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Original article

Cost-effectiveness modelling of biological treatment sequences in moderate to severe rheumatoid arthritis in France

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Abstract

Objectives. Modern treatment of RA includes the use of biologics. Their cost is high and comparison between different treatment strategies is needed.

Method. Direct medical costs of RA in France were evaluated based on expert opinion. Then, simulation–decision analytical models were developed to assess four biologic treatment sequences over 2 years in patients failing to respond to at least one anti-TNF agent. Effectiveness was expressed in theoretical expected number of days (TEND) in remission or low disease activity [low disease activity score (LDAS)] based on DAS-28 scores.

Results. Direct medical costs of RA in France (excluding the cost of biologics) were estimated at €905 (S.D. 263) for 6 months and €696 (S.D. 240) for each subsequent 6 months ($P < 0.001$) for patients achieving LDAS and €1215 for 6 months (S.D. 405) for patients not achieving LDAS. Based on LDAS criteria, using abatacept after an inadequate response to the first anti-TNF agent (etanercept) appeared significantly ($P < 0.01$) more efficacious over a 2-year period (102 TEND) compared with using rituximab at a 6-month re-treatment interval (82 TEND). Mean cost-effectiveness ratios showed significantly lower costs ($P < 0.01$) per TEND with abatacept as second biologic agent (€278) compared with rituximab (€303). After an inadequate response to two anti-TNF agents, using abatacept also appeared significantly more efficacious than an anti-TNF agent ($P < 0.01$). All comparisons were confirmed when using remission criteria instead of LDAS.

Conclusion. Advanced simulation models based on clinical evidence and medical practice appear to be a promising approach for comparing cost-effectiveness of biologic strategies in RA.

Key words: Rheumatoid arthritis, Cost-effectiveness, Abatacept, Rituximab, Modelling.

CLINICAL SCIENCE

Introduction

RA causes progressive destruction of the joints and serious functional disability, and is associated with a considerable socio-economic burden [1]. RA prevalence varies across different European countries and populations. For France, RA prevalence is ~0.31%, with a greater prevalence among women (0.51%; 0.09% in men) [2]. Considering patient variability in prevalence and response to treatment, RA requires continuous monitoring and adjustment of treatment strategies against disease progression.

While the economic impact of RA is substantial, few studies have evaluated the direct medical costs

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associated with RA in France. One recent estimate of annual direct costs in RA reached €4000 in France [3]. As RA progresses, patients experience increasing functional impairment that may lead to work disability and lost wages [4, 5], resulting in significant indirect costs estimated to be twice as high as direct costs [6]. RA being a chronic condition with significant economic impact, there is a need to evaluate the clinical effectiveness of various treatment strategies, and the cost and cost-effectiveness of innovative therapies *vs* existing treatment regimens.

The treatment of RA is complex and requires different drugs used in combination or in sequence in the case of an insufficient response or intolerance to a previous therapy. Clinical and economic estimates are further complicated by the need for continuous adjustment of treatment regimens. When NSAIDs, corticosteroids or traditional DMARDs are no longer efficacious due to disease progression, further treatment options for RA may include biological agents. TNF antagonists (anti-TNF agents) are used as first biological option and are often prescribed in a sequential manner ('cycling') in the case of an insufficient response or intolerance to a first anti-TNF agent. However, there are no randomized controlled clinical trials (RCTs) confirming the overall effectiveness of anti-TNF agents used in a sequential manner in anti-TNF inadequate responders. Hence, clinicians may elect to use alternative treatment strategies [7, 8], including new biological agents that exhibit a different mechanism of action from anti-TNF agents, and which have been studied in anti-TNF-refractory patients.

Some reasons for such scarcity of comparative clinical data are the very high costs of implementing complex protocols that require monitoring a large number of patients in the long term. Sophisticated modelling techniques allow these problems to be circumscribed by generating valid hypothetical data based on existing clinical evidence, validated expert assumptions and current medical practice in a given country. The modelling approach uses a mathematical language to compare various treatment strategies as 'virtual' head-to-head clinical trials. Informative results, such as medium- or long-term RA treatment costs, effectiveness and cost-effectiveness of various sequential biological strategies can thus be generated '*in silico*' when '*in vivo*' is not practicable [9, 10]. The use of simulation modelling in RA treatment is becoming increasingly common in clinical and economic assessments in the USA, Canada and Europe [11–13].

The objective of this cost-effectiveness model was to compare costs, effectiveness and cost-effectiveness of different biological sequential strategies in France in patients with moderate to severe active RA and an insufficient response to at least one anti-TNF agent.

Methods

Costs

French RA direct medical costs were derived from a standard costing approach performed with a panel of three expert clinicians highly experienced in RA management (A.S., L.G. and P.G.). Four categories of disease activity were defined according to 28-joint disease activity score (DAS-28) thresholds: remission (DAS-28 < 2.6), no remission (DAS-28 $\geqslant 2.6$), low DAS (LDAS: DAS-28 $\leqslant 3.2$) and no-LDAS representing moderate to high activity state (DAS-28 > 3.2). Direct medical costs were estimated for 6 months according to standard medical practice. The expert panel described eight RA resource utilization items of RA medical management in France, according to national clinical guidelines: medical visits, laboratory tests, hospitalization, imaging, physiotherapy, nursing, adaptive aids and transportation. Using a standard costing approach, CIs of each resource utilization item were derived from frequency ranges defined by clinical experts for each disease activity category (remission, LDAS and moderate to high disease activity). Using a national payer perspective, unit costs were derived from published national tariffs (for drug costs: *Journal Officiel de la République Française*, for other costs: tariffs from the French National sick funds) [14, 15]. The experts considered that the cost of remission or LDAS would vary over time (first and subsequent 6-month periods). Unit costs from the national payer perspective were collected and simulated using distribution ranges for each item.

For each disease activity category (remission, LDAS and moderate to high disease activity), total management costs were calculated using resource utilization items, costs and frequency. Each item costs (for example, X-ray costs or nurse visit costs) were expressed from a minimum to a maximum value, according to tariff ranges in the French healthcare system, using a uniform distribution. Similarly, each item frequency (for example, number of X-rays in 6 months or number of nurse visits in 6 months) was expressed using a minimum and maximum value (based on medical practice variability in France) and uniform distribution (except for hospitalization which, in agreement with clinical experts, was programmed using a triangular distribution, i.e. using three parameters: minimum, most likely value and maximum).

A sub-simulation model was carried out to compute specific distributions of each resource item. All costs were expressed in 2008 values. Biological drug costs were calculated based on 2008 French price lists (*Journal Officiel de la République Française*) and recommended dosing.

Effectiveness

Two clinically relevant effectiveness end-points aligned with RA treatment goals were used: LDAS and remission. Effectiveness estimates of biological therapies in anti-TNF inadequate responders were derived directly from published clinical trials at the time of model development. For each drug, data from randomized controlled trials were used if they reported DAS status at 6 months; if unavailable, other study designs were sought. Thus, the abatacept trial in treatment of anti-TNF inadequate responders (ATTAIN) trial and long-term extension study were used for abatacept [16, 17], the open-label research

in active rheumatoid arthritis (ReAct) trial for anti-TNF agents [18] and the randomized evaluation of long-term efficacy of rituximab (REFLEX) trial and open-label extension analysis for rituximab in anti-TNF inadequate responders [19, 20]. The ATTAIN and REFLEX clinical trials were deemed comparable in terms of patients' baseline characteristics (age, gender, disease duration and DAS-28 score). Regarding effectiveness data after an insufficient response to two anti-TNF agents, clinical data for abatacept was derived from specific *post-hoc* analyses of the ATTAIN trial [21]. In the absence of published effectiveness data for infliximab after an insufficient response to two anti-TNF agents, the results of the ReAct trial, an open-label study published by Bombardieri *et al*. [18], were used as best surrogate evidence. Although the ReAct study specifically concerns adalimumab, the results correlate with those of the Karlsson *et al.* study [22] that studied treatment response to anti-TNF switches, regardless of the anti-TNF agents used.

Regarding rituximab re-treatment intervals, most of the patients who received additional courses in rituximab RA clinical trials (where the need for repeated courses was at physician's discretion based on specific response criteria), did so 24 weeks after the previous course and none were re-treated sooner than 16 weeks (Rituximab US Product monograph). The model assumed a sustained DAS-28 response over time; the rituximab re-treatment interval was, therefore, set at 6 months for the purpose of this simulation model. A recent analysis of the DAS-28 reduction from baseline with rituximab suggested that the DAS-28 reduction appears intermittent and dependent on re-treatment intervals [23]. Whereas a 6-month re-treatment interval was suggested in the literature [24], in daily practice, the optimal interval for subsequent rituximab treatment courses remains at the discretion of the physician. To reflect potential variations in real life practice, and the French Club Rhumatismes et Inflammation (CRI) recommendations [25], which suggest that re-treatment should be recommended only $\geqslant$24 weeks after the first infusion [25], a 9-month re-treatment interval was simulated as sensitivity analysis and is presented in the 'Results' section.

Assuming comparable patient populations, the percentages of patients achieving LDAS and remission at each simulated 6-month time point were used to populate the model over a 2-year time horizon.

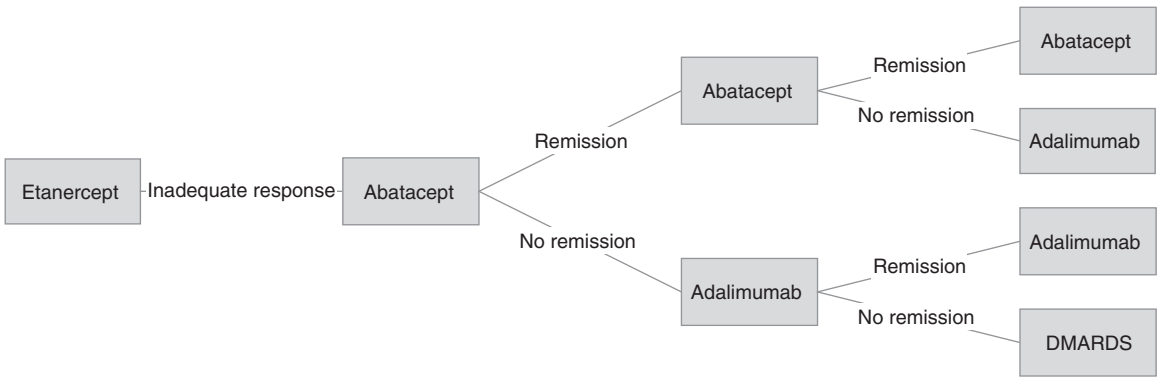
Overall effectiveness was expressed in theoretical expected number of days (TEND) in remission or LDAS for each sequence over 2 years, which is the product of success rates (remission or LDAS) by the number of days in success during each simulation pathway.

Model structure

Using a 2-year time horizon over four 6-month treatment intervals, four biological strategies were simulated to reflect sequential use of biological agents. The model considers etanercept as the first anti-TNF agent most often used in France based on medical practice and market research studies. Two strategies (Sequences S1 and S2) assumed 0% success after the first anti-TNF agent (etanercept), because these simulations focused on a population of inadequate responders to a first anti-TNF agent. After switching to a second agent (abatacept in Sequence S1 or rituximab in Sequence S2), the same treatment was maintained as long as it was efficacious (i.e. for achieving LDAS or remission). The decision to switch biological therapy following an insufficient response was allowed at each 6-month time point. Figure 1 presents the general structure of Sequence S1 using remission as the effectiveness criterion.

The two other sequential strategies (Sequences S3 and S4) assume 0% success of a first (etanercept) and to a second anti-TNF agent (adalimumab) in order to simulate situations of insufficient response to two anti-TNF agents before using a third biological agent (abatacept in Sequence S3 or infliximab in Sequence S4). The four sequential biological strategies simulated are described in Table 1. Each sequence was simulated with one specific model programmed to generate mean values and S.D. of costs, effectiveness and mean cost-effectiveness over 2 years. Statistical tests (mean tests) were performed to calculate potentially significant differences between Sequence 1 and Sequence 2, and between Sequence 3 and Sequence 4.

Fig. 1 General architecture of the model for Sequence 1 using remission as the effectiveness criterion.



Results

Results from the simulation models take into account all probabilities of success/no success at every 6-month time point for all the branches of the tree for each biological sequence. Because the model also takes into account potential failures every 6 months, as well as potential switches to the next biological agent in case of an insufficient response to the previous agent, the overall success rate over 2 years for each biological sequence comprising multiple successive agents (including all potential treatment switches and success/failure probabilities) is necessarily distinct from published long-term data of each individual agent.

Direct medical costs

Direct medical costs of RA in France (excluding the cost of biological therapies, which was calculated separately) were estimated for disease activity level.

For patients achieving remission, costs were estimated at €771 (S.D. 199) for the first 6 months and at €511 (S.D. 162) for each subsequent 6 months ($P < 0.001$). For patients not achieving remission, costs were estimated at €1159 for 6 months (S.D. 339).

For patients achieving LDAS, costs were estimated at €905 (S.D. 263) for the first 6 months and at €696 (S.D. 240) for each subsequent 6 months ($P < 0.001$). For patients not achieving LDAS, costs were estimated at €1215 for 6 months (S.D. 405).

Hence, achieving LDAS or remission was associated with lower medical costs. Key cost drivers were medical visits and laboratory tests for patients in remission or LDAS, and hospitalization and transportation for patients with moderate to high disease activity.

Table 1 Composition of the four biological treatment sequences

Sequence	First biological option	Second biological option	Third biological option
S1	Etanercept →	Abatacept →	Adalimumab
S2	Etanercept →	Rituximab →	Adalimumab
S3	Etanercept →	Adalimumab →	Abatacept
S4	Etanercept →	Adalimumab →	Infliximab

Total costs, effectiveness and cost-effectiveness

Using direct medical costs, the cost of biological therapies and published effectiveness data for each agent composing the different sequences, the eight simulation models generated the following results (Figs 2 and 3).

Success criteria: achieving LDAS. The sequence representing the use of abatacept after an insufficient response to a first anti-TNF agent (etanercept) appeared significantly ($P < 0.01$) more efficacious over 2 years (102 TEND, S.D. 1.12) compared with a similar sequence using rituximab (82 TEND, S.D. 1.2). Corresponding mean cost-effectiveness ratios showed significantly lower costs ($P < 0.01$) per TEND with abatacept used after a first anti-TNF agent (€278, S.D. 32.9) compared with rituximab using a 6-month re-treatment interval (€303, S.D. 29.4). Using a 9-month re-treatment interval for rituximab, the mean cost-effectiveness ratio was €302 for TEND in LDAS, assuming a sustained effectiveness with rituximab between 6 and 9 months.

Following an insufficient response to two anti-TNF agents (etanercept, and then adalimumab), abatacept used as a third biological agent that appeared significantly ($P < 0.01$) more efficacious over 2 years (63 TEND, S.D. 15.0) compared with a similar sequence using infliximab (32 TEND, S.D. 1.39). Mean cost-effectiveness ratios showed significantly lower costs ($P < 0.01$) per TEND to achieve LDAS (€473, S.D. 124) with abatacept as the third biological agent compared with infliximab (€817, S.D. 84).

Success criteria: achieving remission. Using the remission criterion, the sequence using abatacept after a first anti-TNF agent (etanercept) appeared significantly ($P < 0.01$) more efficacious over 2 years (52 TEND,

Fig. 2 TEND in LDAS or remission over 2 years. S1: Sequence 1 (etanercept–abatacept–adalimumab); S2: Sequence 2 (etanercept–rituximab–adalimumab); S3: Sequence 3 (etanercept–adalimumab–abatacept); S4: Sequence 4 (etanercept–adalimumab–infliximab).

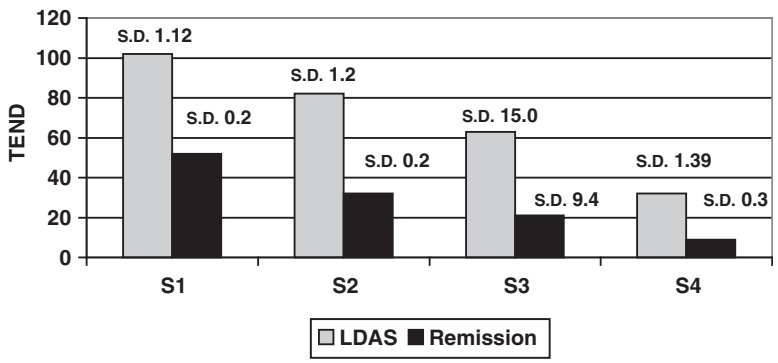
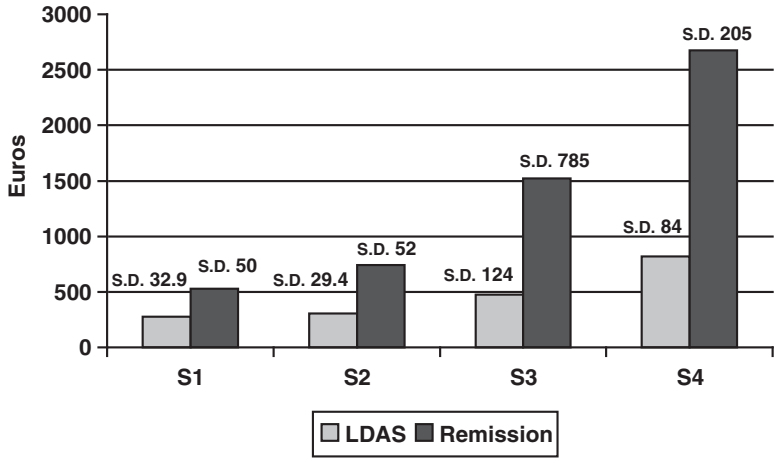


FIG. 3 Overall treatment cost per TEND in LDAS or remission (in euros). S1: Sequence 1 (etanercept–abatacept–adalimumab); S2: Sequence 2 (etanercept–rituximab–adalimumab); S3: Sequence 3 (etanercept–adalimumab–abatacept); and S4: Sequence 4 (etanercept–adalimumab–infliximab).



S.D. 0.2) compared with a similar sequence using rituximab (32 TEND, S.D. 0.2). Corresponding mean cost-effectiveness showed significantly lower costs ($P < 0.01$) per TEND with abatacept used after a first anti-TNF agent (€526, S.D. 50) compared with rituximab (€742, S.D. 52). Using a 9-month re-treatment interval for rituximab resulted in €741 for TEND in remission.

Following an insufficient response to two anti-TNF agents (etanercept, then adalimumab), abatacept used as a third biological agent appeared significantly ($P < 0.01$) more efficacious over 2 years (21 TEND, S.D. 9.4) compared with a similar sequence using infliximab (9 TEND, S.D. 0.3). Mean cost-effectiveness ratios showed significantly lower costs ($P < 0.01$) per TEND to achieve remission (€1521, S.D. 785) with abatacept as a third biological agent compared with infliximab (€2677, S.D. 205).

Discussion

The results of our resource utilization assessment show that RA imposes a substantial economic burden and that achieving remission is associated with lower RA medical costs. Importantly, for chronic progressive diseases requiring long-term treatment, most health gains and any potential economic benefits are often most evident in the long term [26]. As a consequence, the RA field has witnessed an explosion of economic studies estimating the long-term effects of RA treatment strategies. In the context of a medico-economic evaluation, this requires modelling beyond the clinical trial duration to project available knowledge and clinical data into the future. Such projections are known to be more contentious [27]. This explains why most of these studies are driven by hypotheses that would ideally need to be validated in clinical trials, including efficacy scenarios under different therapeutic regimens and time horizons, correlations between different parameters, etc.

Based on both LDAS and remission criteria, a treatment sequence using abatacept straight after an insufficient response to a first anti-TNF agent (etanercept) appeared more efficacious over 2 years compared with a similar biological sequence using rituximab. This is explained by the observed differences in both LDAS and remission rates at 6 months in the ATTAIN trial for abatacept and the REFLEX trial for rituximab. Even if rituximab treatment is cheaper, this difference in effectiveness impacts mean cost-effectiveness ratios, which showed lower overall treatment costs per TEND with abatacept as second biological agent compared with rituximab. Comparing across clinical trials is always a difficult task as populations and methodologies are not necessarily similar. However, patients' baseline characteristics of the ATTAIN and REFLEX trials appear similar. In the present model, data variability was managed using probabilistic sensitivity analyses and validated assumptions to integrate data from heterogeneous sources. Simulation models automatically analyse the effect that variable data inputs have on the outputs of the modelled system. Since different biological treatment sequences have not yet been compared in head-to-head clinical trials in RA, simulation models represent the best approach for comparing various strategies by taking into account the uncertainty inherent to the parameters. This approach is considered a robust sensitivity analysis (probabilistic sensitivity analysis), which is recommended in economic modelling to assess the potential impact of distribution of parameters on the results [10, 28]. Advanced modelling techniques provide valuable information that would not be available to decision makers otherwise (or potentially only at prohibitive cost considering the time and resources that would be required to conduct extremely complex studies, making timely decision-making impractical). Potential concerns about model validity have been addressed both with the introduction of more transparent methods

and by ensuring that necessary assumptions are consistent with medical practice [29].

Most of the published economic models in RA used a subjective outcome measurement of 'Quality Adjusted Life Years' [30–33]. This approach assesses utility measurements of patient preferences calibrated between 0 (death) and 1 (full health). This method is subject to a very active methodological debate in health economics [34, 35], since final results depend heavily on the technique used to measure utility [30, 36–38].

Relevant to this analysis, and as a main goal of RA treatment, tight control of disease activity has been shown to provide major clinical benefits [39, 40]. Welsing *et al*. [41, 42] demonstrated the relationship between a fluctuant DAS and radiological progression in patients with RA. Consequently, slowing the progression of joint damage is dependent on achieving and maintaining a constant LDAS. In addition to a clear relationship between the disease activity and the progression of joint destruction and functional disability, disease activity is also correlated with overall costs [43–45]. For these reasons, this innovative cost-effectiveness model is based on the maintenance of a sustained DAS-28 response over 2 years, by either continuing with an effective biological agent or switching to another agent in the case of insufficient response to the previous biological therapy. In addition, controlling the disease activity also positively affects the quality of life (QoL). A significant inverse correlation of DAS-28 score with the physical health and psychological domains of the World Health Organization (WHO) QoL assessment has been shown [46, 47].

With the emergence of numerous economic evaluations, some international standardization efforts have been deployed to come up with more consistent factors to model clinical and economic outcomes in RA treatment. Specifically, the OMERACT working group proposed some guidance for estimating clinical improvement in RA [29]. In contrast to 'cost–utility analyses', this innovative cost–effectiveness analysis is based on published clinical evidence and involves only a limited number of assumptions, aligned with the OMERACT guidelines in economic evaluations [27].

As for any model, there are some limitations. First, no randomized clinical trials assessing treatment switches are available to provide evidence for the effectiveness data. Secondly, treatment switches occurred in our models regardless of the cause. For example, the effectiveness of a second anti-TNF agent would be expected to be higher if the switch is due to adverse events compared with an inadequate response to a first anti-TNF agent.

RA being a chronic, debilitating and lifelong disease, using longer time horizons would allow the consideration of relevant long-term clinical outcomes and downstream economic consequences. However, this model was based on existing clinical evidence at the time of model development to avoid projecting the effectiveness over a lifetime, which would have brought more uncertainty in the absence of longer term clinical evidence. As the re-treatment interval for rituximab <6 months time period is not formally established [25], this may theoretically impact the costing results. However, altering the re-treatment interval from 6 to 9 months did not significantly impact the model results because this concerns a limited number of patients in the final branches of the decision tree and also because the model assumed a sustained effectiveness with rituximab between 6 and 9 months. However, a recent analysis of the DAS-28 reduction from baseline with rituximab suggested an intermittent DAS-28 response between re-treatments [23]. Given the reactivation of RA symptoms between rituximab re-treatments, a 6-month re-treatment interval for rituximab is now increasingly suggested in the literature [24].

While this model focuses on achieving LDAS or remission, it does not incorporate the significant favourable impact of biological therapies on structural evolution, long-term disability and improvement in QoL (mental and physical components). In particular, a significant inverse correlation of the DAS-28 with physical health and psychological well-being of the WHO QoL assessment has been shown [46, 47]. The improvement in patients' QoL being an important goal of RA treatment, it should be addressed and considered separately, based on clinical evidence measured in RCTs. Economic analyses in RA should also ideally consider total direct and indirect costs associated with the disease [9]. Given that RA indirect costs are considerable (i.e. loss of income due to lost work days, change in employment or salary, productivity loss and long-term disability), the overall cost-effectiveness of different biological strategies is likely to be understated.

In conclusion, this innovative cost-effectiveness simulation model is the first to use LDAS and remission as measurements of effectiveness expressed in natural units of treatment success, and to compare sequential biological strategies aligned with RA treatment goals and French medical practice. This analysis aims at informing the rheumatology community and health authorities in France on the cost-effectiveness of different RA biological strategies, including anti-TNF agents, abatacept and rituximab, used in sequence in patients with moderate to severe active RA and an insufficient response to other DMARDs, including at least one anti-TNF agent.

Advanced simulation models based on clinical evidence and medical practice appear to be a promising approach for comparing costs, effectiveness and cost-effectiveness of complex sequential biological strategies for the management of moderate to severe active RA.

Rheumatology key messages

- Cost-effectiveness analysis expressed in costs per clinical outcome is a clinically meaningful robust approach.
- Biological therapies can be compared using costs to achieve remission or low disease activity.
- Simulation models are a promising approach to assess complex RA biological strategies.

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