11.4% of patients treated with etanercept received more than 32 injections of etanercept 25 mg. However, 23 patients received less than 32 injections (17,4%); 24.5% of patients treated with adalimumab received more than eight injections.

2.5. Direct medical costs estimates

Health care resources observed for each treatment group in the TC2 study were valorized according to the following. As the reason and the length of hospitalization were documented, we could find the corresponding French diagnosis related group (DRG) to estimate hospitalization costs. The drug acquisition costs were accounted for in addition to the top of DRGs, as they were present on the list of costly drugs. Public prices were used to estimate concomitant treatment costs for treatments delivered out of the hospital. Finally, outpatient visits, imaging, biologic tests and hospital-home transport were valued through the tariffs edited by the French national

Table 3
Results of the MTC model in terms of adverse events

Treatment	Median (%)	Percentile 2.5% (%)	Percentile 97.5% (%)
MTX + RTX_{1000}	14.4	4.1	45.4
MTX + ETA_{25}	8.3	1.0	55.3
ETA_{25}	8.9	1.0	64.6
MTX + ADA_{40}	6.2	1.2	26.2
ADA_{40}	45.0	2.0	98.6
MTX + $INF_{3/8}$	6.3	1.9	15.4

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Table 4
Clinical status at baseline of the TC2 observational study

RA status	All patients $n = 277$	Infliximab $n = 43$	Etanercept $n = 132$	Adalimumab $n = 102$
Mean duration of disease (years), mean ± SD	13.2 ± 8.5	12.8 ± 8.5	13.6 ± 8.7	12.7 ± 8.4
DAS28, mean ± SD	5.4 ± 1.2	5.7 ± 0.9	5.3 ± 1.2	5.4 ± 1.2
Positive rheumatoid factor	82.9%	80.6%	85.2%	80.9%
Erosive RA	90.5%	85.0%	91.2%	92.2%
Positive anti-CCP	77.5%	80.0%	81.0%	71.9%

health insurance. Total direct medical cost is €16,000 per year for a patient treated with a TNFα inhibitor. Cost structure is as follows: 81% for treatment acquisition costs (about €13,000), 12% for hospitalization costs and 7% for outpatient costs.

2.6. Sensitivity analysis

The objective of the sensitivity analysis is to compare the level of consumptions for patients in second line of treatment versus patients in subsequent lines. Therefore, multiplication factors were applied to health care resources in order to reflect increased resources use for patients in subsequent lines.

First of all, intensive administration patterns (infusions or injections given more frequently, and/or at higher dosage than recommended in the summary of product characteristics) were observed in the observational study TC2, for some patients in 2nd line of treatment. This was expected to be amplified for patients in subsequent lines. For each TNFα therapy, a multiplication factor (coeff 1) was then deduced from the difference between the expected number of administrations and the observed one. Coeff 1 was applied to TNFα inhibitors acquisition costs for patients who failed more than one biologic treatment. No adjustment was needed for rituximab, as its administration was not expected to depend on the preceding number of failures.

The severity of the disease is also an important criterion to be taken into account. As progressive disability in RA is directly associated with increasing costs, it was assumed that the more a patient fails, the more severe his RA and the higher health care resources, whatever the treatment. Coeff 2 was applied to costs other than acquisition costs for each strategy (including rituximab), for patients who failed more than one biologic treatment. As no estimate of this coefficient was available, it was varied from 5% to 20%.

3. Results

3.1. Base case analysis

If TNFα inhibitors were the only treatment available (H1), the annual global cost of treatment would be €16,555 per patient versus €11,444 for patients treated exclusively with rituximab (H3) (Table 5). This difference is mainly due to acquisition costs, which are decreased by 43% with rituximab compared to TNFα inhibitors. The increased administration cost for rituximab (+72% of TNFα inhibitors administration cost), are widely overbalanced by its lower treatment acquisition cost. With the use of rituximab, total savings per patient and per year is €5000.

Focus is now given on the evolution of medical costs according to the hypotheses of market penetration, H1, H2 and H3, between 2006 and 2009. Under hypothesis H2 (rituximab replaces progressively TNFα inhibitors); total direct medical costs decrease progressively, reaching the level of costs of hypothesis H3 at the end of the 4 years period.

Under hypotheses H1 and H3, costs are almost constant over 4 years. Direct costs can be estimated for the whole period at €378 M under H1 versus €260 M under H3 (Table 6). The evolution of total direct medical cost was greatly influenced by acquisition costs, which represent 80% of TNFα inhibitors' and 65% of rituximab's total cost.

The overall savings with rituximab would reach €118 M, that is to say a 31% decrease of the medical expenses if completely replacing TNFα inhibitors in that population.

3.2. Sensitivity analysis

In the population of patients who have failed one prior TNFα inhibitor therapy, the increase, in percentage, between the expected mean number of administrations and the observed one gave coeff 1 for each TNFα therapy. We can notice here that the increase was much more important in the adalimumab treatment group (22%). During the first year of simulation, the difference between H2 and H2-coeff 1 reaches €3,362,000 in total direct costs. The more rituximab enters the market, the more the gap between the two hypotheses is reduced, with the difference reaching €131,000 for the last year of simulation.

Table 5
Annual cost per patient under H1 and H3 hypotheses

	TNFα inhibitor only H1 (€)	Rituximab only H3 (€)
Hospitalization costs		
Administration cost	915	1577
Other hospitalizations	987	992
Outpatient visits − tests	176	175
Ambulatory costs		
Consultations	136	135
Others	1135	1095
Treatment acquisition costs	13,206	7469
TOTAL	16,555	11,444

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Table 6
Cumulative costs over 4 years

	TNFα inhibitor only H1 (€)	TNFα inhibitor and Rituximab H2 (€)	Rituximab only H3 (€)	Difference H3−H1 (€)
Hospitalization costs				
Administration cost	21,229,782	30,927,500	35,918,183	14,688,401
Other hospitalizations	22,694,003	22,915,328	22,874,045	180,042
Outpatient visits − tests	4,010,283	3,974,787	3,979,668	−30,615
Ambulatory costs				
Consultations	3,102,241	3,100,885	3,102,100	−141
Others	25,832,513	25,202,024	24,496,058	−886,455
Treatment acquisition costs	301,644,646	204,412,229	170,062,585	−131,582,061
TOTAL	378,513,468	290,532,754	260,882,640	−117,630,828

Hypothesis H2 associated with coeff 2 of 20% will be the only scenario considered here for a better reading of the results. During the first year of simulation, the difference between H2 and H2-coeff 2 reaches €5,400,000 in total direct costs. This difference decreases along the period, to reach €2,400,000 the last year of simulation. The more rituximab is used, the less is the impact of the multiplication factors. This is mainly due to the fact that rituximab acquisition costs are independent from the treatment line. The progressive penetration of rituximab on the market reduces the surplus cost linked to patients in 3rd and subsequent lines of treatment.

4. Discussion

The RA treatment costs observed in our study can be compared with two recent studies. Kobelt studied the cost of treatment with TNFα inhibitor in Sweden between 1999 and 2002 [29]. Etanercept and infliximab were the only TNFα inhibitors available at this time in Sweden, and patients were all in 1st line of treatment. However, the results of this study are very close to ours. TNFα inhibitor acquisition costs (etanercept or infliximab) reach €14,704. In our budget impact analysis, these costs are €13,206 in average. In other respects, total direct costs are respectively €17,900 and €16,555 in the Kobelt and in our study. We expected patients in failure to a first TNFα inhibitor to have higher direct costs that in first line of treatment. But the discrepancy between the two studies can be explained by national specificities. The Fautrel study published in 2005 compares the costs of two TNFα inhibitors, infliximab and etanercept, in three French hospitals [30]. Patients included in the study had a severe and active RA justifying the onset with a TNFα inhibitor, as monotherapy or in combination with a DMARD (disease modifying anti-rheumatic drugs). The TNFα inhibitor treatment had to be continued at least 1 year without discontinuation between 1999 and July 2002. Patients could be naïve of treatment or in 2nd or subsequent lines of TNFα inhibitors treatment. Direct total costs were comparable between the two treatment groups with respectively €19,469 and €19,619 for patients treated with infliximab and etanercept respectively. This result is slightly higher than ours, as we observe a total direct cost of €16,555.

The scope of costs taken into account may have influenced the results. Actually, only the costs susceptible to be different between the two treatments were included in the study, assuming that surveillance methods were identical between the two products. Acquisition prices were also different: €711 for infliximab 100 mg and €145 for etanercept 25 mg in the Fautrel study (hospital price) whereas €561 and €126 in our study (ex factory prices).

An observational study was conducted to document the model with resource consumption of patients who have failed a first TNFα inhibitor therapy. Subsequent lines of treatment were excluded. This was a limitation of the model because nothing can guaranty the resources used to be comparable between treatment lines. But we wanted to avoid a non-robust statistical analysis on the subpopulation of patients who failed more than one prior TNFα therapy, as it was expected that they would be underrepresented in the sample. To overcome this limitation, coefficients were applied to TNFα inhibitor acquisition costs (coeff 1) and to the other resources for each strategy (coeff 2). Two different approaches were conceivable to model the course of patients suffering from RA after failure of TNFα inhibitor therapies with a Markov model. The most popular one is to consider a closed cohort of patients. However, in the context of RA, this approach does not reflect the target population structure in terms of treatment line, which is an essential piece of information as health care costs depend on it.

We therefore privileged another approach, which consists of following a dynamic cohort. For each new model cycle, some patients exit the model while new patients enter it, with respect of the proportion of patients in each treatment line. The main weakness of this approach is that a patient who failed a biologic treatment could receive exactly the same treatment after a switch. However, we are not interested in individual patient patterns, but in the global budget impact of rituximab for the whole target population. Thus, we preferred a model that estimates accurately the budget impact to a model more transparent about patient patterns, but unable to respect the population allocation between treatment lines.

In France, direct medical cost of rituximab treatment in RA is up to €11,444 per patient per year, decreasing costs by 31% compared to the cost of replacing a TNFα inhibitor by another. Rituximab is expected to produce important savings when used after failure of one or more TNFα inhibitor therapies. This is mainly due to its lower drug acquisition cost with €7469 per year that is to say a decrease of 43% compared to TNFα inhibitors. Although administration costs are increased, rituximab treatment remains cheaper thanks to important savings on acquisition costs. These savings could increase with the development of rituximab in earlier stages of treatment.

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5. Conflict of Interest

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