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Mixed Treatment Comparison and Bayesian Integrated Economic Evaluation of Cost-Effectiveness and Budget Impact of TNF-alpha inhibitors for Rheumatoid Arthritis after Failure of Conventional DMARD Therapy

Méta analyse en réseau et évaluation de l'efficience des traitements de la polyarthrite rhumatoïde par anti TNF-alpha utilisant un modèle bayésien intégré

R. LAUNOIS*[1], J.-G. LE MOINE*[2] and TMT HUYNH*

* French Network for Evaluation in Health Economics

[1] Email: launois.reesfrance@wanadoo.fr
[2] Email: jglemoine.reesfrance@orange.fr

ABSTRACT

Background: Eighteen percent of patients with rheumatoid arthritis (RA) do not respond adequately to conventional treatment with Methotrexate, upon which biological agents known as TNF-α inhibitors may be used.

Objectives: Our objective was three-fold: first, to assess the efficacy and safety of second line biotherapies on a patient population presenting moderate to severe RA and who were unsuccessfully treated with conventional DMARDs, second, to evaluate the cost-effectiveness of different RA therapeutic strategies, and third, to estimate the budget impact of RA management in France.

Method: We conducted a systematic review of randomized control trials, conducted between 1999 and 2010, targeting RA patients undergoing treatment with a biological agent, as well as a quantitative synthesis using a mixed treatment comparison approach. A Markov model was built to reproduce RA patients' care trajectories within the French healthcare system. Data on resource consumption were collected from an observational study and used to as model parameters in order to assess the cost-effectiveness and budget impact of biotherapies available in France.

Results: Our analysis revealed significant differences between biotherapies and DMARDs, in terms of ACR50 response. When considering a willingness-to-pay (WTP) of €1,715, adalimumab was the most efficient treatment within, and etanercept the most effective beyond this threshold. The Budget Impact Analysis (BIA) showed that a decision to replace etanercept with more expensive and less effective therapies could result in a €28 million loss over 5 years.

Conclusion: As cost-effective second-line treatments in RA management, adalimumab and etanercept should constitute the preferred therapeutic options in France.

Keywords: Rheumatoid arthritis, TNF-alpha inhibitors, Cost-effectiveness, Budget impact, Markov model, Mixed treatment comparison.

RÉSUMÉ

Contexte : 80% des patients souffrant de polyarthrite rhumatoïde ne répondent pas aux traitements à base de méthotrexate et font l'objet d'une prise en charge par anti TNF-α.

Objectifs : Cette étude se propose d'évaluer l'efficacité et l'innocuité des biothérapies utilisées en seconde ligne de traitement sur les patients atteints de polyarthrite rhumatoïde modérée ou sévère dont la réponse aux traitements conventionnels est inadéquate, d'estimer leur efficience respective et d'estimer l'impact budgétaire des traitements mis en œuvre.

Méthode : Une revue systématique de la littérature disponible entre 1999 et 2013 a été faites en respectant les recommandations Prisma. La synthèse quantitative des résultats publiés dans les essais randomisés retenus a fait l'objet d'une méta-analyse en réseau. Un modèle de Markov a été développé pour retracer l'évolution de la pathologie sous traitement et le parcours de soins des malades. Les consommations de biens et services médicaux ont été extraites d'une étude observationnelle dont les résultats ont alimenté l'analyse cout efficacité et le modèle d'impact budgétaire.

Résultat : La méta-analyse montre des différences significatives sur le critère ACR 20 des biothérapies par rapport au méthotrexate mais aucune différence significative entre les biothérapies sur la base de ce même critère. L'analyse cout efficacité révèle que l'adalimumab se situe sur la frontière des meilleurs traitements financièrement acceptables en deçà du seuil de 1,715 € et qu'au-delà, c'est l'etanercept qui est le meilleur traitement. Le modèle d'impact budgétaire montre que le remplacement de l'etanercept par des molécules plus onéreuse et moins efficace couterait à la collectivité 28 millions d'euros en cinq ans.

Mots-clés : Polyarthrite rhumatoïde, anti-TNF-α, méta-analyse en réseau, bénéfice monétaire net, analyse d'impact budgétaire.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease with an estimated 0.31% prevalence in France [1]. Women constitute the majority of the patient population, giving a 5.7-fold increase in prevalence relative to men [1]. Between 120,000 and 220,000 individuals suffer from the disease, making it the most common inflammatory arthritis in the country. The annual incidence is estimated at 90 per million with an overrepresented population of sufferers aged 25 to 55 years old [2]. As such, the importance of this disease prescribes a regularly optimized therapy.

To this day, a number of treatments have been developed to manage this condition. The conventional first-line therapy proposed is a disease-modifying anti-rheumatic drug (DMARD), which can result in either halting or slowing down disease progression. DMARD treatment consists of administering sulfasalazine or methotrexate (MTX). Both these treatments have similar efficacy [3], though MTX remains the preferred choice for most physicians [4].

Following DMARD therapeutic failure, the favored treatment is either tocilizumab (TCZ), an anti-IL-6 or any one of the following five TNF-α inhibitors: infliximab (INF), golimumab (GOL), etanercept (ETA), certolizumab pegol (CZP), and adalimumab (ADA) or This group of treatments is sometimes referred to as biotherapies. In case of inadequate response to biotherapies, the therapeutic arsenal for RA includes molecules like rituximab (RTX) and abatacept (ABA).

These biotherapies have all been approved by the French health authorities as second line treatments. Yet, evidence on the relative efficiencies of biotherapies remains scarce in the current body of knowledge. Such information on efficiency is crucial when deciding an RA patient's course of treatment. An insightful comparison of treatments should encompass not only an assessment of efficacy, safety, and discontinuation rates, but also a complete medico-economic analysis including a budgetary impact (BIA) and cost-effectiveness (CEA) analysis. In this paper, we present the results of a sim (CE) and budget impact (BI) in order to support and nuance the future therapeutic choices facing clinicians specialized in RA.

MATERIALS & METHODS

Systematic review

A systematic review of the literature was conducted in accordance with PRISMA recommendations [5-7]. We sought to identify randomized clinical trials (RCT) conducted between 1999 and 2010 targeting RA patients who were treated with ADA, CZP, ETA, GOL, INF, or TCZ. The search equations were constructed from PICOS criteria [5, 8, 9]. The PICOS acronym refers to the following five search components: characteristics of the target population(P), nature of the intervention(I); chosen comparators(C), outcomes(O) and study designs(S). These were strategically considered in order to provide a robust level of evidence. We searched the bibliographic databases MEDLINE and EMBASE in October 2010 and updated in June 2011, using descriptors from EMTREE, CISMef and MeSH. In addition, the publications referenced in the selected articles were considered in the selection process. Selection criteria were: (i)the target population was aged 18 years or older diagnosed with RA and non-responsive to conventional DMARD therapy; (ii)the second-line treatment was either ADA, CZP, ETA, GOL, INF, or TCZ; (iii)the comparators used included either conventional DMARD or a biotherapy; (iv)the outcome was estimated to be ACR50 response[1] at 24±10 weeks, early discontinuations at 12±10weeks, and infections at 24±10 weeks; and (v)the study was designed as a randomized controlled trial (RCT). Duplicate refer-

ences were eliminated and the first selection round began on the basis of abstract and title screening. The remaining articles were read by two independent reviewers. Clinical data were extracted using a standardized form implemented in Excel®. Prior to quantitative synthesis, Higgins I^2 and Cochrane's heterogeneity tests were performed on the final selection of articles.

Mixed treatment comparison

Most available data are contained in pairwise treatments comparisons. However, even when several comparisons (*A* vs. *B*, *A* vs. *C*, *C* vs. *D*, etc.) are performed for a single indication, it is rather rare to obtain data for each comparison. Mixed treatment comparison (MTC) is a Bayesian method that combines both direct and indirect evidence [10] and estimates the effectiveness of a particular treatment relative to another, regardless of whether direct comparisons were actually performed or not. The MTC model used for this approach is as follows:

where p_{jk} is the response rate of treatment k in trial j, μ_{jb} is the effectiveness outcome presented as log-odds of treatment b in trial j, and δ_{jbk} is the additional effectiveness of treatment

$$logit(p_{jk}) = \begin{cases} \mu_{jb}, & if\ k = b; b = A, B, C, \ldots \\ \mu_{jb} + \delta_{jbk}, & if\ k \neq b; b = A, B, C, \ldots \end{cases}$$

k relative to treatment b in trial j corresponding to the log-odds ratio between b and k. We then consider that

where d_{bk} is the pooled log odds ratio of k relative to b.

$$\delta_{jbk} \sim N\left(d_{bk}, \sigma^{2}_{bk}\right),$$

The absolute rate of response of treatment k (T_k) is hence calculated from its log-odds ratio when compared to standard treatment b, and obtained as a result of the MTC. Thus, it is calculated as:

$$Log\left(\frac{T_k}{1-T_k}\right) = \mu_b + \delta_{bk} \leftrightarrow \left(\frac{T_k}{1-T_k}\right) =$$

$$exp[\mu_b + \delta_{bk}] \leftrightarrow T_k = \frac{exp[\mu_b + \delta_{bk}]}{1 + exp[\mu_b + \delta_{bk}]}$$

Markov model

A Markov model was developed to reproduce an RA patient's trajectory within the healthcare system, an approach that allows us to simulate the cyclical aspect of RA management. The model comprises 22 mutually exclusive health states: 20 are related with the biotherapies of interest, one is the absorbing state and corresponds to third line therapies, and the last one is used to allow for incident patients to enter the model.

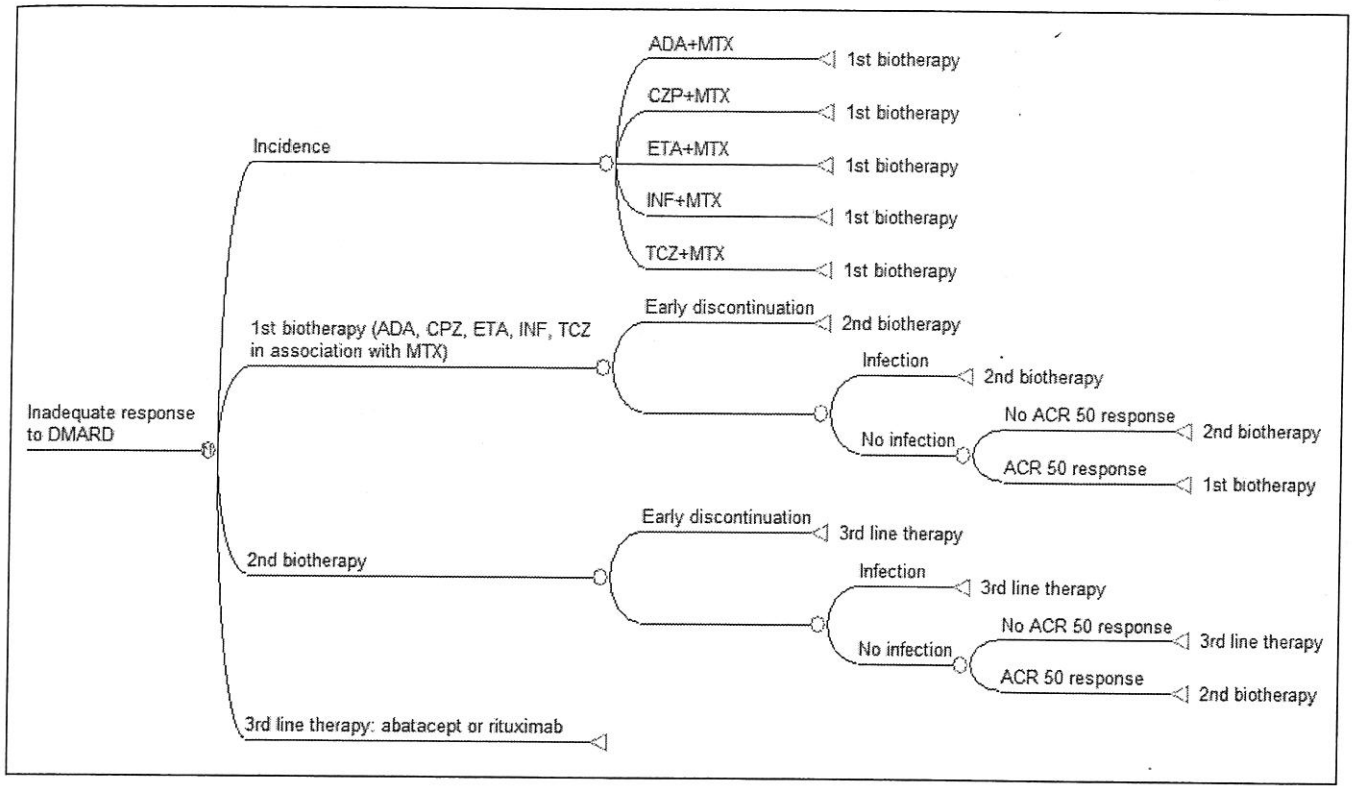
After failure of conventional DMARDs, the patient enters the second line of treatment and receives one of the five available biotherapies[2]. The patient can then, drop out of the treatment, develop an infection or be non-responsive to the therapy. Otherwise, the patient is considered responsive, with regards to the ACR50 criteria, and proceeds with treatment. After failure of two successive biotherapies, patients are treated with either RTX or ABA, which corresponds to the third line of treatment. A simplified version of the model is presented in Figure 1.

We considered a five-year horizon, divided in six-month cycles. At the end of each cycle, new incident cases were injected into the

[1] ACR 50 response is defined as a 50 percent improvement in tender or swollen joint counts as well as 50 percent improvement in three of the following five criteria: acute phase reactant, patient assessment, physician assessment, pain scale, disability/functional questionnaire.

[2] At the time of the study, Golimumab was not available on the French market for rheumatoid arthritis. Thus, it was not considered any further in the economic evaluation.

Figure 1: Simplified structure of the Markov model used in the economic evaluation.



model. Thus, the model enables us to follow cohorts across time while taking different treatment conditions (i.e. first, second and third treatment lines) into account [11].

Population data

The study focused on patients aged 18 years or older who present with active RA and are non-responsive to conventional DMARDs. We used appraisals from the Transparency Commission to estimate the size of our target population. According to Guillemin and Saraux [1] 0.31% of France's residents aged 18 and older are affected by RA. This translates to 151,000 RA patients in the year 2009, based on the census data obtained by INSEE.

According to the French National Health Insurance Fund (CNAM), 150,032 individuals had severe progressive long-term RA in 2007. An increase of 6.2% was observed between 2005 and 2006, followed by 6.8% between 2006 and 2007. Assuming a 6% yearly increase, we hypothesized that there would be 168,576 RA patients in 2009. Considering that CNAM covers 88% of the French population, the total number of patients with severe RA in France is estimated at 191,000. Of these patients, 45% to 60% are treated with MTX, 18% of which do not respond to the treatment and require a second line therapeutic alternative [12]. Consequently, the estimated number of prevalent patients eligible for second line treatment is situated between 16,000 and 20,000. We used the latter estimate in our model. Moreover, we used the incidence findings published by Guillemin et al, which estimates the number of new cases per year as 90 per million inhabitants [2].

Resource use and unit cost

The consumption of resources related to the management of RA was categorized into five groups: drug acquisition, drug administration, follow-up visits, laboratory, and imaging. The distinction was made between hospital and ambulatory care. The data came from

an ad hoc observational study conducted in 2006, which included 277 French patients with severe RA undergoing a second line of treatment [13]. In the study, consumption associated with certolizumab and tocilizumab were not available, thus it was assumed that patients receiving certolizumab had consumption patterns identical to the average study patient. Due to identical administration patterns, user consumption of tocilizumab was assumed to be equivalent to infliximab in all respects except posology. Probability distributions (i.e. beta, normal, and gamma) were fitted to all parameters in order to take uncertainty into account.

We retained the French health insurance perspective for the economic evaluation. All resource uses were valued on the basis of the latest tariffs of the French health insurance nomenclatures (i.e. CCAM v32, NABM, v22, NGAP and Ameli.fr drug database). The cost of drug administration was estimated as a weighted average of five diagnostic-related groups (DRG) established by the CNAM and the cost of third line therapies was extracted from a 2010 French observational study [14]. Following French authorities' recommendations [15], a 4% discount rate was applied on costs and effectiveness.

Health economic evaluations

Following the mixed treatment comparison, we conducted a full economic evaluation using a Bayesian framework. This included a CEA together with a BIA. This approach is otherwise denominated as 'integrated' [16] giving that it does not separate the evidence synthesis from the occurrence of clinical events in the study of their economic consequences. Both of the analyses relied on the Markov model described previously. Probabilistic sensitivity analyses [17] were run so as to quantify the uncertainty around the estimates.

The cost-effectiveness of the biotherapies was analyzed in terms of treatment retention rates, also understood as adequate treatment response, and calculated using the following formula:

$$retention\ rate = (1 - dropout\ rate) \times (1 - infection\ rate) \times (1 - ACR50\ response)$$

The CEA was designed as a three-step process, including: (1) the estimation of incremental cost-effectiveness ratios (ICERs) and construction of the efficiency frontier, (2) the pairwise comparison of strategies introducing the traditional four-quadrant plot and the willingness-to-pay (WTP), and (3) the use of the net health benefit (NHB) framework to build the acceptability frontier.

The first step of our CEA was to calculate ICERs, and to build the efficiency frontier. When comparing two interventions, ICER is calculated as the difference in cost (ΔC) divided by the difference in effectiveness (ΔE). ICER allows for the identification and elimination of the most costly and less effective strategies, which are also known as dominated. It also enables the construction of the efficiency frontier. A strategy is part of the frontier when its ICER is lowest compared to all other therapeutic options. Hence, the efficiency frontier exposes strategies increasing in efficiency from left to right and in cost downward, with a slope that corresponds to the ICER. Though widely used in economic evaluation, this approach is no longer sufficient as uncertainty is not taken into account [18].

A complementary approach to ICER results from plotting results in the cost-effectiveness plane, whereby differences in cost are displayed on the Y-axis and differences in effectiveness on the X-axis. The resulting graph includes four quadrants. The new strategy is preferred when it is displayed in the south-east quadrant (i.e. less costly and more effective) while the reference strategy is displayed in the north-west one (i.e. more costly and less effective). Within the remaining two quadrants, no distinction can be made between the interventions. Thus, we introduce willingness-to-pay

(WTP), which corresponds to the amount that the health care system is willing to pay in order to receive an additional health unit. As such, the probability of an intervention being cost-effective compared to a reference can be calculated in accordance with the retained WTP, and a decision made.

The net health benefit framework offers a more straightforward approach than cost-effectiveness ratios. NHB was defined by Stinnet and Mullahy [19] as the net benefit of investing resources in a strategy instead of investing the same resources in an alternative, albeit marginally cost-effective, one. It is calculated according to the following formula: $NHB=\mu_{Ei}-\mu_{Ci}/\lambda$, where λ represents the willingness-to-pay. Thus, NHB can be used to classify the considered strategies as it enables an argument in favor of the strategy with the highest NHB. Furthermore, when used in a probabilistic sensitivity analysis, it depicts the strength of the evidence favoring the cost-effectiveness of strategies. By plotting these probabilities for a range of WTP values, it is possible to construct the acceptability frontier.

Finally, a budget impact analysis was conducted with three scenarios considered. The baseline scenario considers that the market shares remain constant over the period of interest. Scenario one simulates a 10-point increase of ETA shares over a five-year period while scenario two, a 10-point drop of drug shares. The fluctuations were assumed to be linear. The changes in ETA market shares were compensated by those of existing therapies, which were proportional to their original market shares. We calculated the cumulated and annual costs, both for the entire cohort and per patient, while comparing each scenario.

Statistical software

All statistical and economic analyses were conducted using WinBUGS® version 1.4.3 and R version 2.3.

RESULTS

Systematic review

Figure 2 presents the article selection process using the PRISMA flowchart. Two thousand articles were initially identified. After removing duplicates, 1,286 articles were shortlisted, from which 1,185 references were eliminated following the screening of relevant titles. The abstracts of 101 articles were read and 59 publications were selected to be fully read. Eventually, 24 trials were deemed relevant to the study [20-43].

Two of them [28, 40] were excluded after running the heterogeneity tests. We selected a final list of 22 articles from which we were able to establish a network of evidence including: 11 protocols, 10 direct comparisons, and a cumulative total of 7,182 patients (Figure 3).

Bayesian network meta-analysis

The mixed treatment comparison assessed the efficacy and safety of the six biotherapies. The observed results concerning ACR50 response, infections and early discontinuations were measured as log-odds ratios (log OR) and are presented solely for combination protocols.

Figure 4 presents the forest plot with the log OR for ACR50 response, infection, and dropout rates across different therapy courses in comparison to DMARDs. All the considered biotherapeutic alternatives have a significantly higher efficacy than DMARDs. We did not observe any significant differences between biotherapies in terms of efficacy and infections. However, as it regards early discontinuations, the MTC analysis demonstrates that CZP+MTX, ETA+MTX and TCZ+MTX have significantly less dropouts than DMARDs. Furthermore, CZP+MTX have significantly lower early discontinuation rates than the other associations, with the exception of ETA+MTX.

Figure 2: Flowchart of the selection process.

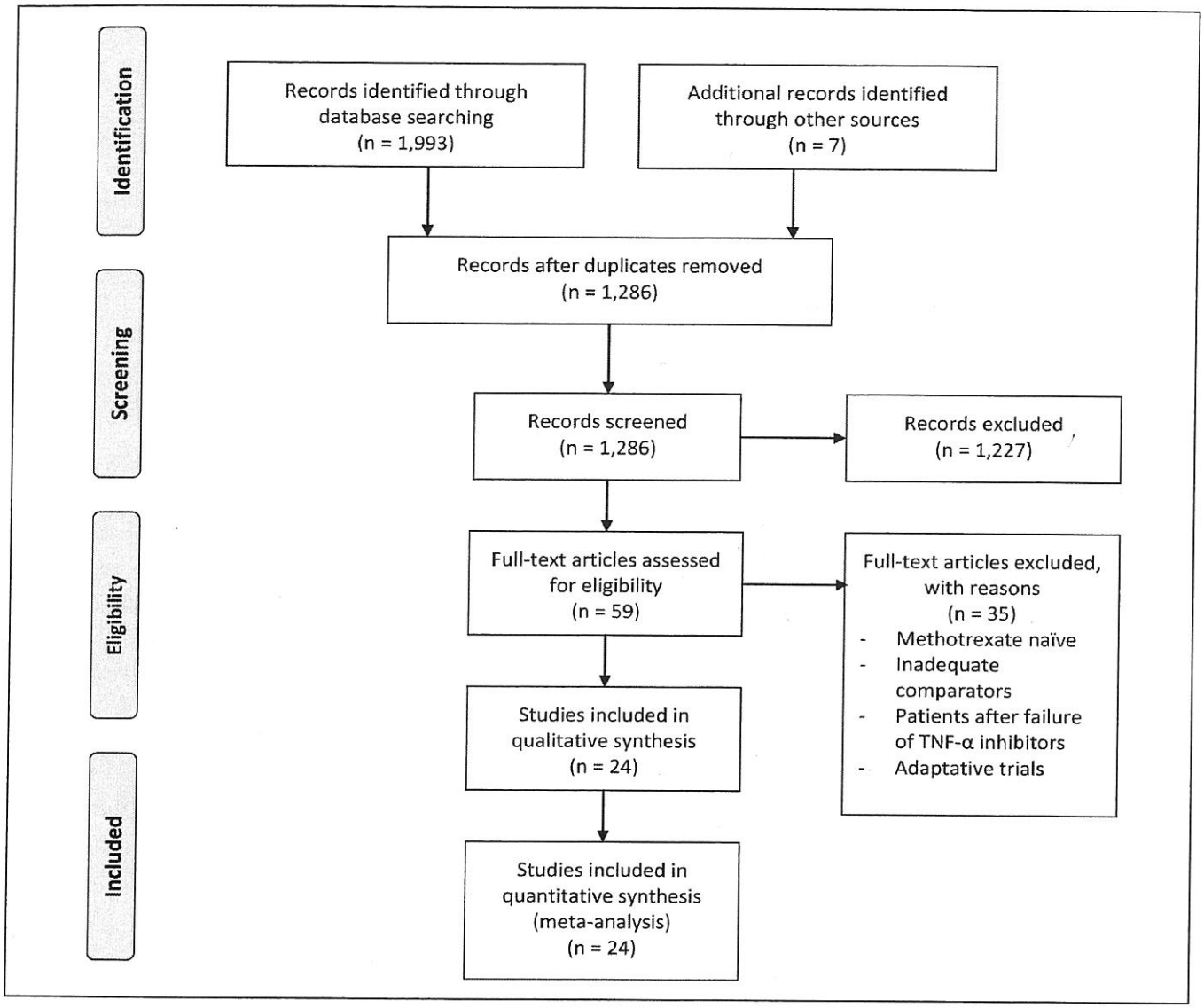
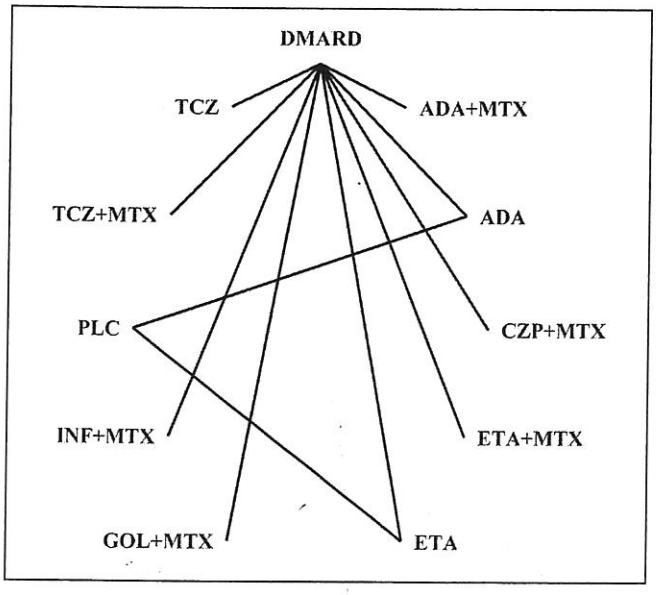


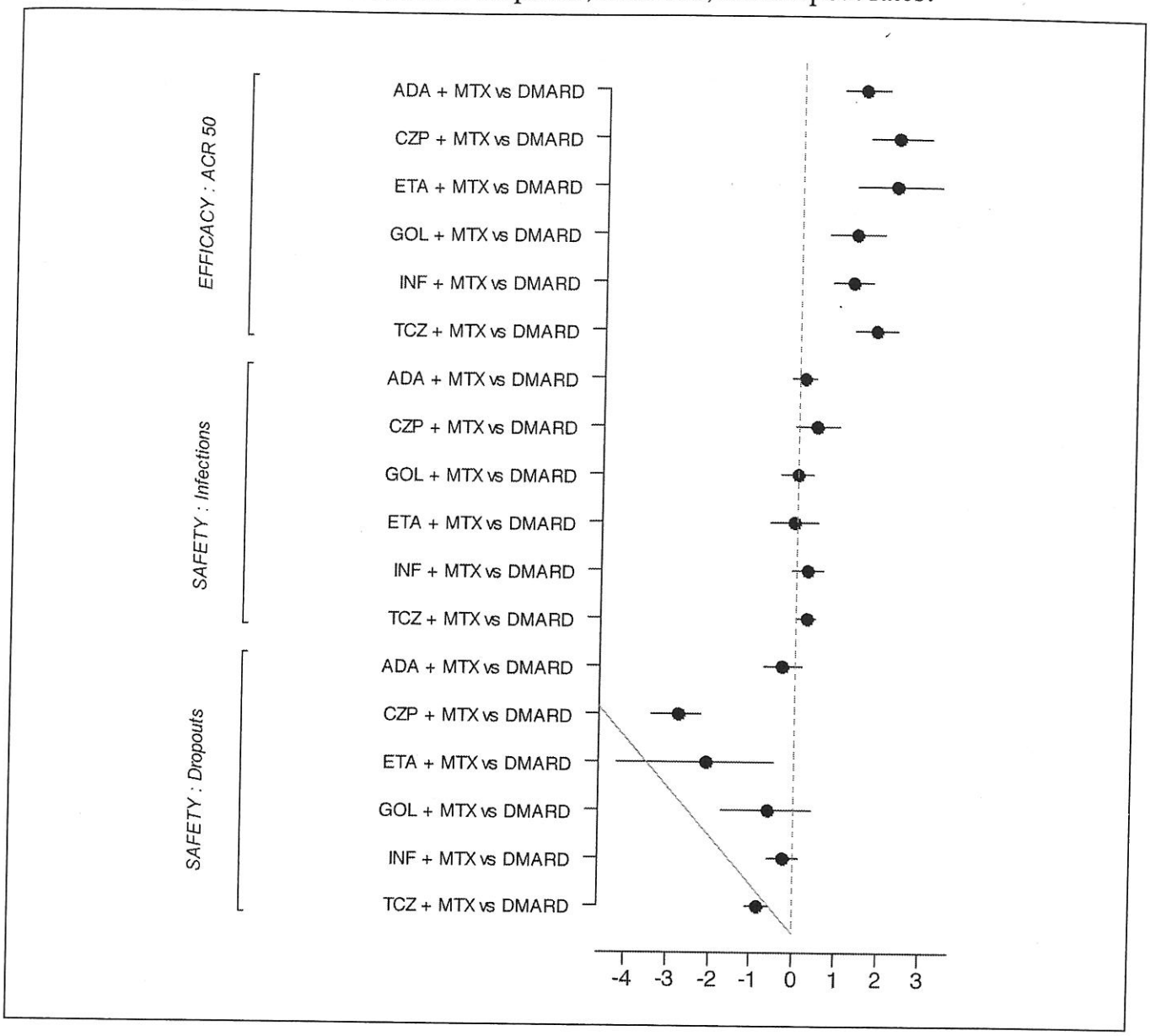
Figure 3: Network of evidence.



Cost-effectiveness analysis

The efficiency frontier was constructed from the results of 3,000 simulations, based on the average annual cost per patient (i.e. cost criterion) and the average annual treatment retention rate (i.e. efficacy endpoint). ADA and ETA are part of the efficiency frontier, dominating the remaining three treatments, as such, they are identified as less costly and more effective than their counterparts. ADA was identified as the less costly and less efficient therapy while ETA was identified as the most efficient and most costly. This would mean that ETA proposes a sustained response to treat-

Figure 4: Log-odds ratio for ACR 50 response, infection, and dropout rates.



ment over a longer period of time for an additional €1,715.

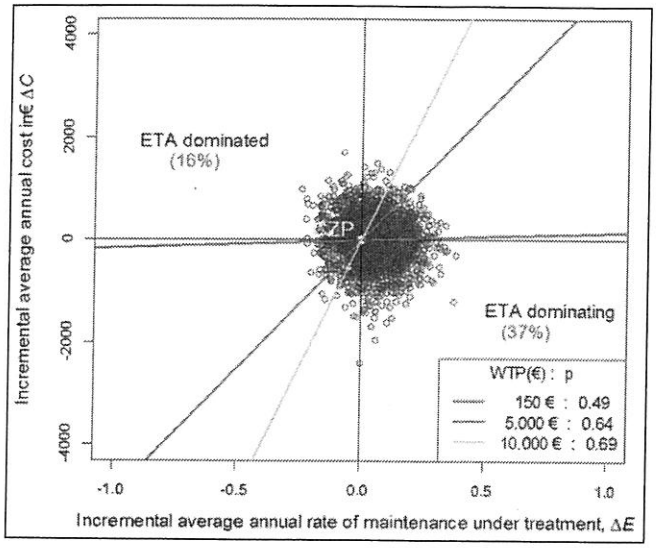
In the probabilistic sensitivity analysis, ADA and ETA were found to be part of the efficiency frontier in 61% and 84% of the 3,000 simulations, respectively, followed by CZP (54%), TCZ (0%) and INF (0%).

Treatment comparisons concerning differences in cost and effectiveness were also measured in the cost-effectiveness plane by introducing willingness-to-pay (WTP). When comparing ETA to CZP, inadequate response to DMARDs, ETA dominates CZP in 37% of the simulations and is dominated in 16% of them (Figure 5a). Moreover, ETA dominates in 64% of the simulations when the WTP is set to €5,000 and in 69% when the WTP is set to €10,000.

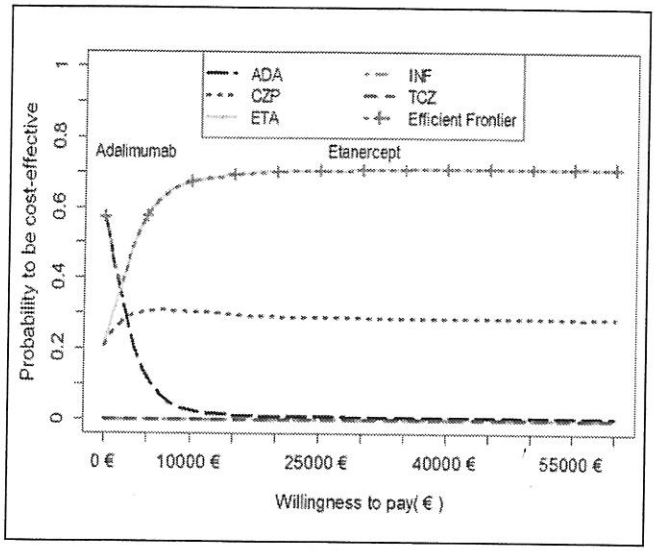
Figure 5b displays the acceptability frontier representing the probability of being the most efficient treatment according to the WTP value.

This probability was calculated from the estimated net health benefits of biological ther-

Figure 5: (a) Incremental cost-effectiveness plane of ETA compared to CZP; (b) Acceptability frontier.



(a)



(b)

apies. Compared to their counterparts, ADA and ETA are the sole biotherapies located on the acceptability frontier. ADA is the most efficient treatment situated under the €1,715 WTP, while ETA is the most efficient beyond the same threshold.

The two figures are connected when focusing on ETA and CZP. In figure 5b, the probability for ETA being more effective than CZP increases in parallel to the WTP. Similarly, in figure 5a, the probability of ETA dominating CZP increases with the WTP. The more ETA is dominating CZP, the more its probability of being efficient is superior to CZP's.

Budget impact analysis

With a 10-point increase in ETA's market shares over a 5-year period, the model predicted a reduction in the overall expenditure equal to 7 million euros (all expenses included). The potential savings amounted to an average of €200 per patient per year, which reduced the annual cost of care by nearly 1.2%. Detailed results are presented in Table 1.

Conversely, when ETA's market shares decreased by 10 points in favor of its competitors over the same 5-year period, our model estimated an overall additional cost of 21 million euros (all expenses included). This corresponds to an average 510€ cost increase per patient per year; – nearly 3% (Table 2).

DISCUSSION

Our study aimed to synthesize the existing evidence concerning the efficacy and safety of biotherapies in the management of rheumatoid arthritis following non-response to conventional DMARDs. This quantitative synthesis was then mobilized to conduct a full Bayesian economic evaluation. We identified significant efficacy differences in favor of TNFα inhibitors when compared to conventional DMARDs. Our results suggest that both ADA+MTX and ETA+MTX should be considered reference treatments to be used separately when RA patients are non-responsive to conventional DMARDs treatment. While we did not use QALYs to measure treatment efficacy, our findings were consistent with previous studies identifying ADA or ETA as cost-effective in the management of rheumatoid arthritis [44, 45].

Table 1: Budget impact of a 10-point increase in ETA's market shares.

	Cohort costs 2011-2015					
	Cumulative cost	**Δ Cumulative cost**	**Δ in %**	**Annual cost**	**Δ Annual cost**	**Δ in %**
Biotherapy	660 000 000 €	1 100 000 €	0,17%	132 000 000 €	200 000 €	0,15%
Hospitalization	204,600,000 €	-6 600 000 €	-3,13%	40 930 000 €	-1 320 000 €	-3,12%
Ambulatory care	65 640 000 €	-150 000 €	-0,23%	13 130 000 €	-30 000 €	-0,23%
Total L2	930 300 000 €	-5 700 000 €	-0,61%	186 100 000 €	-1 100 000 €	-0,59%
L3	1 725 000 000 €	-2 000 000 €	-0,12%	345 000 000 €	-500 000 €	-0,14%
Total L2+L3	2 656 000 000 €	-7 000 000 €	-0,26%	531 100 000 €	-1 600 000 €	-0,30%
	Patient costs 2011-2015					
	Annual cost	**Δ Annual cost**	**Δ in %**	**Daily costs**	**Δ Daily costs**	**Δ in %**
Biotherapy	11 950 €	-10 €	-0,08%	33 €	-0,03 €	-0,08%
Hospitalization	3 722 €	-174 €	-4,47%	10 €	-0,48 €	-4,47%
Ambulatory care	1 189 €	-8 €	-0,67%	3 €	-0,02 €	-0,67%
Total L2	16 860 €	-200 €	-1,17%	46 €	-0,55 €	-1,17%

Table 2: Budget impact of a 10-point reduction in ETA's market shares.

	Cohort costs 2011-2015					
	Cumulative cost	**Δ Cumulative cost**	**Δ in %**	**Annual cost**	**Δ annual cost**	**Δ in %**
Biotherapy	659 700 000 €	800 000 €	0,12%	131 900 000 €	100 000 €	0,08%
Hospitalization	228 800 000 €	17 600 000 €	8,33%	45 760 000 €	3 510 000 €	8,31%
Ambulatory care	66 250 000 €	460 000 €	0,70%	13 250 000 €	90 000 €	0,68%
Total L2	954 700 000 €	18 700 000 €	2,00%	190 900 000 €	3 700 000 €	1,98%
L3	1 729 000 000 €	2 000 000 €	0,12%	345 900 000 €	400 000 €	0,12%
Total L2+L3	2 684 000 000 €	21 000 000 €	0,79%	536 800 000 €	4 100 000 €	0,77%
	Patient costs 2011-2015					
	Annual cost	**Δ Annual cost**	**Δ in %**	**Daily cost**	**Δ Daily cost**	**Δ in %**
Biotherapy	12 020 €	60 €	0,50%	33 €	0,16 €	0,50%
Hospitalization	4 341 €	445 €	11,42%	12 €	1,22 €	11,42%
Ambulatory care	1 212 €	15 €	1,25%	3 €	0,04 €	1,25%
Total L2	17 570 €	510 €	2,99%	48 €	1,40 €	2,99%

Regarding the treatments' safety profiles, we revealed that CZP, ETA, and TCZ, in association with MTX, induced significantly less cases of early discontinuation than DMARDs. In addition, using CZP resulted in significantly fewer dropouts than its biological counterparts, with the exception of ETA due to overlapping confidence intervals. The CEA demonstrated ADA and ETA to be cost-effective in the second line management of RA. Among the two therapies, ADA was identified as the less costly and less efficient therapy while ETA was identified as the most efficient and most costly with an associated ICER of €1,715. The willingness-to-pay and the acceptability frontier analyses led to the same conclusion – advocating for the use of ADA if WTP fell under €1,700 and for ETA otherwise. We further analyzed the impact that changes in market shares would incur on the budget by introducing a 10-point increase or decrease of ETA shares. Increasing ETA market shares by 10 points over five years was associated with average savings corresponding to seven million euros in RA management. Conversely, a 10-point reduction of ETA's market share was responsible for an average increase of 21 million euros in care costs related to the disease.

Our methodological concern was to build the model within a full Bayesian framework that could benefit from the 'integrated' approach advocated by Spiegelhalter and Best [16]. This type of model uses the posterior distribution of clinical parameters, such as efficacy and safety, enabling the analyst to extend the resulting uncertainty through to the economic evaluation. Compared with a two-stage approach, the integrated approach does not need to fit a parametric distribution for the posterior probability distribution. Hence no correlation loss between parameters occurs. Furthermore, the integrated approach is judged to be more transparent due to the fact that it is programmed within only one framework.

Present findings should be interpreted in light of the following limitations. First, the Markov model built to reproduce the management of rheumatoid arthritis did not include a "death" health state. This could have led to the overestimation of RA management costs. While this may be viewed as a major limitation, the absence of a "death" health state is in accordance with the death rates reported in the randomized controlled trials, which were close to 0%. Second, our cost-effectiveness analysis is based on the treatment retention rate, a unique effectiveness criterion, defined as the probability to observe an adequate treatment response. While most cost-effectiveness analyses use quality of life outcomes, we believe our use of the treatment retention rate as the effectiveness criterion provides insightful evidence for clinicians and policy makers. Treatment retention rate relies on an effectiveness parameter, the ACR 50 response, as well as, on the early discontinuation and infection rates, which we believe provide more complete results. A criterion that is built upon three diverse aspects of effectiveness may be more useful in guiding clinical decision making concerning RA treatment options. Third, at the time when this economic analysis was conducted, only five treatments were available for RA management following non-response to DMARDs in France. Notwithstanding, the literature review identified six biotherapies of potential interest. As no data were available for the sixth therapy (i.e. golimumab) regarding pricing, resource use, and market shares, we opted not to include it in the analysis as it would have added major assumptions, thus weakening the results. Moreover, hypothesizing an ASMR level for golimumab would have been hazardous to our analysis. Fourth, the resource use parameters included in our model were derived from a French observational study conducted in 2006. We recognize that the data could be considered as outdated. We used it nonetheless giving that, to our knowledge, this is the latest study that collected both outpatient and hospital data on the management of rheumatoid arthritis in France. Finally, we advocated the use of French individual data in

order to provide more relevant results to decision makers working within the French public health system. We acknowledge that this may limit the generalizability of our study's findings.

CONCLUSION

As cost-effective second-line treatments in RA management, adalimumab and etanercept should constitute the preferred therapeutic options in France. The increasing use of these biotherapies and subsequent replacement of comparatively more expensive therapies and less effective therapies could lead to a substantial reduction of the care-related costs associated with the management of rheumatoid arthritis in France. The emergence of new data could enable us to update the latest second line therapeutic options for RA available to French patients.

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