Cost-effectiveness of rituximab versus azathioprine for maintenance treatment in antineutrophil cytoplasmic antibody-associated vasculitis

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ABSTRACT

Objective. *Rituximab was proven superior to azathioprine for maintenance treatment of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). The high cost of rituximab might, however, limit its routine use. This study determined the cost-effectiveness of intravenous rituximab (5 x 500 mg until month 18), versus oral azathioprine (2 mg/kg per day, gradually decreased between month 12 and 22), for maintenance treatment of patients with granulomatosis with polyangiitis, microscopic polyangiitis, or renal-limited vasculitis, aged 18–75.*

Methods. *We performed a single-trial based economic evaluation. MAINRITSAN was a 28-month multicentre, prospective, randomised, controlled open-label trial. We estimated the cost of healthcare resources and quality of life using prospectively collected data. Healthcare costs were estimated from the perspective of the French Social Health Insurance's perspective, using 2016 tariffs for reimbursement. Utilities were derived from Short Form 36 scores. We estimated total average cost, incremental cost per incremental relapse averted and per quality-adjusted life-year (QALY) gained. Sensitivity analyses were performed to assess uncertainty over relapses, severe adverse events, discount rate, utility weights, time horizon and the cost of rituximab. Costs drivers were tested using a generalised linear model.*

Results. *Total average costs were €13,387 (€11,605–€15,646) and €10,217 (€7,567–12,949) in the rituximab and azathioprine groups respectively. The incremental cost-effectiveness ratio (ICER) was €12,824 per relapse averted and the incremental cost-utility ratio (ICUR) €37,782 per QALY gained. Besides the unit cost of rituximab, the major cost drivers were relapses and severe adverse events.*

Conclusion. *Maintenance treatment by rituximab could be cost-effective for preventing relapses in patients with AAV.*

Introduction

The therapeutic strategy for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) has evolved over the past decade with the emergence of biological agents, targeting specific mechanisms, such as rituximab (RTX): a chimeric anti-CD20 monoclonal antibody which targets B lymphocytes (1). RTX was proven to be not inferior to the standard-of-care therapy for the induction of remission in two prospective trials (2-4). MAINRITSAN was the first randomised controlled trial assessing the effectiveness of rituximab in maintaining remission of AAV. RTX was proven to be superior to azathioprine (AZA) for maintenance treatment of AAV after a follow-up of 28 months with the major relapse rate significantly reduced from 29% in the AZA group to 5% in the RTX group (p=0.002). No significant between-group difference was observed for minor relapses and severe adverse events (SAEs) (5). The quality of life of MAINRITSAN patients was significantly impaired compared with age- and sex-matched norms (6). These findings are in line with the results of another study that showed that AAV affects quality of life negatively across all domains (7).

The high unit cost of RTX, combined with additional costs for its intravenous administration, might, however, limit its routine use. The economic impact of AAV and RTX for the treatment of AAV has been only partially investigated so far (8-11) and no study has explored the impact of RTX as a maintenance therapy as yet.

Our objective was to determine the cost-effectiveness and the cost-utility of RTX compared to AZA in patients with AAV in full remission.

Materials and methods

We followed the French guidelines and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) for the economic evaluation (12, 13).

Population, treatment protocol, follow-up

We performed a single-trial based economic evaluation. The methods set for the trial have been previously described (5). Briefly, MAINRITSAN was a prospective, randomised, controlled open-label trial conducted in 54 centres in France between 2008 and 2012. It included 115 patients with granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) or renal-limited AAV and aged 18-75 at the beginning of their remission phase achieved with a combination of intravenous cyclophosphamide and glucocorticoids; 58 were randomised in the AZA group and 57 in the RTX group. With regards to their disease status, 80% were newly-diagnosed AAV, and the remaining 20% had relapsing AAV. Patients were randomised to receive either intravenous rituximab (500 mg) on days 0 and 14, at months 6, 12 and 18, or daily oral azathioprine at 2 mg/kg per day for 12 months then a decreasing dosage until month 22. The patients enrolled were followed until month 28 and disease monitoring was scheduled every 3 months.

The trial obtained prior authorisation from the French Data Protection Authority and the Ethical Research Committee. It was sponsored by the Assistance Publique-Hôpitaux de Paris (AP-HP). Rituximab was provided in part by Hoffmann-La Roche.

Data

We used the Case Report Form (CRF) of the trial combined with patient-level record linkage of hospital discharge data.

We used linked hospital records to identify each admission (overnight and day admissions) and extract the standardised discharge summary with diagnoses coded using the 10th edition of the International Classification of Diseases (ICD-10), procedures and the diagnosis-related group (DRG).

The classification of hospital admissions was performed by combining event date and CRF data with information contained in the discharge summary (date, DRG, diagnoses and procedures). The following resources were included: study medication, study medication administration (hospital day cases – where the patient is admitted for a day – or inpatient admissions), disease monitoring day cases and outpatient care (physician visits and laboratory tests), relapses (hospital stays and treatment), SAEs (hospital stays and treatment), other hospital admissions and therapies associated to the evolution of AAV (*e.g.* dialysis, erythropoietin to treat renal failure-induced anaemia).

The trial follow-up protocol (physician visits and laboratory tests) corresponded to routine follow-up scheduled by AAV French guidelines: hence these resources were not regarded as protocol driven (14). Resource use associated with the induction treatment of relapses was fully taken into account, even when the treatment schedule ended after the 28-month period, whereas for maintenance therapy, only resource use incurred during the 28-month period was included in the analysis.

As for SAEs, firstly, we identified the hospital admissions associated to events reported in the CRF. Secondly, to validate the completeness of medical data by means of routine data extracted from hospital records, we checked all the hospital stays to identify other admissions potentially associated to SAEs not reported in the CRF. Events identified through either one of these two steps were finally reviewed by the principal investigator. Only discharge diagnoses with a reasonably possible causal relationship with the treatment (*e.g.* infectious events) were included in the economic evaluation.

Costs

Costs were assessed from the perspective of the French Social Health Insurance (SHI); patients with AAV are eligible for 100% coverage of all health expenditures. We used official 2016 DRG tariffs for public hospitals. Additional costs associated to intensive care unit admissions or expensive drugs were added to the DRG tariff. SHI's schedule and official price for drugs, laboratory tests and specialists' visits within the framework of a regular follow-up were used. Unit costs are presented in Tables S1 and S2 in the Supplementary Appendix.

We used a 4% discount rate for costs and effects. All costs are reported in euros in 2016.

Measurement of effectiveness and quality of life

The effectiveness was measured by the rate of major relapses averted at month 28 (primary endpoint of the trial), defined as reappearance or worsening of disease with a Birmingham Vasculitis Activity score (BVAS) > 0 and involvement of at least one major organ, a life-threatening manifestation or both. The rate of minor relapses (BVAS >0 and mild treatment increase) and SAEs were assessed as secondary endpoints.

The quality of life was measured by the self-administered 36-item Short-form (SF-36) standardised questionnaire at baseline and at each protocol visit (6). SF-36 scores were converted into health state SF-6D utility values by Brazier's algorithm (15) and hence into quality-adjusted life-years (QALYs) by multiplying utility values to the corresponding time period. For deceased patients a utility value of zero was imputed from the time of death.

Economic evaluation

We calculated the incremental cost-utility (ICUR) and cost-effectiveness (ICER) ratios. Total costs for each of the RTX and AZA groups were calculated by summing each individual patient cost. Incremental costs were taken as the difference in per-patient costs between groups. Incremental effects were defined as the difference in per-patient event rates (major relapses) and QALYs between groups.

One-way deterministic sensitivity analyses (DSA) were performed to explore uncertainty over costs and health out-

comes. We included the following input parameters: between-group difference in effectiveness using the 95% CI of the difference in major relapse rates (0.126–0.382), discount rate (3–6%), time horizon (12–28 months), cost of biosimilar RTX (recently approved by European Medicines Agency – EMA), with an estimated 30% cost reduction compared to the current brand price, and utility values without utility decrements for relapses and SAEs. Since the base case analysis did not consider pancreatic cancer in the AZA group as a treatment related SAE (no evidence so far) which biased the result in favor of RTX, its impact when regarded as a SAE was tested in the DSA. Finally, we tried to remove the potential effect of heterogeneity of clinical practice across centres, by applying a standard care pathway to all the participants: disease monitoring was defined as outpatient visits except for M6, M12 and M18 in the RTX group, for which the visits would be performed in a hospital setting at the time of the admission for RTX infusion.

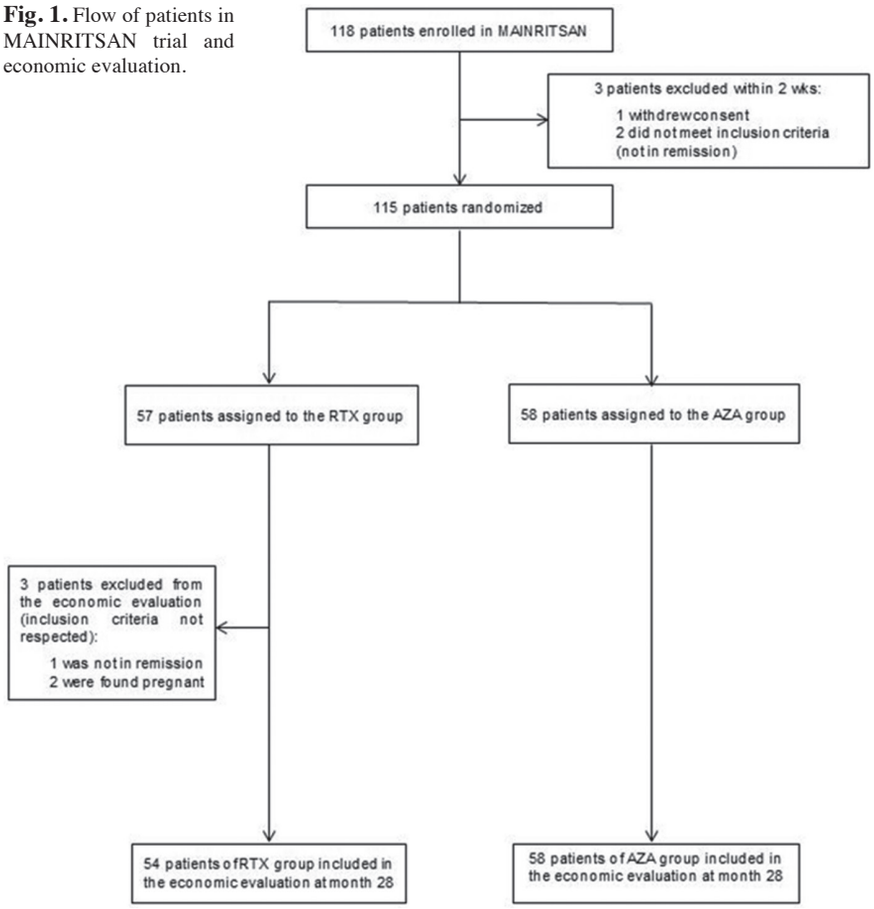

Fig. 1. Flow of patients in MAINRITSAN trial and economic evaluation.

Statistical analysis

The unit of analysis was the patient. We used descriptive analyses with counts (and proportions), means (with SDs), or medians (with interquartile ranges [IQRs]) to report resource use (number and total length of stay for hospital admissions), effects and costs. We tested differences in resource use, costs and effects using standard parametric or nonparametric tests (2-sample *t*-test, and Wilcoxon rank sum test) as appropriate. For non-normally distributed variables 95% CIs were generated with bootstrap resamples.

To deal with missing data in utility scores, Markov Chain Monte Carlo (MCMC) multiple full-data imputation was performed for each protocol visit and each treatment group separately. The pattern of missingness was previously assessed (16). Sex, age, previous utility score and renal impairment were taken into account for the imputation. While the occurrence of relapses and SAEs could not be taken into account in the MCMC multiple imputation step due to their rarity, we used utility decrements to account for relapses and SAEs. These decrements were the average decrements calculated for relapses and SAEs observed for the patients with a utility score available at the time of the event. These decrements were consequently attributed to all the patients with no utility measure over the period of time of the event, extending from 15 days before to 1 month after the CRF date of relapse and from the entry hospital admission to discharge for SAEs.

The uncertainty on the joint distribution of costs and outcomes was explored by a probabilistic sensitivity analysis using 1,000 bootstrap replications. Results were plotted on the cost-effectiveness plane and the acceptability curves were generated.

A generalised linear model with gamma distribution was used to study the relationship between the following explanatory factors and total per-patient expenditure as the dependent variable: treatment group, age, sex, AAV subtype, relapse and SAEs occurrence, severe renal impairment (creatinine clearance <30 ml/min) and disease status (newly-diagnosed/relapsing AAV)(17). Explanatory variables for the model were selected after testing the correlations among the variables previously listed. The final choice of variables of the model was made according to the statistical significance in bivariate analysis ($p<0.20$) and clinical plausibility. p-values <0.05 were considered statistically significant for all statistical analyses. We used SAS 9.3 for our analyses (SAS Institute, Cary, NC).

Results

Out of 115 patients enrolled in the MAINRITSAN trial, 3 were excluded from the economic study (all in the RTX group) due to their ineligibility: one patient was not in remission at the time of inclusion in the trial and did not receive the intervention, whereas two patients were found to be pregnant during the study (Fig. 1).

In the intervention group, 85% of RTX infusions were performed during a day

Table I. Resource use and per-patient cost (total and per category) in each treatment group.

Resource use	Azathioprine (n=58)		Rituximab (n=54)		
	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]	*p*-value
Impatient stays, number	1.9 (2.6)	1 (0-2.8)	1.8 (2.8)	1 (0-2)	0.82
Day cases*, number	4.1 (8.9)	1.5 (0.3-5)	6.4 (2.8)	6 (5-7.8)	< 0.001
Length of stay (days)[¥]	15.9 (19.7)	11 (3-18.3)	12.2 (13.5)	7.5 (5-13.5)	0.31
Costs (€)					
Study medication	412 (536)	335 (260-386)	5,967 (323)	6,411 (6,011-6,011)	< 0.001
Study medication administration	46 (353)	0 (0-0)	2,447 (1,067)	2,005 (1,817-2,851)	< 0.001
Disease monitoring (day cases)*	932 (1,623)	183 (0-911)	891 (1,361)	0 (0-1,301)	0.93
Disease monitoring (outpatient visits + lab tests)	954 (386)	1,013 (735-1,270)	729 (278)	831 (599-919)	< 0.001
Relapses[§]	2,718 (4,762)	0 (0-6,122)	711 (3,308)	0 (0-0)	0.001
Maintenance treatment (following relapse)	530 (1,590)	0 (0-0)	0 (0)	0 (0-0)	-
Severe adverse events	2,786 (6,843)	0 (0-2,531)	1844 (4,350)	0 (0-2,434)	0.66
Other AAV related care[¶]	1,839 (6,692)	0 (0-1,203)	798 (3,483)	0 (0-606)	0.10
Total cost	**10,217** (11,036)	7,235 (2,051-13,993)	**13,387** (7,399)	10,801 (9,018-13,920)	0.002

*"Day cases" refer to episodes where a person make a planned admission to an available staffed bed or trolley for clinical care and the patient is discharged on the same day as planned.

[¥]The total length of stay per patient is calculated from the total number of days spent in hospitals over the 28-month period. Day cases were counted as one-night inpatient stays.

[§]Costs for hospital stays and remission induction treatment (medication use and administration).

[¶] Hospital admissions and therapies associated to the evolution of AAV (*e.g.* dialysis, erythropoietin to treat renal failure-induced anaemia etc…).

case, whereas the remaining 15% were performed as inpatients.

Resource use, costs per patient and per category are presented Table I. The number of inpatient stays was almost the same in the two groups, whereas the number of day cases was significantly higher in the RTX group. The mean total length of stay was 15.9 days in the AZA group compared to 12.2 days in the RTX group ($p>0.05$).

In the RTX group, the study medication and its administration accounted for 45% and 18% of the total cost, respectively, compared to 4.5% in the AZA group. Costs for disease monitoring did not significantly differ between treatment arms. Most centres elected to monitor RTX-treated patients during a day case for medication administration (especially at M6, M12 and M18). AZA-treated patients were monitored either as outpatients or day patients.

For the RTX and AZA groups, relapses accounted for 5% and 27% of the total per-patient cost respectively. The higher cost of RTX was partly offset by lower costs of relapses and SAEs. The total incremental cost difference between groups was €3,170 ($p=0.002$), favouring AZA (Table I). The major relapses' rate was significantly lower in the RTX group compared to AZA group (0.054 *vs.* 0.301, with $p=0.001$) (Suppl. Table S3).

The median cost of a relapse was €8,107 *vs.* €7,432 ($p=0.31$) in the RTX and AZA groups.

The number of missing utility scores per patient in each group is showed in Table S4 in the Supplementary Appendix. The number of missing utilities increased over time, reaching 41% and 39% at M28 in the AZA and RTX group, respectively (Suppl. Table S5). RTX compared to AZA showed a significant incremental gain of 0.084 QALYs over the 28-month period (Suppl. Table S3). The 28-month ICER was €12,824 per relapse averted and the 28-month ICUR was €37,782/QALY. About 95% of ICERs and 97% of ICURs estimates were plotted in the upper right quadrant of the scatter plot indicating better clinical outcome and higher cost (Fig. 2 and 3). The acceptability curves are presented in Fig. S1 and S2 in the Supplementary Appendix and show that 46% of replications of ICURs fell below €34,500/QALY (£30,000/QALY: the UK National Institute for Health and Care Excellence (NICE)'s threshold) and 80% of replications of ICERs and ICURs fell below €22,000/relapses averted and €65,000/QALY, respectively.

The results of one-way deterministic sensitivity analyses for the estimated ICUR and ICER are presented on a Tornado diagram (Fig. 4). After 12 months the ICER and ICUR were higher (€28,547/relapse averted and €92,700/QALY, respectively). The ICER was largely dependent on the incremental effectiveness of RTX, ranging from €8,297 to €25,155 over the 95% CI of the difference in major relapses' rate. Assuming that the cost of RTX could be reduced by 30% (which corresponds to the average drop in price for biosimilars in France), the ICER became €7,363/relapse averted and the ICUR €21,693/QALY. The other parameters tested had little effect on the ICER and ICUR.

The general linear model (Suppl. Table S6) found that treatment group, major relapses and SAEs were significantly associated to total per-patient expenditure (for treatment group: rate ratio=2.06 with $p<0.001$; for relapses: rate ratio =2.60 with $p<0.001$; for SAEs: rate ratio=2.40 with $p<0.001$). For severe renal impairment the rate ratio was close to the significance (1.44, with 95% CI=0.95-2.24 and $p=0.09$).

Discussion

In this first economic evaluation of the management of AAV patients in complete remission, based on the MAINRISTAN trial, we found that maintenance treatment with RTX was more expensive than AZA and was associated with lower rates of relapses and better quality of life. The incre-

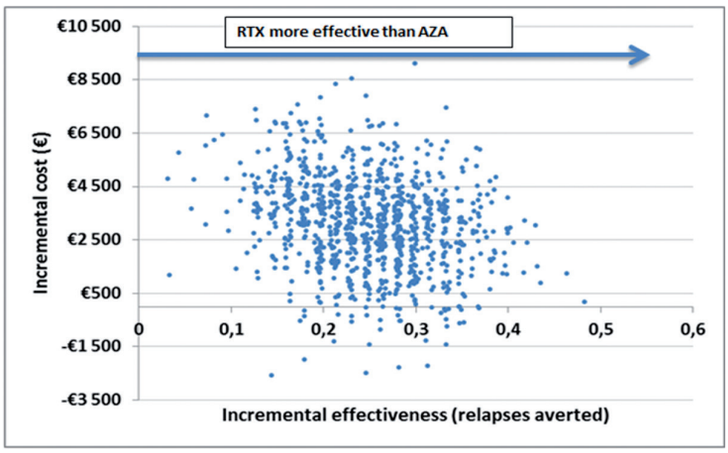

Fig. 2. Incremental cost and effectiveness (relapses averted) of RTX compared to AZA: the scatter plot.

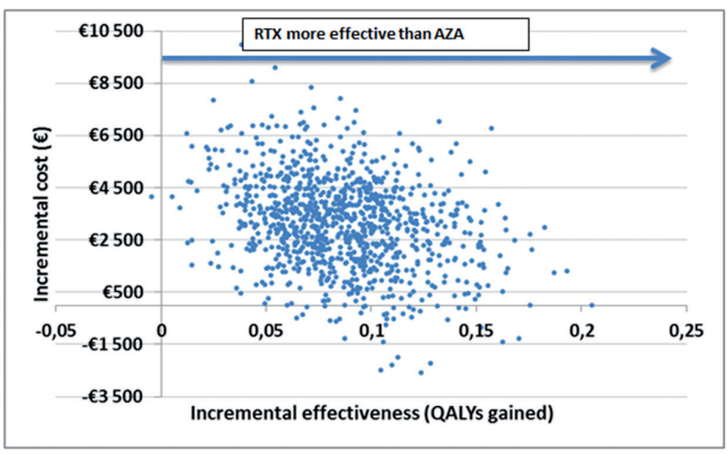

Fig. 3. Incremental cost and effectiveness (QALYs) of RTX compared to AZA: the scatter plot.

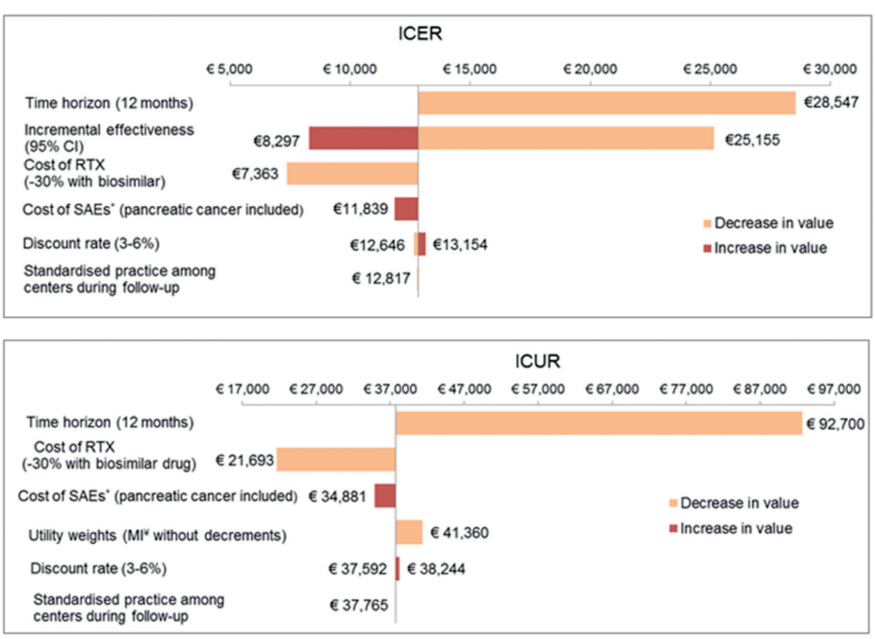

Fig. 4. Tornado diagrams of one-way deterministic sensitivity analysis: estimated ICERs and ICURs when changing parameter value.
*SAEs: severe adverse events. ¥MI: multiple imputation.

mental cost-utility ratio was €37,782/QALY, for which the acceptability curve showed a probability that RTX will be cost-effective of 45.7%, according to the NICE's threshold, and between 17.6% and 87.4% within the accepted range of $20,000 to $100,000 in the United States and Canada (18). Cost differences were mainly driven by the unit cost and administration cost of rituximab. However, decreases in major relapses and accompanying resource use partially offset the higher medication cost.

In sensitivity analyses, the differences in incremental effects favored RTX with higher costs in all replications on the cost-effectiveness plane. Sensitivity analyses demonstrated that a strategy using biosimilar rituximab (recently approved by European Medicines Agency – EMA) was most cost-effective in the DSA.

Our study has several strengths. As a trial-based economic evaluation, this study provided unbiased and generalisable estimates of the relative effect of RTX compared to the standard of care and an early opportunity to produce reliable estimates of cost-effectiveness for an internationally relevant decision problem (19-21). The prospective collection of resource utilisation and quality of life, the use of actual patient-level data to estimate resource utilisation for relapses and SAEs and the availability of data from multiple sources are also strong assets of this study. Indeed, the linkage of medical information reported in the CRF with routine data extracted from hospital discharges allowed us to validate the medical data and limited potential information bias. MAINRITSAN had many features of a pragmatic trial (22). First, as AAV is a group of rare autoimmune diseases, participants are representative of real-world clinical practice and are monitored by investigators reflecting the usual clinical setting across France; second, the primary outcome was directly relevant to participants and compared the intervention of interest with current practice, third, follow-up was conducted under routine conditions. As a result, an economic evaluation based on this kind of trial could be easily transferred in an-

other context, by simply applying, if needed, some adjustments (*e.g.* on unit costs, practice variations, GPA/MPA distribution in the country of interest, etc.) (19, 23-25). For this purpose, the general linear model provided some useful information about major cost determinants.

The economic analysis might have been partially limited by the high proportion of missing utility scores after 1 year of follow-up, though imputed using multiple imputation. Moreover, quarterly questionnaires did not necessarily capture the quality of life during relapses, which may have led to an underestimation of the cost-utility of RTX. Given the constantly varying dose of glucocorticoid treatment and its low cost, it was excluded from our analysis. Whereas the gradual tapering scheme used for azathioprine between month 12 and 22 could have altered the relapse rate in the AZA group and consequently the cost-analysis, on the other hand, an induction of remission obtained primarily with RTX (rather than with cyclophosphamide, as performed in MAINRITSAN trial) might have possibly improved the cost-effectiveness of RTX.

Due to ineligibility, three patients from MAINRITSAN trial were excluded from our analyses as they could possibly introduce bias in the economic evaluation, especially as these patients were all randomised in the same treatment group. Indeed, the aim of the economic evaluation is to provide a basis for decision-making about resource allocation and patients not eligible to the intervention are not the designated target of the assessment.

We explored the impact of time horizon over the estimates in the sensitivity analyses and inferred that 28-month-time horizon might be adequate to capture the actual differences in economic outcomes, whereas one-year time horizon would have underestimated the cost-effectiveness of RTX. Indeed, the cost of the study medication incurred mostly during the first year, while relapses often occurred later. Assessment of the 60-month cost-effectiveness is planned as part of the MAINRITSAN follow-up and results could be further extrapolated over a lifetime horizon to capture late relapses and long-term sequelae (19). The effects of a personalised therapy according to possible predictors of relapse, such as persistent ANCA positivity, PR3-ANCA specificity and CD19+B cell reappearance, remain to be clarified (26). The present analysis could be refined in the future with data of risk-adapted optimal maintenance RTX regimens.

Raimundo *et al*. estimated the cost per case of GPA in the United States at $44,740 (or €36,313) over a 24-month period, by using administrative claims data and with no information on inpatient drug use (10). This figure is higher than our own and might be explained by higher unit costs for drugs and hospital admissions. Their study estimated the cost of relapses to be as high as $64,230 (or €52,132) by comparing disease-related costs in patients with and without relapses. These findings, along with our own, emphasise the relevance of having effective and efficient prevention of relapses (10).

Our findings provide a cost-effectiveness rationale that complements clinical effectiveness knowledge from MAINRITSAN on the care of patients with AAV and support the use of RTX.

In conclusion, from the SHI's perspective, prevention of relapses with RTX in AAV patients could be a cost-effective option. These findings, driven by lower rates of relapses and corresponding higher quality of life in RTX-treated patients, support the use of RTX for maintenance, over previously standard, conventional immunosuppressants such as AZA.

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