Mixed treatment comparison, cost-effectiveness analysis and budget impact model in the treatment of rheumatoid arthritis after failure of conventional DMARD therapy using comprehensive Bayesian decision analytical modelling.

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Aims: Estimation of the direct medical cost of rheumatoid arthritis (RA) in France (2011-2016) after failure of conventional DMARDs therapies, using comprehensive bayèsian decision analytical modelling.

Methods: We searched 2 electronic database: Embase (January 1999 -April 2010) and Medline (January 1999 -June 2010). Inclusion criteria were: 1.Randomized double-blind trials; 2.Monotherapy and combination; 3.Marketing authorization dosage; 4.ACR50 response at 24+/- 8 weeks; 5.Infections and treatment discontinuation. Trials were excluded if naive patients or third-line therapy. Data were extracted in duplicate by 2 investigators. Higgins' I^2 and Cochrane's Q-tests were calculated to assess heterogeneity. Quantitative data analysis was made with mixed-treatment comparisons for clinical effectiveness, infection and early dropouts. Residual heterogeneity addressed with a random-effects model. In developing the budget impact model, we account for two types of cohorts—a prevalent and an incident cohort. The model simulates the management of RA patients that didn't respond to previous DMARD therapy. Six treatments were selected: 5 TNF-α inhibitor (adalimumab –ADA-, certolizumab-pegol –CZP-, etanercept –ETN-, infliximab -INF- and golimumab -GOL) and an interleukin-6 inhibitor (tocilizumab -TCZ). A time horizon of five years has been selected. French health-care system perspective was adopted. These elements were processed simultaneously in WinBUGS 1.43.

Data: Due to available data, only combinations with methotrexate were introduced in the model. Resources consumption were collected in an observational study (272 patients). Costs valuation were based on health insurance relative value scales. Nine market uptake assumptions were explored: stability of current market shares; growth of ETN (3%, 5%, 10%, 15% or 20%) increase of CZP (+3 %); progression of CZP (3%), of TCZ (+5%) and entrance of GOL (0.5%); increase of CZP (+3%) at the expense of etanercept only.

Results: 2606 references have been identified. 2580 articles were eliminated: 1325 duplicates, 1184 on titles, and 43 after reading the abstracts. 54 articles were selected for full reading. 23 randomized trials were included in the meta-analysis, corresponding to 6612 patients. Considering ACR50

response, ETN has the highest odds-ratio compared to DMARDs, of all comparators used (odds-ratio: 9.18 [3.67, 27.1]). Relative risk of infection with ETN drops by 7% compared with DMARDs (odds-ratio, 0.93 [0.52, 1.64]). Number of discontinuations was lower with CZP (odds-ratio, 0.06 [0.03, 0.11]). Patient-level cost of cares for a 24 weeks period ranges from €3314 for golimumab to €15451 for tocilizumab. The model estimates the average cost of cares for an open cohort of 20000 prevalent patients and 5394 yearly incidents patients between 3.08 and 3.1 billion euros depending on assumptions. The expenditure is mainly impacted by acquisition and administration costs in hospital sector and transition to third-line therapies. The analysis shows that increase in market share of etanercept, no matter the size, is accompanied by a reduction of expenditure ranged from €2 million (ETN+3%) to €11 million (ETN+20%).

Conclusion : Our model shows that etanercept is expected to produce savings if used in a wider proportion on rheumatoid arthritis population. Potential savings are mainly due to the decrease of intravenous therapies shares and to efficacy that prevent from 3rd line of treatment.

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disease whose prevalence in France was estimated at 0.31% (0.51% for women with a sex ratio of 5.7) [1]. It is estimated that 120 000 to 220 000 people suffer from this disease in France, making it the most common inflammatory arthritis (spondyloarthropathies, systemic lupus erythematous...). The disease is most common in the South[2]. It has a strong female predominance, and its annual incidence is estimated at 90 cases per 1 million. The incidence peak is between 25 and 55[3].

The management of the disease is mainly made using conventional therapies designed to stop or slow the progression of the disease. This earned them the name of disease-modifying antirheumatic drug (DMARDs).

Among the conventional treatment of RA, methotrexate (MTX) is the standard treatment. According to expert, from 45 to 60% of patients with RA are treated with MTX and 18% of them escape treatment[4].

In addition to conventional therapies, biotherapies are also used in the treatment of RA. These include biological agents such as TNF-α inhibitors: adalimumab (ADA), certolizumab pegol (CZP), etanercept (ETA), golimumab (GOL) and infliximab (INF). After inadequate response to MTX, TNF-α inhibitors are effective in two thirds of cases[5]. The administration of a second TNF-α inhibitor, in case of the failure of a first one, is only effective in one out of two[6].

Other biological therapies complete the available therapeutic arsenal: tocilizumab (TCZ), rituximab (RTX) and abatacept (ABA).

To study efficacy, toxicity and discontinuation of approved biotherapies[7] (ADA, CZP, ETA, GOL, INF and TCZ) is the first step to justify their relevance in the treatment of RA. However, it also is necessary to use medico-economic analysis, such as budgetary impact and cost-effectiveness, to take into account the cost of treatment.

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[1] Guillemin F, Saraux A, Guggenbuhl P, Roux CH, Fardellone P, Le Bihan E, Cantagrel A, Chary-Valckenaere I, Euller-Ziegler L, Flipo RM, Juvin R, Behier JM, Fautrel B, Masson C, Coste J. Prevalence of rheumatoid arthritis in France: 2001. Ann Rheum Dis. 2005 Oct;64(10):1427-30.

[2] Roux CH, Saraux A, Le Bihan E, Fardellone P, Guggenbuhl P, Fautrel B, Masson C, Chary-Valckenaere I, Cantagrel A, Juvin R, Flipo RM, Euller-Ziegler L, Coste J, Guillemin F. Rheumatoid arthritis and spondyloarthropathies: geographical variations in prevalence in France. J Rheumatol. 2007 Jan;34(1):117-22.

[3] Guillemin F et al. Low incidence of rheumatoid arthritis in France. Scand J Rheumatol, 1994;23:264-8.

[4] HAS (Haute Autorité de Santé), Avis de la commission de la transparence sur Cimzia, mars 2010

[5] Mariette X. Biothérapies émergentes dans la polyarthrite rhumatoïde. Revue du rhumatisme, 2004;71:848-853.

[6] Hansen KE, Hildebrand JP, Genovese MC et al., The efficacy of switching from etanercept to infliximab in patients with rheumatoid arthritis. J Rheumatol, 2004;31:98-102.

[7] A finer separation can be established based on administration mode : subcutaneous for ADA, ETA, CZP and GOL; intravenous for INF and TCZ.

Today, such analysis can be performed in a fully Bayesian approach to take into account all available evidence and uncertainty information. In this context, we conducted analysis in WinBUGS as part of a single study.

1. Objectives

There are four objectives to our study: (i) To assess efficacy (ACR 50 response to week 24) and safety (infection to week 24, dropout to week 12) given a population of patients with severe RA and after failure of DMARD; (ii) To estimate budget impact of the management of RA in France; (iii) To compare between treatments the average annual cost of maintaining a patient under treatment; (iv) To evaluate the cost-effectiveness of different available strategies.

2. Methods

The evaluation is based on review of randomized controlled trials. In order to put their results in perspective, we used three tools: a systematic review of the literature, a quantitative synthesis of evidences (random effects mixed treatment comparison) and a Markov model to assess budget impact and cost-effectiveness. First method is used to collect, organize, evaluate, and synthesize all arguments in favor of a treatment without quantitatively combining the results. It is called qualitative evidences synthesis. Second one is used to quantitatively estimate effect size of treatment in the published randomized clinical trials. This approach explicitly refers to meta-analysis and statistical methods of mixed treatment comparisons. In order to estimate budget impact and efficiency of the use of biological agents, results from MTC have been include into a Markov model designed to replicate the management of a patient with RA after inadequate response to DMARD. Indeed, the model allows modulating transition probabilities as the patient advances in treatment.

2.1. Systematic review

The selected research strategy had for objective to identify all randomized clinical trials conducted between 1999 and 2010 on patient with RA and treated using one of the following biotherapies: ADA, CZP, ETA, GOL, INF or TCZ. PICOS criterions were used to identify and summary objectives of the review. PICOS is an acronym whose components indicate: the characteristics of the target population in which we shall be interested «P» (this supposes to analyze therapeutic indications by treatment line in order to study what can the place of ETA be in the therapeutic sequence); the nature of the intervention «I»; the chosen comparators «C»; the outcomes «O» chosen as assessment criteria, in other words, the implemented quantitative measure to estimate the efficiency; the design of the studies «S» considered appropriate to supply a strong proof level.

The bibliographic databases which presented an interest for the subject, MEDLINE and EMBASE were investigated. Corresponding descriptors for each of these bases (EMTREE and CISMef MESH) were used to build research equations. Interrogations of the bibliographical bases were conducted in

October, 2010. References published within selected articles were also mobilized to complete the literature analysis. Studies were selected upon the following criterions: (i) eligible population: patients aged 18 years or more, presenting RA with inadequate response to a conventional DMARD (including MTX). (ii) intervention: ETA; (iii) comparators: ADA, CZP, GOL, INF, TCZ; (iv) outcomes : ACR50 in 24 ± 10 weeks, early discontinuations in 24 ± 10 weeks, infections in 24 ± 10 weeks ; (v) design: double-blind RCT with control group. After elimination of duplicates references, the selection was made on titles and abstracts. Remaining articles were then fully read by two independent assessors. A selection diagram was built according to PRISMA statements. Clinical data were extracted using a standardized form implemented in Excel®.

2.2. Mixed treatment comparison

2.2.1. Definition

Efficacy of medical treatments is usually evaluated within randomized controlled trials, through direct comparison with one or more comparators (treatment "A" versus treatment "B"). When such comparisons are not available (treatments of interest have never been directly compared), it is possible to use indirect comparisons, provided that these treatments have both been directly compared to a third ("A" versus "C" and "B" versus "C"). Mixed treatment comparison (MTC) is based on a statistical model that will mobilize all available evidences, both direct and indirect ones. This tool will help to position treatments against each other. MTC also presents the advantage of providing unbiased estimates since it preserves the randomization.

MTC's model is a hierarchical Bayesian one. Those models are updating knowledge (*prior*) in the light of new available data. Conducting a MTC supposes to argue in terms of relative treatment effect (e.g. odds ratio).

Let p_{ik} be absolute efficacy (for example, ACR 50 response rate) of treatment k in trial i. It is calculated as below:

$$\log it(p_{ik}) = \begin{cases} \mu_{ib} & si\ \mathrm{k} = \mathrm{b} \\ \mu_{ib} + \delta_{ibk} & si\ \mathrm{k} \neq \mathrm{b}\ \text{avec}\ \delta_{\mathrm{ibk}} \sim \mathrm{Normal}(\mathrm{d}_{\mathrm{bk}}, \sigma^2)\ (\text{random effect model}) \end{cases}$$

Where b is the control treatment (baseline treatment); μ_{ib} is the log-odds of treatment b in study i; and δ_{ibk} is the log-odds ratio (log-OR) of treatment k versus treatment b in study i. For studies comparing more than two treatments, it is necessary to take into account the covariance between arms being compared to the reference treatment. This covariance is $\sigma/2$.

Directed acyclic graph for mixed treatment comparison is presented in figure 1.

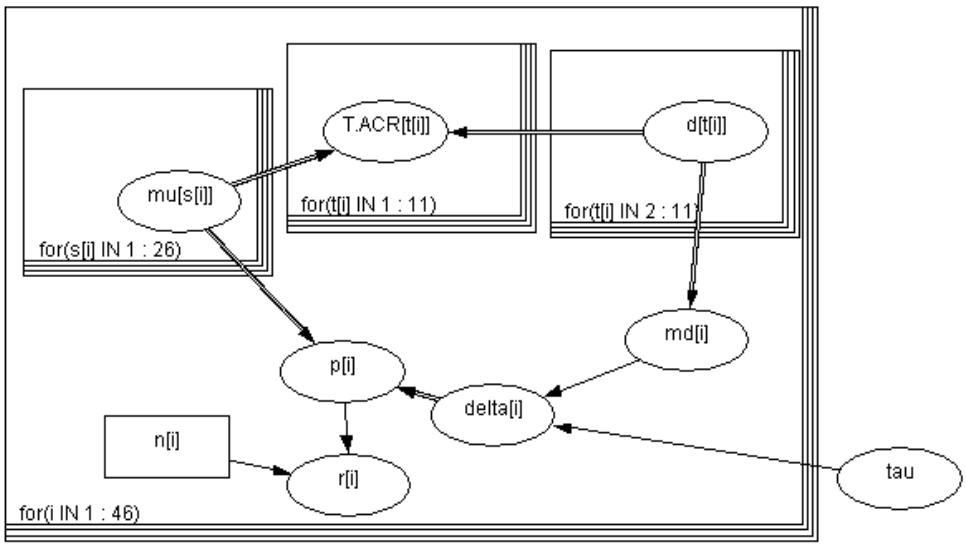


Figure 1: Directed acyclic graph for ACR 50 random effect MTC

Legend: single line: stochastic relationship, double line: deterministic relationship, square: deterministic variable, round: random variable, ***index*****:** i: arm, s[i]: study, t[i]: treatment: r[i]: number of responders, p[i]: response probability, n[i]: number, mu[s[i]]: log of the odds for each study, delta[i]: log odds ratio, d[t[i]]: mean of the distribution of log-OR for treatment; md[i]: centered average of the distribution of log-OR; tau: accuracy logOR, T. CAB [t[i]]: ACR50 response rates

2.2.2. From relative to absolute

Absolute response rates (ACR50 response rate, dropout rate and infection rate) are estimated from log-OR of treatment k versus treatment b (baseline):

$$\text{logit}(p_k)=\log[p_k/(1-p_k)]=\mu_b+\delta_{bk}$$

Therefore,

$$p_k=\exp(\mu_b+\delta_{bk})/(1-\exp(\mu_b+\delta_{bk}))$$

Three MTC models were realized: first one for ACR50 response rate after 24 weeks, second one for early discontinuations after 12 weeks and third one for infection rate in 24 weeks. All three models are using non informative priors.

2.3. Medico-economic evaluation

2.3.1. Markov Model

A dynamic Markov model was constructed under the assumption that patients remain alive during the study, so there is no "death" absorbing state:

$$Dynamic\ cohort_{(t)} = prevalence_{(t)} = prevalence_{(t-1)} + incidence_{(i)} - exit_{(i)}$$

The Markov model was constructed to simulate the trajectory of a patient after failure of DMARDs. It is based on results of efficacy (ACR 50) and safety (early dropouts and infections) measured at 6 months. At the end of each semester, the therapeutic management of the patient is evaluated.

The model is designed around 25 Markov states. Among them, 24 states are corresponding to treatments: for every treatment, we distinguish the line of biotherapy (first or second line) and the treatment phase (induction or maintenance). In addition, an absorbing state, corresponding to third line of treatment allows for a dynamic cohort (Figure 4).

To build this model, 4 clinical trajectories have been identified. Every patient who experienced inadequate response to DMARD is receiving 1 of the 6 biotherapies. Around the 12th week of treatment, patients have the possibility to early discontinue their treatment (trajectory 1). For those who continued their treatment, the therapy can either be a success or a failure. Treatment is considered a failure if the patient develops an infection (trajectory 2) or if the ACR50 response is not fulfilled (trajectory 3). A patient following one of those pathways will receive a new therapy at the beginning of the next cycle.

Treatment is considered as a success if patient didn't drop out his treatment, if he didn't develop an infection and if he meets ACR50 response (trajectory 4). In the latter case, treatment is extended to the next cycle.

According to HAS recommendations, patients will receive a 3rd line treatment after inadequate response to 2 out of the 6 therapies of interest.

The tree develops the four identified clinical pathways and ventilates patients according to the associated probabilities of occurrence. The distribution between treatments at the waning of the occurrence of events is known as market share (PM) conditional. The transition probabilities were calculated by combining these pieces of information.

2.3.2. Cost-effectiveness analysis

2.3.2.1. Assumptions

The model chosen to make this cost-effectiveness analysis is an incident model, that is to say which simulated the management of a single cohort, without the introduction of new cohorts over time.

We made four assumptions: (i) model results, in terms of costs and effectiveness, were calculated considering 1st line, 2nd line and both, (ii) response, discontinuation and infections rates remain constant over time, (iii) probability to extend treatment (success with no discontinuation and no infection) is depreciated by 10% in 2nd line of biotherapy compared to 1st line; (iv) both costs and probability to remain under treatment were discounted using an annual rate of 4% (preferably for the present time) (Lebègue 2004).

2.3.2.2. Framework

Probabilities to remain under treatment were calculated using the following formula and referring to the results of previous MTC:

Probability to remain under treatment = response rate(1- discontinuation rate)*(1-infection rate),*

The average annual cost per patient is calculated taking into account market shares, prevalence, incidence, unit prices and consumption of resources. The latter are probabilistic.

These semi-annual rates and costs were updated using the formula

$$Present\ value = value*(1+t)^{-j},$$

Where $(1+t)^{-j} = (1+0.04)^{-2}$

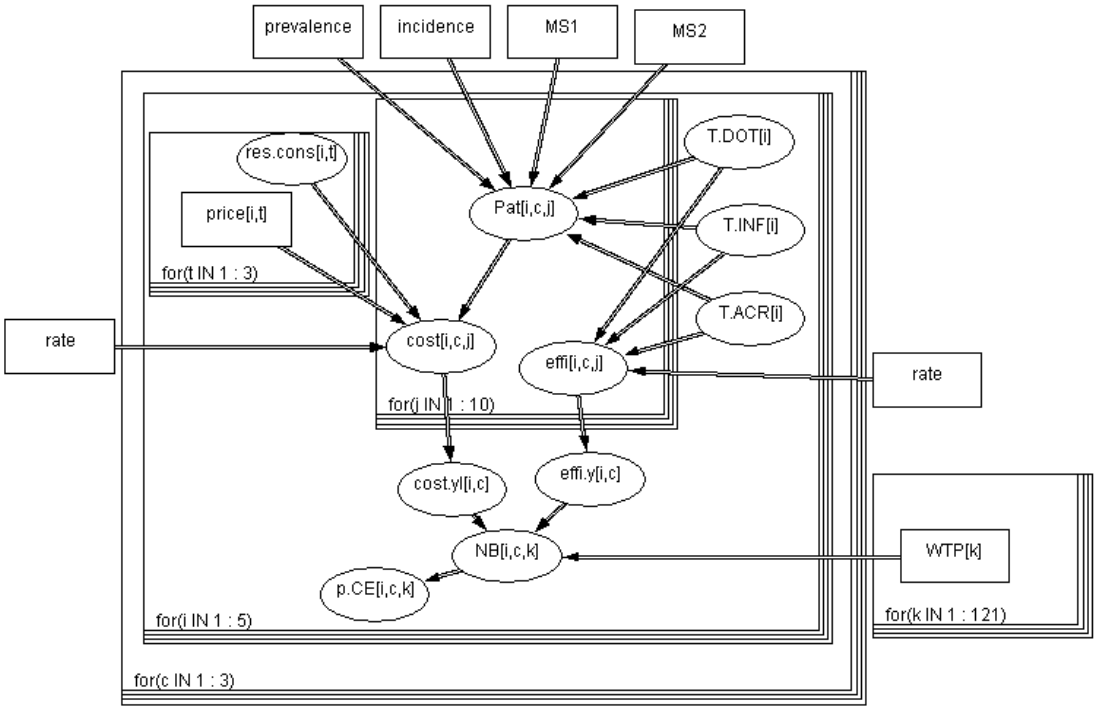


Figure 2 : Graphe orienté acyclique (DAG) simplifié du modèle coût-efficacité

Legend: pcs[i,c,k]: probability of being more efficient than comparators; BN[i,c,k]: net collective benefit; Cout.a[i,c]: annual cost per treatment support; effi.a[i, c]: annual efficiency by treatment WTP[k]: willingness to pay [i, c, j]: retention rates in treatment cost[i,c,j]: cost per treatment support; con.res[i,t]: resource consumption; rate [i,t]: rate of processing (acquisition, administration and exams), Pat[i,c,j]: number of patients, PM1 and PM2: in the first and second lines of treatment rates: discount rate; T.ACR[i]: ACR50 response rate; T.DOT[i]: rate dropouts, T.INF[i]: infection rate

The socio-economic net benefits (NB) were then calculated for each treatment, considering a Willingness To Pay (WTP) from 0 to 60000€ per year:

$$NB= WTP*Efficiency-Cost$$

A treatment is considered more efficient than its comparator(s) when its WTP is the highest

To complete those aggregates, efficiency and acceptability frontiers were build.

2.3.3. Budget impact analysis

2.3.3.3. Assumptions

Our study evaluates the cost of care for RA patients after an inadequate response to DMARD. Three hypotheses of market trends have been developed and compared: (i) H0, market shares in first

and second line biotherapies remain stable throughout the period, (ii) H1, ETA's market shares are falling by 10% in 5 years, for both 1st and 2nd line; (iii) H2, ETA's market shares, for both 1st and 2nd line, are increasing by 10% in 5 years.

2.3.3.4. Framework

Our budget impact analysis was based on a prevalence model, that is to say, it estimated costs to manage a prevalent cohort, plus yearly added incident cohorts (new patients every year). As time horizon for an impact assessment has to be short, we used a 5-year period, corresponding to the simulation of 10 cycles. No discounting of costs was used.

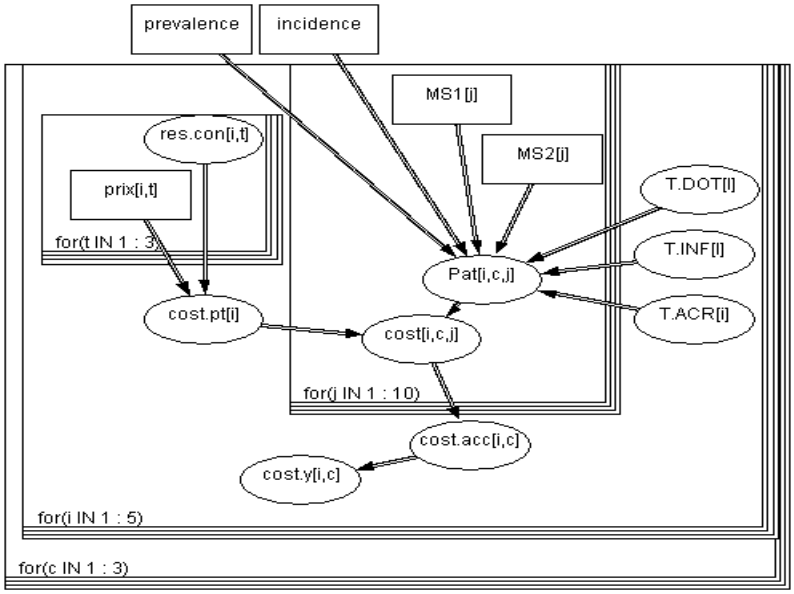


Figure 3 : Simplified directed acyclic graph for budget impact analysis

Legend: i: treatment j: cycle c: line of treatment as "3"mean L1+L2; t: type of cost (acquisition, administration, examinations), Cout.a[i, c, j]: average annual cost of treatment; cout.cum[i,c,j]: cumulative cost to 5 years of treatment, cost[i,c,j]: cost of txt; cost. pt[i]: cost of treatment per patient, Pat[i,c,j]: number of patients; rate[i,t]: processing fee (acquisition, administration and exams); con.res[i,t] : consumption of resources; PM1[j], PM2[j]: market shares in the first and second lines of treatment; T.ACR[i]: ACR50 response rate; T.DOT[i]: dropout rates; T.INF[i]: infection rates

From consumed resources and their appreciation, we were able to estimate the overall cost to 5 years in support of RA patients after failure of background therapy. The average annual costs for the cohort and per patient were also calculated. These aggregates were detailed per line of biotherapy and for all lines.

Results from the three hypotheses were compared in absolute and in relative terms.

2.4. Sources data

2.4.1. Population

The targeted population consists of patients aged 18 years or more, with active RA and who experienced inadequate response (lack of efficacy or intolerance) to conventional DMARDs (including methotrexate).

Appraisals from the Transparency Commission were used to estimate the size of the target population as follows: "Prevalence of RA in France can be estimated, using 2001 Guillemin and Saraux[8] study, at 0.31% in population aged 18 years old or more". By applying this figure to 2009 INSEE data (48,750,000), population with RA in France can be estimated at 151 000 patients.

Furthermore, based on data from CNAMTS on the number of people with ALD due to RA, and after adjustment, the population of patients with severe progressive RA in 2009 can be estimated at about 200,000 patients.

According to the CNAMTS data, this same population was estimated 150,032 people in 2007. An increase of 6.2% was observed between 2005 and 2006, then 6.8% between 2006 and 2007. Assuming 6% per year increasing rate for patient with ALD due to rheumatoid arthritis, the number of people with ALD due to RA would be about 168,576 in 2009. Considering that the data from CNAMTS are covering up 88% of the French population, the number of people suffering from severe progressive arthritis in France in 2009 can be estimated at 191,000.

According to expert opinion, 45% to 60% of these patients are currently treated with methotrexate. About 18% of patients treated with methotrexate escape treatment (expert opinion) resulting in a population estimated between 16,000 and 20,000 patients".

The latter was used in the model.

2.4.2. Resources consumption

Resources consumed as part of the management of RA were categorized into 5 groups: drug acquisition, drug administration, follow-up visits, laboratory and medical imaging.

For each therapy, the number of boxes, bottles or bags needed for 6 months of therapy was calculated according to dosages from Transparency Commission appraisals and packaging information available in France National Health Insurance drugs database. For treatments whose dose is expressed as mg / kg, an average weight of 66 kg was used.

Resource consumptions related to drug administration were estimated from expert opinion: subcutaneous treatments are initially administered by a nurse, the patient then carry his own injections on; intravenous therapies are routinely administered in hospital.

Data about follow-up consultations, laboratory and medical imaging have all been extracted from an observational study. This study was conducted in 2006 among 277 patients with severe RA and who

[8] Guillemin F., Saraux A., Guggenbuhl P., Roux C.-H., Fardellone P. et al. 2005 «Prevalence of rheumatoid arthritis in France: 2001», Ann Rheum Dis., 64(10) : 1427-30

previously experienced inadequate response to DMARD. It details the resource use in patients treated with ADA, ETA or INF. Due to the lack of data for TCZ (available since December 2009), CZP (available since September 2010) and GOL (pending), assumptions of resource consumption were made: patients treated with CZP or GOL behave as the general population, patients treated with TCZ behave as patients treated with INF (as these two treatments are administered intravenously). Parameters for distribution of probability used in the model to simulate the consumption of resources correspond to the information extracted from this study.

2.4.3. Appreciation for resources consumption

Resources consumptions were valued. The French care system perspective was retained. For every item, ambulatory and hospital expenses were separated.

Acquisition costs of targeted therapies were valued using tariff information from the French National Health Insurance medicine drugs, consulted in December, 2010. Valuation of drugs administration realized in hospital required the use of GHM (homogeneous Groups of patients), March 2011 version. Five GHM were retained. A weighted average of costs was calculated, based on experts' opinion. Cost payoff concerning follow-up visits, laboratory and medical imaging were estimated using available data from National Health Insurance. As data collected in the observational study were observed over a four months period, they have been recalculated to match the chosen cycle length of 6 months. The cost of management after failure of two biotherapies, using abatacept or rituximab, was found in the 2011 Maravic article.

3. Results

3.1. Systematic review

Figure 3 shows the different stages of the articles selection process, in order to perform MTC. From the literature search, 2000 articles were identified. After removing duplicates, 1286 articles were selected to have their titles read. This step allowed eliminating 1,185 articles. Abstracts of the 101 remaining articles were read, from which 59 were fully read. At the end of the process, 24 trials were selected for the study.

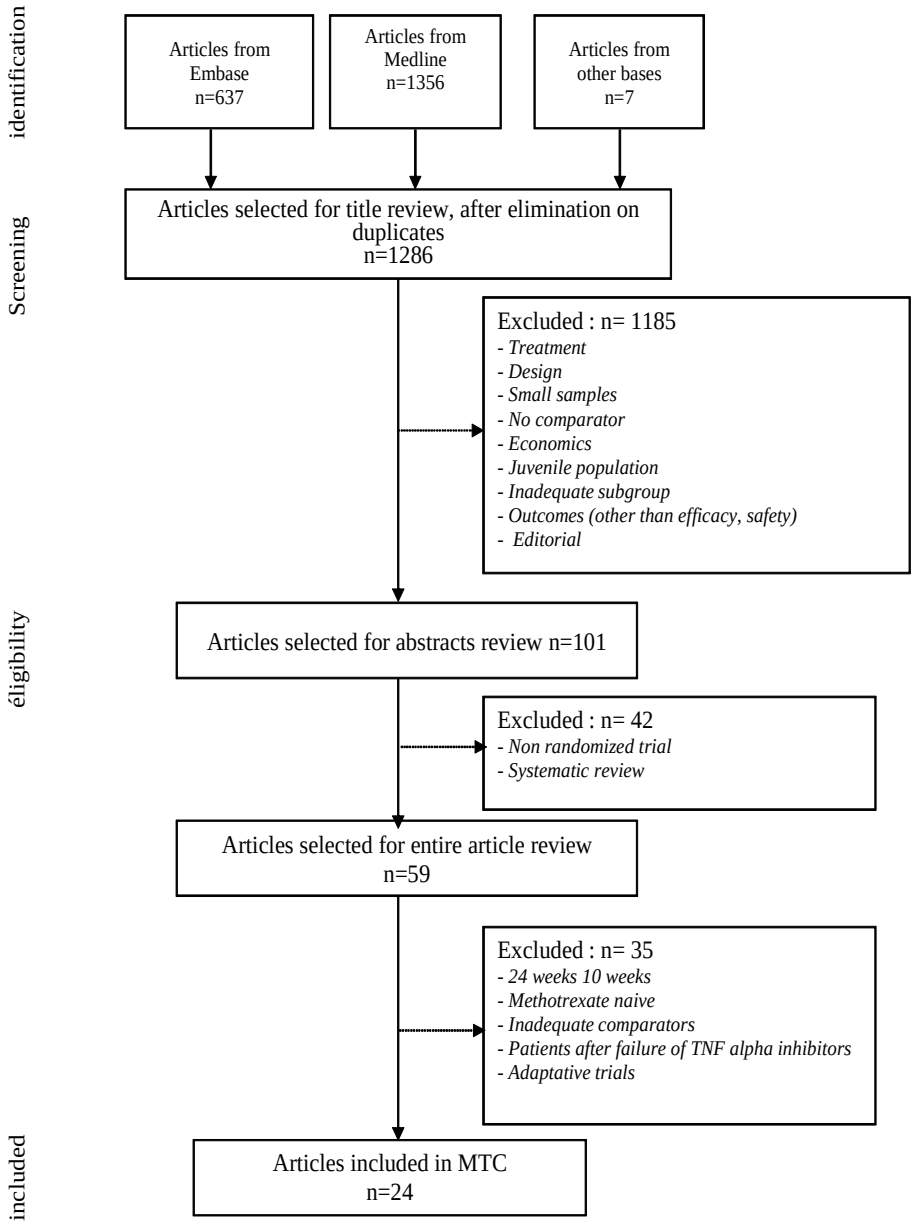


Figure 4 : Flow of information through the different phases of the systematic review

3.2. Network of evidence

From the 24 selected trials at the end of the review of the literature, we have established a network of evidence including 11 protocols and 10 direct comparisons (Figure 6).

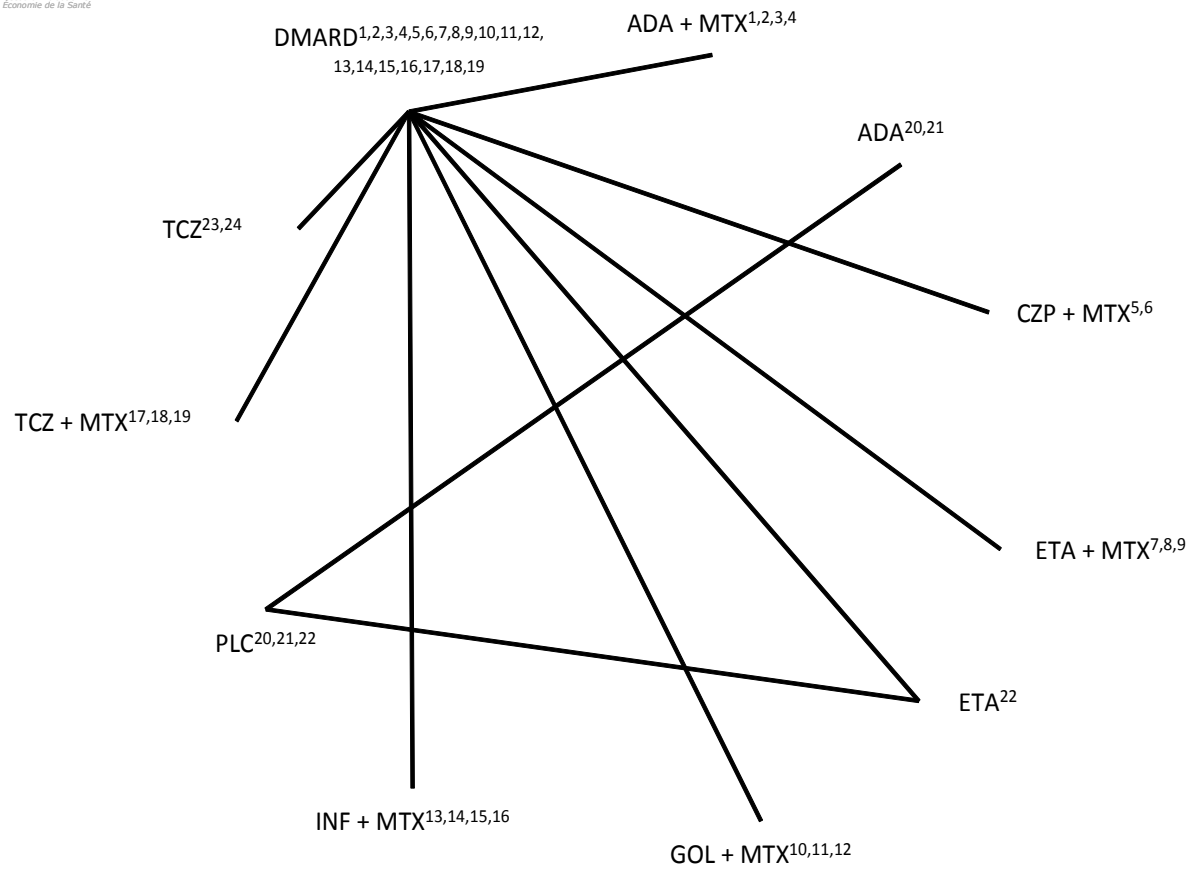


Figure 5 : Network of evidence

Trials that make up this network of evidence are featuring a cumulative total of 7953 patients.

Table 1 : RCTs References and number of patients include in MTC

	Trial	n		Trial	n
1	Furst 03 (STAR)	636	13	Maini 99 (ATTRACT)	174
2	Keystone 04 (DEO19)	407	14	Schiff 08 (ATTEST)	275
3	Kim 07	128	15	Westhoven 06 (START)	723
4	Weinblatt 03 (ARMADA)	129	16	Zhang 06	173
5	Keystone 08 (RAPID1)	592	17	Genovese 08	1216
6	Smollen 09 (RAPID2)	373	18	Maini 06 (CHARISMA)	151
7	Combe 06	254	19	Smolen 08 (OPTION)	409
8	Klareskog 04 (TEMPO)	682	20	Miyasaka 08 (CHANGE)	178
9	Weinblatt 99	89	21	Van de Putte 04	223
10	Kay 08	70	22	Moreland 99	158
11	Keystone 09 (GO-FORWARD)	222	23	Nishimoto 2007	306
12	Kremer 10	258	24	Nishimoto 2008	127
				Total	**7953**

We conducted an analysis of heterogeneity within selected articles, using two aggregates: Higgins I^2 and Cochrane's Q test. The analysis shows heterogeneity in trials regarding ETA (ETA+MTX : I^2=77,5% ; Q = 8,88 p-value=0,01) and ADA (ADA+MTX : I^2=64,4% ; Q = 8,42 p-value=0,04). In

response, Klareskog 04 (TEMPO) and Weinblatt 03 (ARMADA) trials were excluded. The number of trials actually used for the meta-analysis multiprocessing is therefore equal to 22.

3.3. Mixed treatment comparison

Results from the three MTC models are presented below as forest plots and as absolute response rate in table 2.

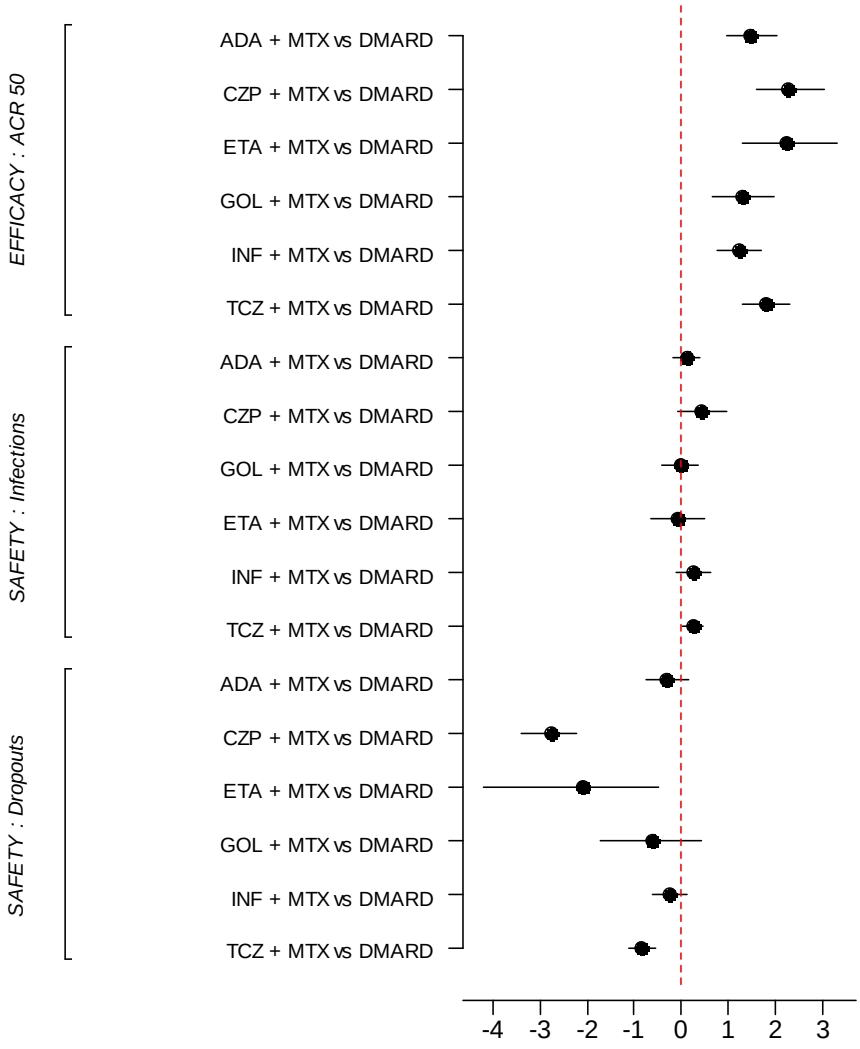


Figure 6 : Log-odds ratio for ACR 50 response rate, infection rate and dropout rate.

The forest plot shows results in terms of ACR 50 response, infections and discontinuation of treatment for association protocols only. Each biotherapy differs significantly from DMARDs in terms of ACR 50 response; however, it is not possible to decide between them, as confidence intervals overlap. Infections criterion can't show significant differences between DMARD and biotherapies, nor between biotherapies. Three treatments induce significantly fewer discontinuations than DMARDs: CZP, ETA, and TCZ. Furthermore, CZP has, on this criterion, a significant difference with its comparators, ETA excepted.

Table 2 : Results from MTC presented as absolute response rates

	ACR 50	Infections	Dropout	Maintenance	References
Adalimumab+MTX	32,40% [22%;45%]	38,10% [31%;45%]	16,10% [11%;23%]	16,83% [11%;24%]	1,2,3
Certolizumab pegol+MTX	51,11% [35%;69%]	45,70% [34%;58%]	1,60% [1%;3%]	27,31% [17%;39%]	4,5
Etanercept+MTX	50,32% [30%;73%]	33,80% [23%;46%]	3,10% [0%;13%]	32,28% [18%;48%]	6,7
Golimumab+MTX	28,54% [18%;43%]	34,90% [27%;43%]	12,40% [5%;27%]	16,28% [10%;25%]	8,9,10
Infliximab+MTX	27,48% [19%;37%]	41,80% [33%;51%]	16,8% [12%;22%]	13,31% [9%;19%]	11,12,13,14
Tocilizumab+MTX	39,93% [28%;52%]	41,40% [36%;47%]	10,1% [8%;13%]	21,03% [15%;28%]	15,16,17

[1] $Furst_{03}$; [2] $Keystone_{04}$; [3] Kim_{07} ; [4] $Keystone_{08}$; [5] $Smolen_{09}$; [6] $Combe_{06}$; [7] $Weinblatt_{99}$; [8] Kay_{08} ; [9] $Keystone_{09}$; [10] $Kremer_{10}$; [11] $Maini_{99}$; [12] $Schiff_{08}$; [13] $Westhoven_{06}$; [14] $Zhang_{06}$; [15] $Genovese_{08}$; [16] $Maini_{06}$; [17] $Smolen_{08}$

3.4. Medico-economic models

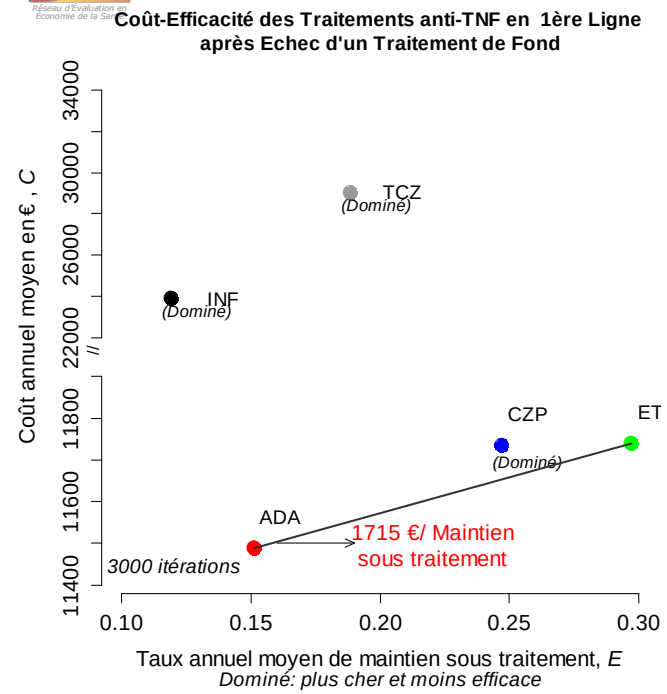
3.4.1. Cost-effectiveness analysis

3.4.1.1. Baseline analysis

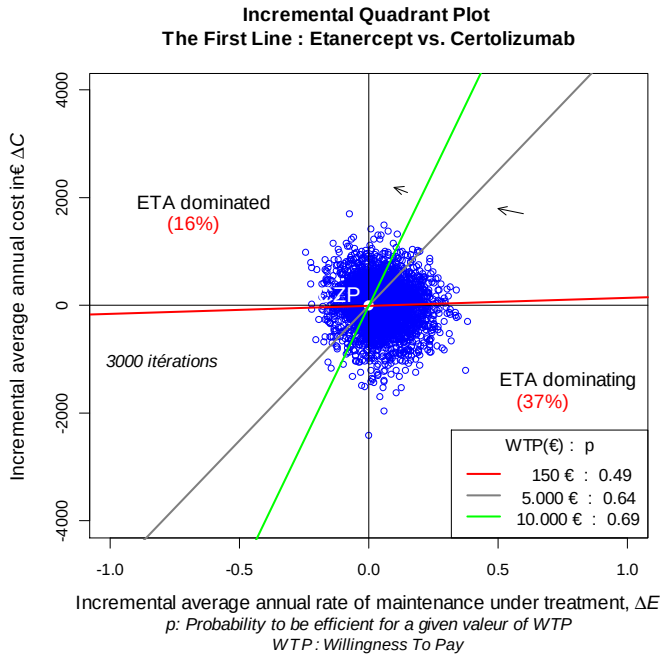
The first step of the analysis consists in evaluating whether a therapy is dominated by an alternative, cheaper and more efficient. It then, among the remaining strategies, tries to determine whether one of them is dominated by a linear combination of others. Finally, we calculate the cost-effectiveness ratio for non-dominated strategies. This process created an efficiency frontier.

Results from 3000 iterations are shown in Figure 7 (a) in terms of average cost and average efficacy per treatment. This figure clearly shows that INF, TCZ are strongly dominated (they are more expensive and less effective than at least one of the comparators): INF is dominated by ADA, CZP and ETA; TCZ is dominated by CZP and ETA. CZP is weakly dominated by combination of ADA and ETA. ADA and ETA form the efficiency frontier.

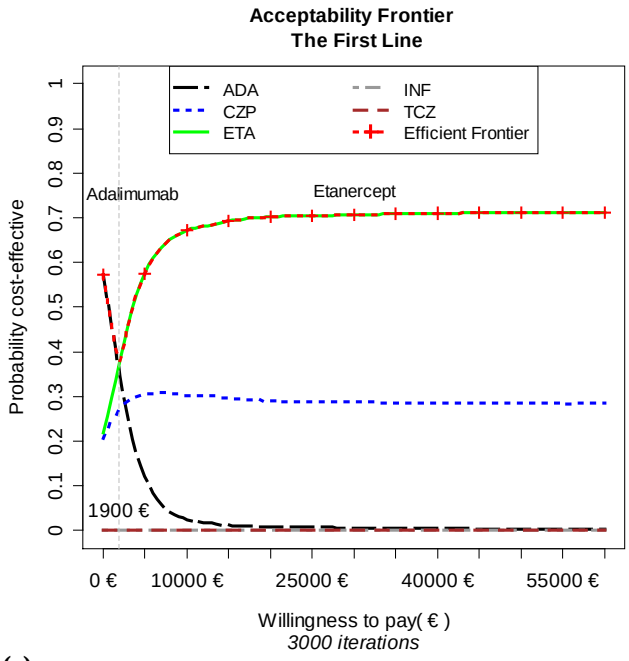
The slope of the frontier reflects Willingness to pay (WTP), that is to say, the expenditure required for an additional patient maintained under treatment, amounts to €1715.



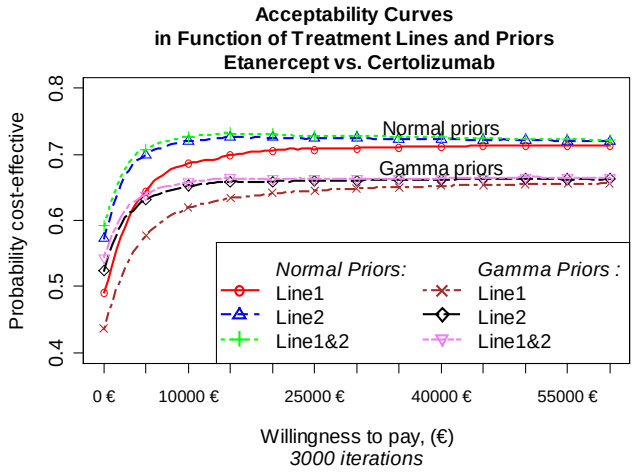
(a)



(b)



(c)



V_{ESA}	Normal priors			Gamma priors		
	Line1	Line2	Line1&2	Line1	Line2	Line1&2
0	0.49	0.57	0.59	0.44	0.52	0.54
5000	0.64	0.7	0.71	0.58	0.63	0.64
10000	0.69	0.72	0.73	0.62	0.65	0.66

(d)

Figure 7 : Cost-effectiveness analysis results

These results are confirmed calculating the number of times these treatments are part of the efficiency frontier. Table 3 summarizes the proportion of 3000 simulations in which each treatment forms part of the border. INF and TCZ do not form frontier.

Table 3 : Probability to take part to the efficiency frontier

Adalimumab	Certolizumab pegol	Etanercept	Infliximab	Tocilizumab

Line 1	61.5%	54.1%	84.3%	0%	0.1%
Line 2	64.4%	51.5%	84.0%	0%	0.1%
All	65.2%	51.1%	83.7%	0%	0.1%

Results from comparisons of treatments can be represented as scatter plot of costs and efficacy differences. Comparing pairs of treatment, for example CZP and ETA, figure 7 (b) shows that in 37% of simulations, ETA dominates CZP, but is dominated in 16% of cases. Furthermore, given a €150 WTP, the probability that ETA is more efficient than CZP is 0.49. When WTP is estimated at €5,000, this probability is 0.64.

However, this information can first be converted to net benefits, then pairwise comparisons (or comparison including all treatments) are carried out based on those net benefits, in order to find treatment with the highest net benefit.

Figure 7(c) represents the probability of being the most efficient among the five treatments according to WTP. This probability was calculated from the estimated net benefits of biological therapies. Thus, by comparing five treatments, ADA and ETA are located on the acceptability curve: ADA is the most efficient treatment given a WTP under €1,900. Any higher WTP is making ETA the most efficient treatment.

3.4.1.2. Sensibility analysis

Two sensitivity analyses were performed: first one on priors used for resources consumptions, second one on the line of treatment.

As part of the first sensitivity analyses, we evaluated the impact of prior distributions chosen for resources consumption. The use of truncated normal distributions has been replaced with gamma distributions. For the 2nd analysis, results were estimated for second-line biological therapy and for all lines together.

Results obtained through the comparison between ETA and CZP are shown in Figure 5d. The modification of the prior distribution reduced by 5 percentage points the probability that ETA is cost-effective, but does not alter the conclusions of the analysis. Similarly, the line of biotherapy does not impact results of the cost-effectiveness analysis.

3.4.2. Budget impact analysis

The budget impact analysis compared three assumptions: stability of market shares in 1st and 2nd line of biotherapy (H0), reduction of ETA's market shares by 10 points in both 1st and 2nd line (H1), and increase of ETA's market shares by 10 points in both 1st and 2nd line of biotherapy (H2). Assumptions H1 and H2 have been compared to the hypothesis H0, before being compared to each to other.

In the case of a 10 points reduction in ETA's market shares, the 5 years cumulative cost for the cohort are estimated at 2.68 billion euros (Table 3), corresponding to an average of €540 000 per year. The incremental cost resulting from the evolution of the market is about 21 million euros over 5 years (4 million euros per year), representing an increase of almost 1% of total expenditures. At the patient

level, average annual cost amounts to €510, that is an increase of 3% of the annual management cost of a patient, 1st and 2nd line confused.

Table 4 : Budget impact of a 10 points reduction of etanercept's market shares (H1) compared to statut quo (H1)

	Cohort costs 2011-2015					
	Cumulative cost (H1)	*Δ Cumulative cost*	*Δ in %*	*Annual cost (H1)*	*ΔAnnual cost*	*Δ in %*
Selected therapies	661 200 000 €	700 000 €	0,11%	132 200 000 €	100 000 €	0,08%
Hospitalization	228 800 000 €	17 600 000 €	8,33%	45 760 000 €	3 510 000 €	8,31%
Ambulatory	66 250 000 €	460 000 €	0,70%	13 250 000 €	90 000 €	0,68%
Total L1+L2	956 300 000 €	18 700 000 €	1,99%	191 300 000 €	3 800 000 €	2,03%
L3	1 729 000 000 €	2 000 000 €	0,12%	345 900 000 €	400 000 €	0,12%
Total L1+L2+L3	2 686 000 000 €	21 000 000 €	0,79%	537 100 000 €	4 100 000 €	0,77%
	Costs per patients 2011-2015					
	Annual cost (H2)	*Δ Annual cost*	*Δ in %*	*Daily cost (H2)*	*Δ Daily cost*	*Δ in %*
Selected therapies	12 040 €	50 €	0,42%	33 €	0,14 €	0,42%
Hospitalization	4 341 €	445 €	11,42%	12 €	1,22 €	11,42%
Ambulatory	1 212 €	15 €	1,25%	3 €	0,04 €	1,25%
Total L1+L2	17 600 €	510 €	2,98%	48 €	1,40 €	2,98%

Contrary to H1, hypothesis H2 (increase of etanercept's market shares by 10 points in 5 years) induce à reduction of the expenditure for the management of PR. Over the 5 years considered period, this reduction amounts to 8 million euros, i.e. 1,6 million euros per year on average. Most of those savings are made on hospital costs, especially drugs administration costs.

Table 5 : Budget impact of a 10 points increase of etanercept's market shares (H2), compared to statut quo (H0)

	Cohort costs 2011-2015					
	Cumulative cost (H2)	*Δ Cumulative cost*	*Δ in %*	*Annual cost(H2)*	*ΔAnnual cost*	*Δ in %*
Selected therapies	661 600 000 €	1 100 000 €	0,17%	132 300 000 €	200 000 €	0,15%
Hospitalization	204 600 000 €	-6 600 000 €	-3,13%	40 930 000 €	-1 320 000 €	-3,12%
Ambulatory	65 640 000 €	-150 000 €	-0,23%	13 130 000 €	-30 000 €	-0,23%
Total L1+L2	931 900 000 €	-5 700 000 €	-0,61%	186 400 000 €	-1 100 000 €	-0,59%
L3	1 725 000 000 €	-2 000 000 €	-0,12%	345 000 000 €	-500 000 €	-0,14%
Total L1+L2+L3	2 657 000 000 €	-8 000 000 €	-0,30%	531 400 000 €	-1 600 000 €	-0,30%
	Costs per patients 2011-2015					
	Annual cost(H2)	*Δ Annual cost*	*Δ in %*	*Daily cost(H2)*	*Δ Daily cost*	*Δ in %*
Selected therapies	11 980 €	-10 €	-0,08%	33 €	-0,03 €	-0,08%
Hospitalization	3 722 €	-174 €	-4,47%	10 €	-0,48 €	-4,47%
Ambulatory	1 189 €	-8 €	-0,67%	3 €	-0,02 €	-0,67%
Total L1+L2	16 890 €	-200 €	-1,17%	46 €	-0,55 €	-1,17%

Comparison of the extreme assumptions (H1 and H2) shows that the replacement of ETA by more expensive and / or less effective therapies results in a loss estimated at 29 million euros over 5 years, that is 6 million euros a year. Considering only 1st and 2nd line of biotherapy, additional cost is around €700 per year per patient, i.e. a 4.03% increase of average annual cost for managing a patient with RA after failure of DMARDs.

Table 6 : Optimistic case (etanercept+10 points, H2) compared the worst case (etanercept -10 points, H1)

	Cohort costs 2011-2015					
	Cumulative cost (H2)	*Δ Cumulative cost*	*Δ in %*	*Annual cost (H2)*	*ΔAnnual cost*	*Δ in %*
Selected therapies	661 600 000 €	400 000 €	0,06%	132 300 000 €	100 000 €	0,08%
Hospitalization	204 600 000 €	-24 200 000 €	-10,58%	40 930 000 €	-4 830 000 €	-10,56%
Ambulatory	65 640 000 €	-610 000 €	-0,92%	13 130 000 €	-120 000 €	-0,91%
Total L1+L2	931 900 000 €	-24 400 000 €	-2,55%	186 400 000 €	-4 900 000 €	-2,56%
L3	1 725 000 000 €	-4 000 000 €	-0,23%	345 000 000 €	-900 000 €	-0,26%
Total L1+L2+L3	2 657 000 000 €	-29 000 000 €	-1,08%	531 400 000 €	-5 700 000 €	-1,06%
	Costs per patients 2011-2015					
	Annual cost (H2)	*Δ Annual cost*	*Δ in %*	*Daily cost (H2)*	*Δ Daily cost*	*Δ in %*
Selected therapies	11 980 €	-60 €	-0,50%	33 €	-0,16 €	-0,50%
Hospitalization	3 722 €	-619 €	-14,26%	10 €	-1,70 €	-14,26%
Ambulatory	1 189 €	-23 €	-1,90%	3 €	-0,06 €	-1,90%
Total L1+L2	16 890 €	-710 €	-4,03%	46 €	-1,95 €	-4,03%

4. Conclusion

In case of a deterministic sensitivity analysis ADA and ETA, used in combination, are the only treatments belonging to efficiency frontier. ADA and ETA are the only treatments located on the acceptability frontier. Other treatments were dominated.

In terms of budget impact, substitution of more expensive biological therapies that do not offer additional therapeutic benefit for the patient implies economic losses for society which is estimated at 29 million euros, i.e. around 1% of the cost current biological therapies, if we reason from a situation where etanercept could increase sales by 10%.

5. Bibliography

1. Abrams K, Sanso B. Approximate Bayesian inference for random effects meta-analysis. Stat Med. Jan 30 1998;17(2):201-218.
2. Abrams KR, Gillies CL, Lambert PC. Meta-analysis of heterogeneously reported trials assessing change from baseline. Stat Med. Dec 30 2005;24(24):3823-3844.

3. Ades AE, Lu G, Higgins JP. The interpretation of random-effects meta-analysis in decision models. Med Decis Making. Nov-Dec 2005;25(6):646-654.
4. Ades AE, Sculpher M, Sutton A, et al. Bayesian methods for evidence synthesis in cost-effectiveness analysis. Pharmacoeconomics. 2006;24(1):1-19.
5. Ades AE, Welton NJ, Caldwell D, Price M, Goubar A, Lu G. Multiparameter evidence synthesis in epidemiology and medical decision-making. J Health Serv Res Policy. Oct 2008;13 Suppl 3:12-22.
6. Annemans L. Budget impact analysis. Pharmaco-economics : from theory to practice2009.
7. Briggs AH. A Bayesian approach to stochastic cost-effectiveness analysis. Health Econ. May 1999;8(3):257-261.
8. Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics. May 2000;17(5):479-500.
9. Briggs AH. A Bayesian approach to stochastic cost-effectiveness analysis. An illustration and application to blood pressure control in type 2 diabetes. Int J Technol Assess Health Care. Winter 2001;17(1):69-82.
10. CES. Guide méthodologique pour l'évaluation économique des stratégies de santé - Recommandations méthodologiques. Paris: Collège des économistes de la santé;2003.
11. CES. Guide méthodologique pour la mise en place d'une analyse d'impact budgétaire. Paris: Collège des économistes de la santé;2008.
12. Cohen JP, Stolk E, Niezen M. Role of budget impact in drug reimbursement decisions. J Health Polit Policy Law. Apr 2008;33(2):225-247.
13. Combe B, Codreanu C, Fiocco U, et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. Ann Rheum Dis. Oct 2006;65(10):1357-1362.
14. Cooper N, Abrams K, Sutton A, Turner D, Lambert P. A Bayesian approach to Markov modelling in cost-effectiveness analyses: application to taxane use in advanced breast cancer. J. R. Statistics. 2003;166:389-405.
15. Cooper N, Sutton A, Abrams K. Decision analytical economic modelling within bayesian framework: University of Leceister 2003.
16. Cooper NJ, Sutton AJ, Abrams KR, Turner D, Wailoo A. Comprehensive decision analytical modelling in economic evaluation: a Bayesian approach. Health Econ. Mar 2004;13(3):203-226.
17. Cooper NJ, Sutton AJ, Mugford M, Abrams KR. Use of Bayesian Markov Chain Monte Carlo methods to model cost-of-illness data. Med Decis Making. Jan-Feb 2003;23(1):38-53.
18. Cucherat M. Guide de lecture critique des comparaisons indirectes. 2009; http://www.spc.univ-lyon1.fr/polycop/comp%20ind%20lecture.htm.
19. Cucherat M. Interprétation des essais cliniques pour la pratique médicale. 2009; http://www.spc.univ-lyon1.fr/polycop/.
20. Cucherat M. Les comparaisons indirectes : méthodes et validité: Haute Autorité de Santé;2009.
21. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med. Mar 30 2010;29(7-8):932-944.
22. Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol. Dec 2003;30(12):2563-2571.
23. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum. Oct 2008;58(10):2968-2980.
24. HIQA. Guidelines for the Budget Impact Analysis of Health Technologies in Ireland. Dublin: Health Information and Quality Authority;2010.
25. Huang E, Esrailian E, Spiegel BM. The cost-effectiveness and budget impact of competing therapies in hepatic encephalopathy - a decision analysis. Aliment Pharmacol Ther. Oct 15 2007;26(8):1147-1161.

26. Jansen J, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons & network meta-analysis for health care decision making: ISPOR;2010.
27. Kay J, Matteson EL, Dasgupta B, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. Arthritis Rheum. Apr 2008;58(4):964-975.
28. Keystone E, Heijde D, Mason D, Jr., et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. Nov 2008;58(11):3319-3329.
29. Keystone EC, Genovese MC, Klareskog L, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis. Jun 2009;68(6):789-796.
30. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. May 2004;50(5):1400-1411.
31. Kim HY, Lee SK, Song YW, et al. A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. APLAR Journal of Rheumatology. 2007;10:9-16.
32. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet. Feb 28 2004;363(9410):675-681.
33. Kremer J, Ritchlin C, Mendelsohn A, et al. Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. Arthritis Rheum. Apr 2010;62(4):917-928.
34. Launois R, Avouac B, Berenbaum F, et al. Comparison of Certolizumab Pegol with Other Anticytokine Agents for Treatment of Rheumatoid Arthritis: A Multiple-treatment Bayesian Metaanalysis. J Rheumatol. Jan 20 2011.
35. Launois R, Payet S. Évaluation pharmacoéconomique des épisodes dépressifs majeurs et des récidives. Neuropsy news. 2003;2(5):209-221.
36. Launois R, Payet S, Riou Franca L, et al. L'évaluation des technologies de santé : les protocoles de deuxième génération. Journal d'Économie Médicale. 2006;24(5).
37. Launois R, Payet S, Saidenberg-Kermanac'h N, Francesconi C, Franca LR, Boissier MC. Budget impact model of rituximab after failure of one or more TNFalpha inhibitor therapies in the treatment of rheumatoid arthritis. Joint Bone Spine. Dec 2008;75(6):688-695.
38. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. Oct 2009;62(10):e1-34.
39. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med. Oct 30 2004;23(20):3105-3124.
40. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. Dec 4 1999;354(9194):1932-1939.
41. Maini RN, Taylor PC, Szechinski J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Arthritis Rheum. Sep 2006;54(9):2817-2829.
42. Mauskopf J. Prevalence-based economic evaluation. Value Health. Nov 1998;1(4):251-259.
43. Mauskopf J. Meeting the NICE requirements: a Markov model approach. Value Health. Jul-Aug 2000;3(4):287-293.
44. Mauskopf JA, Earnshaw S, Mullins CD. Budget impact analysis: review of the state of the art. Expert Rev Pharmacoecon Outcomes Res. Feb 2005;5(1):65-79.

45. Mauskopf JA, Sullivan SD, 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. Sep-Oct 2007;10(5):336-347.
46. Miyasaka N. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. Mod Rheumatol. 2008;18(3):252-262.
47. Moher D. Corrigendum to: Preferred Reporting Items For Systematic Reviews And Meta-Analyses: The PRISMA Statement International Journal of Surgery 2010; 8: 336-341. Int J Surg. Aug 3 2010.
48. Moher D, Altman DG, Liberati A, Tetzlaff J. PRISMA statement. Epidemiology. Jan 2011;22(1):128; author reply 128.
49. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. Oct 2009;62(10):1006-1012.
50. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med. Mar 16 1999;130(6):478-486.
51. NICE. Developing costing tools - Methods guide. London: National Institute for Health and Clinical Excellence;2008.
52. Niezen MG, de Bont A, Busschbach JJ, Cohen JP, Stolk EA. Finding legitimacy for the role of budget impact in drug reimbursement decisions. Int J Technol Assess Health Care. Jan 2009;25(1):49-55.
53. Nishimoto N, Hashimoto J, Miyasaka N, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis. Sep 2007;66(9):1162-1167.
54. Nishimoto N, Miyasaka N, Yamamoto K, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol. 2009;19(1):12-19.
55. Nony P, Cucherat M, Haugh MC, Boissel JP. Critères de qualité d'une méta-analyse d'essais cliniques. Sang Thrombose Vaisseaux. 1997;9(3):157-166.
56. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. Feb 2011;64(2):163-171.
57. Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis. Aug 2008;67(8):1096-1103.
58. Smolen J, Landewe RB, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis. Jun 2009;68(6):797-804.
59. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. Mar 22 2008;371(9617):987-997.
60. Spiegelhalter DJ, Abrams KR, Myles JP. Bayesian approaches to clinical trials and health care evaluation. Chichester ; Hoboken, NJ: Wiley; 2004.
61. Sutton A, Ades AE, Cooper N, Abrams K. Use of indirect and mixed treatment comparisons for technology assessment. Pharmacoeconomics. 2008;26(9):753-767.
62. Sutton AJ, Abrams KR. Bayesian methods in meta-analysis and evidence synthesis. Stat Methods Med Res. Aug 2001;10(4):277-303.
63. Sutton AJ, Abrams KR, Jones DR. An illustrated guide to the methods of meta-analysis. J Eval Clin Pract. May 2001;7(2):135-148.
64. Sutton AJ, Cooper NJ, Goodacre S, Stevenson M. Integration of meta-analysis and economic decision modeling for evaluating diagnostic tests. Med Decis Making. Sep-Oct 2008;28(5):650-667.

65. van de Putte LB, Atkins C, Malaise M, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis. May 2004;63(5):508-516.
66. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. Jan 2003;48(1):35-45.
67. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med. Jan 28 1999;340(4):253-259.
68. Westhovens R, Yocum D, Han J, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum. Apr 2006;54(4):1075-1086.
69. Zhang FC, Hou Y, Huang F, et al. Infliximab versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a preliminary study from China. APLAR Journal of Rheumatology. 2006;9:127-130.