The extra cost of biologics as first-line treatment in uncontrolled chronic rhinosinusitis with nasal polyps with no previous sinus surgery is overwhelming: a budget impact analysis

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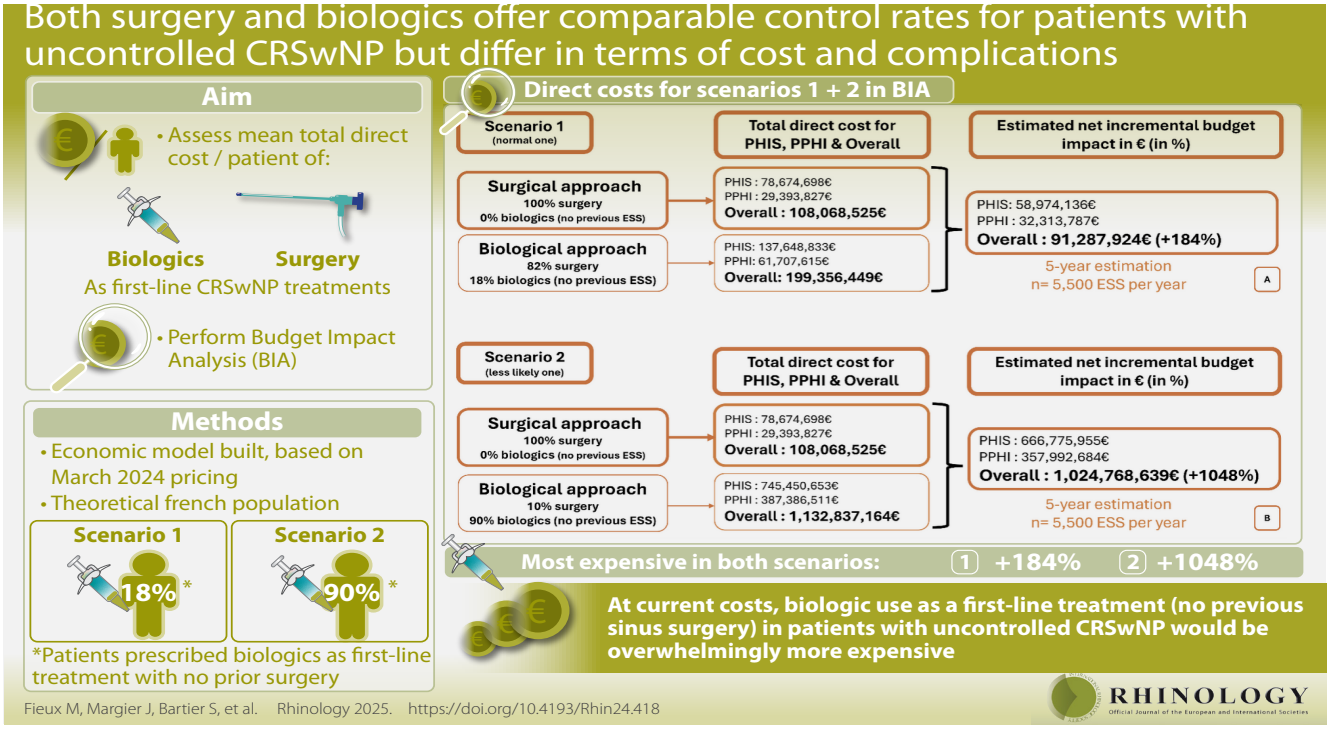
Rhinology 63: 4, 0 - 0, 2025 https://doi.org/10.4193/Rhin24.418



Abstract

Background: Both surgery and biologics offer comparable control rates for patients with uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP) but differ in terms of cost and complications. The aim was to assess the mean total direct cost per patient of biologics or surgery as first-line treatment in uncontrolled CRSwNP and to perform a budget impact analysis (BIA).

Methods: An economic model was build based on pricing of March 2024, and on the theoretical French population to simulate both the 5-year mean direct cost per patient and the BIA. For the BIA, two scenarios were evaluated: in scenario 1 (the normal one), 18% of patients received biologics as first-line (vs 82% surgery) and in scenario 2 (the less likely one), 90% of patients received biologics as first-line (vs 10% surgery). Within both scenarios, two approaches were considered, the surgical one (when patients received surgery as first-line) and the biological one (when patients received biologics as first-line, no previous sinus surgery).

Results: Over 5 years, the estimated mean direct cost per patient per year was significantly lower in the surgical approach compared to the biological one (60,026€). The BIA found that the estimated net overall incremental budget impact was 91,287,924€ in scenario 1 and 1,024,768,639€ in scenario 2. In both scenarios, the biological approach was the most expensive (+184% and +1048%, respectively).

Conclusion: At current costs, if biologics were used as a first-line treatment (no previous sinus surgery) in patients with uncontrolled CRSwNP, the extra direct cost would be overwhelming.

Key words: chronic rhinosinusitis, biologics, surgery, cost, nasal polyps

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) affects 2 to 4% of the western population [1], and represents an important economic burden [2,3]. The medical standard of care is topical therapy with normal saline nasal irrigation and intranasal corticosteroid spray with or without oral courses of steroids [1]. When this treatment is not sufficient, patients are considered as uncontrolled CRSwNP patients and an appropriate and extensive endoscopic sinus surgery (ESS, functional or radical ethmoidectomy) is recommended as first-line treatment [4,5]. Unfortunately, only 69.7% of patients are considered to have their disease under control 5 years after surgery [6,7]. Since 2019, biologics have become available in western countries for prescription in patients with uncontrolled CRSwNP, i.e. those who do not respond to the medical standard of care [1,4,5,8]. The control rate under such treatment is around 80% [9–11] and remains stable at 1-year follow-up; however, no long-term data is available and the direct cost of this treatment is substantial [12–20]. In Europe and in the United States of America (USA), biologics are usually prescribed as second-line treatment (patients with uncontrolled CRSwNP despite previous ESS) based on the latest guidelines available [1,4,21,22]. They can nevertheless be prescribed as first-line treatment (no previous ESS) [1,4,21,22] in rare circumstances where there is a surgical contraindication or if the patient refuses ESS. Moreover, some primary care doctors and allergists consider biologics as a first-line treatment (no previous ESS) [23]. However, in France, biologics are only available as second-line treatment but without detail on the extent of the surgical procedure required [24,25].

Surgery and biologics both offer control in patients with uncontrolled CRSwNP, but they differ in terms of efficacy, cost, complications, and quality of life for patients [4,8,13,21]. Although establishing cost-effectiveness of a new treatment is necessary [5], it has already been performed, and authors found that even if biologics are more costly and sometimes more effective than surgery, the latter is not always the case [12–19]. However, in the current environment of escalating healthcare costs and expenditures, it is of the utmost importance to understand if adopting a new technology is affordable [26]. To seek this answer, one must evaluate the incremental budgetary impact of a new scenario, where incorporating biologics for uncontrolled CRSwNP patients as first line treatment (no previous ESS) will be compared to the reference scenario (i.e. current practice). To the best of our knowledge, such an economic analysis, also known as budget impact analysis (BIA), has never been carried out for biologics in uncontrolled CRSwNP patients.

The main objective of this study was to perform a BIA for two scenarios in which biologics could be prescribed as first-line treatment for uncontrolled CRSwNP. A normal scenario (18% of biologics as first-line) and a less likely one (90% of biologics as first-line) were compared to the reference scenario (biologics only as second-line treatment). First, the mean total direct cost per patient over 5 years associated with either biologics or ESS as first-line treatment for patients with uncontrolled CRSwNP was assessed. The incremental budgetary impact of both scenarios was then evaluated. All analyses were carried out based on French pricing and from three different perspectives: the public healthcare insurance system (PHIS), patients and private health insurers (PPHI), and overall (PHIS + PPHI).

Materials and methods

Ethics

No patients were involved. This study complies with the ethical and legal requirements of the French law (April 15, 2019) and the Declaration of Helsinki. This study followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guideline (https://www.equator-network.org/reporting-guidelines/cheers/).

Study population

This economic study was based on the theoretical French population and the prevalence of uncontrolled CRSwNP. The French hospital discharge database (Programme de Médicalisation des Systèmes d'Information) [27] regarding the management of CRSwNP in France (Table S1 for demographics) and international published data were used to gather evidence on epidemiological characteristics in France, Europe, and the USA. While the epidemiolocal characteristics were obtained mainly from multicenter descriptive studies, data on biologics were based on randomized controlled trials with high level of evidence. In France, the study by Fieux et al. reported 92,141 patients having undergone sinus surgery over a 7-year period (2011-2018), corresponding to about 11,000 per year [27]. Among them, we selected patients with CRSwNP who underwent ESS (n=5,500 patients per year in France).

Setting and location

All analyses were carried out in March 2024 based on French pricing and European management of CRSwNP.

Comparators

Two approaches were considered for patients with uncontrolled CRSwNP (i.e. those who did not respond to the medical standard of care): the surgical approach, in which ESS is performed as first-line treatment, and the biological approach, in which biologics are administered as first-line treatment (no previous ESS; Figure 1).

Perspective

The analyses were carried out using three different perspectives (PHIS, PPHI, and PHIS + PPHI) to ensure the generalizability of the results.

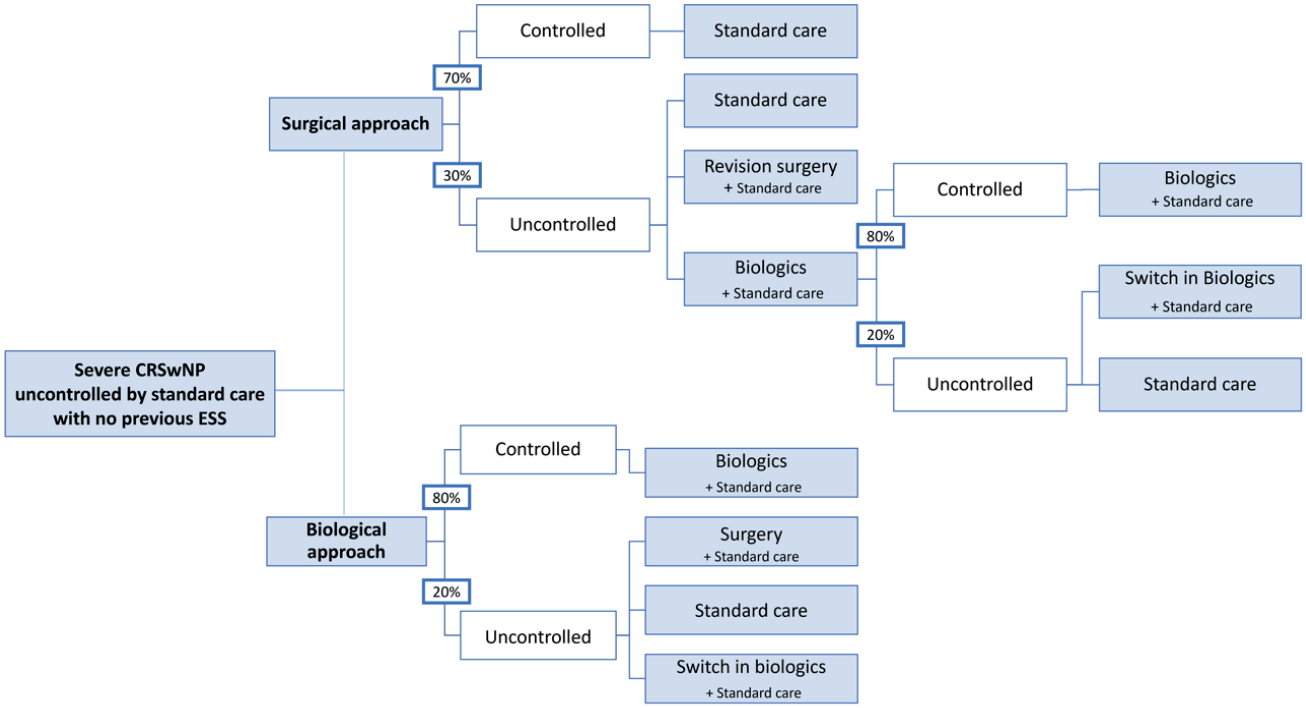


Figure 1. Care pathways for both the surgical and biological approaches. In the surgical approach, patients undergo surgery as first-line treatment and, in case of an uncontrolled disease during the 5-year follow-up (estimated at 30%), they can either be administered standard care, receive a biologic, or undergo a revision surgery. In the biological approach, patients receive biologics as first-line treatment (no previous surgery) and, in case of uncontrolled disease during the 5-year follow-up, they can either be administered standard care, undergo surgery, or benefit from a switch in biologics. Both mepolizumab and dupilumab were considered as biologics herein. Details of direct cost per patient for each treatment were as follows: standard care (134€//5year), dupilumab (1333€//month), mepolizumab (947€//month), and endoscopic sinus surgery (1915€/month).

Time horizon

The time period considered for the economic modeling was 5 years as this was considered long enough to correctly estimate disease control in a patient who underwent ESS for uncontrolled CRSwNP. Patient pathways were thus constructed over 5 years based on expert opinions and existing literature for both approaches (surgical and biological, Figure 1). The Markov model used and the patient pathways are detailed in supplementary materials (Appendix A). Duration of use of biologics were also considered over a 5-year period in the model as, according to recently published data [28–30], it is unlikely that patients who achieve disease control will discontinue treatment or switch therapies.

Discount rate

As recommended, costs were discounted at 2.5% per year [31]. Full details are available in Table S2 and Table S3.

Selection, measurements, and valuation of outcomes

The standard care for CRSwNP is daily nasal irrigation combined with nasal corticosteroids for all patients. Short courses of oral corticosteroids are sometimes prescribed in the event of an inflammatory phase of the disease [1]. In case of uncontrolled CRSwNP, ESS may be proposed (Table 1). The control rate at 5 years after ESS estimated herein was 70% (60-80%), based on a compromise between the studies of DeConde et al. and Hopkins et al. [6,7]. Regarding biologics, only those approved in France (dupilumab and mepolizumab) were studied here. The biological control rate was estimated in the present study at 80% based on the main randomized controlled clinical trials published for both mepolizumab (75%) [10,32] and dupilumab (85%) [9,33], as well as real-life data without assuming any difference between these two biologics regarding their effectiveness [9–11,32–35]. Although control rate was evaluated at 1-year in these trials, we extrapolated a similar control rate at 5 years based on longer term results with biologics in asthma patients [28,36–38]. The biological complication rate was estimated at 7%, with only minor complications [9–11]. The rate of re-intervention in patients receiving biologics was one of the few criteria enabling direct comparison between dupilumab and mepolizumab [9,10]. Given that it was 2% with dupilumab and 9% with mepolizumab, and based on real-life data [39], we retained 96% as an upper limit for the control rate of biologics. Among patients uncontrolled by ESS, it was estimated that 20% of patients would benefit from revision ESS [27] and 15% would receive biologics as second-line treatment [5–8]. Based on recently published data [6,27,39–41], the change in the proportion of

Table 1. Parameters considered for the direct cost analysis and the budget impact analysis.

Parameter	Value %	Source
Distribution of surgery by DRG code		
03C07J1	35	the ScanSanté website for 2023
03C0712	58	
03C0723	7	
Complications following surgery		
Major complications	0.7	Fieux et al.
Minor complications	6.5	Re et al.
CRSwNP control after surgery		
Baseline estimate	69.7	
Upper value	79.4	Hopkins et al.
Lower value	60	DeConde et al.
Distribution of biologics		
Dupilumab	80	Hypothesis
Mepolizumab	20	Hypothesis
Complication of biologics		
Minor complications	7	Bachert et al.; Han et al.
CRSwNP control under biologics		
Baseline value	80	
Upper value	96	DeCorso et al.; Meier et al.
Lower value	52	Bachert et al.; Han et al.
Surgery in case of failure of biologics		
Baseline value	5.5	
Upper value	2	Han et al.
Lower value	9	Bachert et al.

patients over time who would receive biologics as second-line treatment was estimated as follows: 4% in the first year, rising to 6% in the second year, 11% in the third, and 18% in the fourth and fifth years. In the biological approach, it was assumed that dupilumab would be prescribed in 80% of cases compared to 20% for mepolizumab, given that the former received its approval first [31]. Public sales data could not be used to support this choice, due to confidentiality restrictions. However, this limitation is considered negligible, as the effectiveness of both biologics is regarded as nearly equivalent as stated above [9–11]. In patients uncontrolled by a first biologic, it was considered that a switch to another biologic would be made after 6 months, in line with current recommendations. Since there are currently no data on the efficacy of a second biologic after failure of the first, we opted for a maximum control rate of 88% after switching between biologics. This choice was made based on preliminary unpublished results from a French national registry, the protocol of which is available online [35]. Among patients who remain uncontrolled despite a switch in biologics, we estimated that revision ESS would be performed in 10% of these patients [27].

Measurement and valuation of resources and costs

For both approaches, the cost of standard care, surgical procedures, biologics, consultations, and imaging examinations was set on French healthcare tariffs. More details are available Appendix A, Table S2 and Table S3.

Currency, price date, and conversion

Costs were calculated in Euros 2023 as it is the main currency in Europe and the one used in France.

Analytics assumption, and characterization of heterogeneity and uncertainty

Deterministic (tornado diagram) and probabilistic sensitivity analyses were performed to test the robustness of the results. For the probabilistic analysis, costs were assumed to follow gamma distributions and probabilities beta distributions. Non-parametric bootstrapping with 1000 samples was used to simulate a 95% confidence interval (95%CI) for the difference in costs between the biological approach and surgical approach. All model parameters (Table 1) [6,7,9–11,27,32,33,41–44] were included in the analysis.

Rationale and description of the budget impact analysis at 5 years

The aim of the BIA was to estimate the financial impact of an increase in biologics prescription in patients with uncontrolled CRSwNP with no previous ESS, based on data reporting a gradual increase in biologics since they were first approved [41]. To that end, two scenarios were considered, in which the reference situation was always management by the surgical approach (100% of patients undergo ESS as first-line treatment). Scenario 1 was designed to reflect the European recommendations regarding the use of biologics as first-line treatment in uncontrolled CRSwNP patients with no previous ESS. In this scenario, the reference was compared to an alternative situation, considered herein as the normal one, in which there would be a progressive increase in the proportion of patients using the biological approach (i.e. biologics as first-line treatment in patients with no previous ESS), reaching 18% at 5 years (Figure 2). This proportion was based on the estimated rate of patients receiving biologics as second-line treatment from the 2nd postoperative year (15%, see methods above). In scenario 2, we considered an alternative situation, considered herein as the less likely one, in which the proportion of patients using the biological approach would be 90% (Figure 2). In this less likely scenario, 90% of patients with

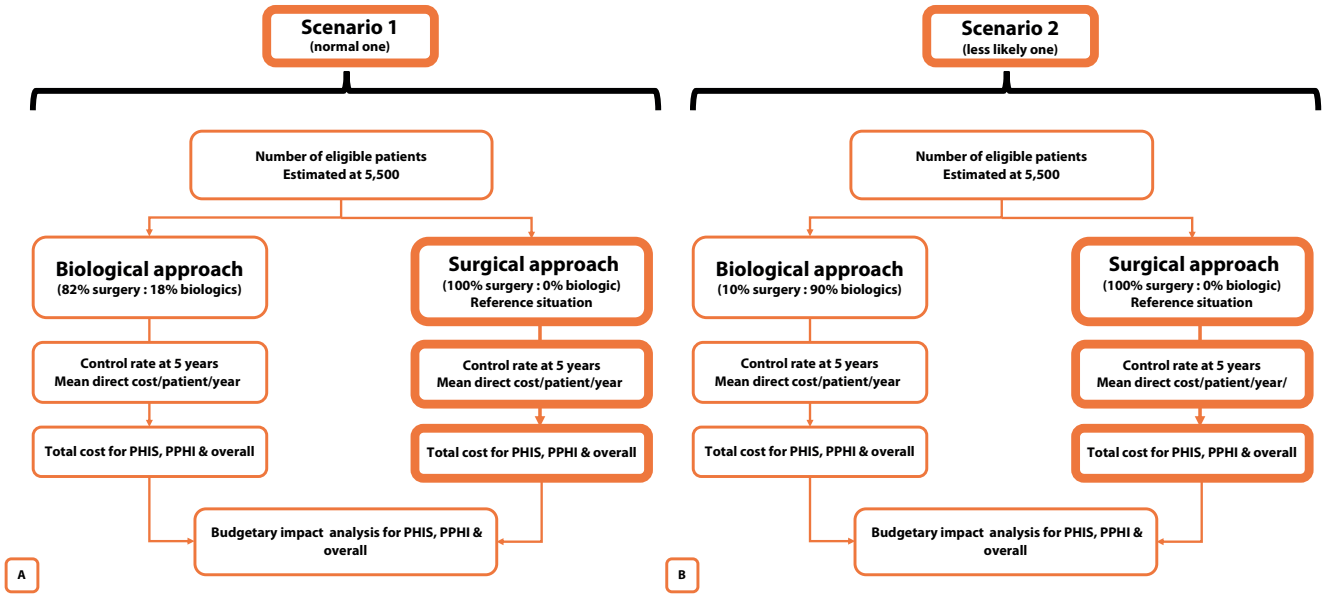


Figure 2. Schematic representation of the budget impact analysis model for scenario 1 (A) and 2 (B). (%) corresponds to the proportion of patients starting with either a biologic or a surgery as first-line treatment (no previous ESS). PHIS, public healthcare insurance system; PPHI, patients and private health insurers.

uncontrolled CRSwNP with no previous ESS would receive a biologic each year, with the remaining 10% of patients undergoing ESS as first-line treatment. The patient care pathways (Table S2 and Table S3) and the parameters of the model (Table 1) were the same as those used in the cost analysis per patient previously described.

Approach to engagement with patients and others affected by the study

Contrary to guidelines recommending a single perspective [31], we considered direct costs from three perspectives, namely PHIS, PPHI, and overall (PHIS + PPHI). As recommended, for the BIA, the costs were not discounted [18]. Indirect costs (per sick leave) were excluded from the reference case analysis but included in the sensitivity analysis as recommended [31]. BIA and cost analysis were performed using Excel. Results were considered statistically significant at $P < .05$, and all tests were 2-tailed. More details are available Appendix A.

Results

Over 5 years, the estimated mean direct cost per patient per year was significantly lower in the surgical approach compared to the biological one (5,222€ vs 65,248€; mean difference 60,026€ [95%CI: 38,798€– 72,490€]). The 5-year control rate was 77% for the surgical approach compared to 88.8% for the biological one. Sensitivity analyses were then carried out. When considering an increase in the prescription rate of biologics from 18% to 90% in the biological approach, this would result in a mean direct cost per patient per year of 16,843€ representing an increase of 11,631€ with a 5-year adjusted control rate of 94%. Similarly, if we were to modify the control rate of ESS down to 60% (lower limit), the mean direct cost per patient per year would be 6,010€ and the adjusted 5-year control rate would be 69% for the surgical approach. Assuming that biologics are prescribed to 90% of patients with a control rate of 60% thanks to surgery, the mean direct cost per patient per year would be 21,351€ with an adjusted 5-year control rate of 92% for the biological approach. When considering a decrease in the price of biologics by 20%, the estimated mean direct cost per patient would still be significantly lower in the surgical approach than in the biological one (5,222€ vs 47,000€). Deterministic sensitivity analyses are shown in Figure 3 and Table S4.

For the BIA, the direct cost of the surgical approach (reference situation) in France over 5 years was estimated at 78,674,698€ for the PHIS and 29,393,827€ for PPHI, representing an overall cost of 108,068,525€.

When applying scenario 1 of the BIA (Figure 2), the direct cost of the biological approach over 5 years would be 137,648,833€ for the PHIS and 61,707,615€ for PPHI; hence, the overall direct cost would be 199,356,449€. The estimated net incremental budget impact of the biological approach would therefore be 58,974,136€ for the PHIS and 32,313,787€ for PPHI; hence, the overall difference would be 91,287,924€ (+184% more costly than the reference situation). If performed in private hospitals and considering a 200% increase in the price of surgery, the overall difference would be 83,011,115€.

When applying scenario 2 of the BIA (Figure 2), the direct cost of the biological approach over 5 years would be 745,450,653€ for the PHIS and 387,386,511€ for PPHI; hence, the overall direct cost would be 1,132,837,164€. The estimated net incremental

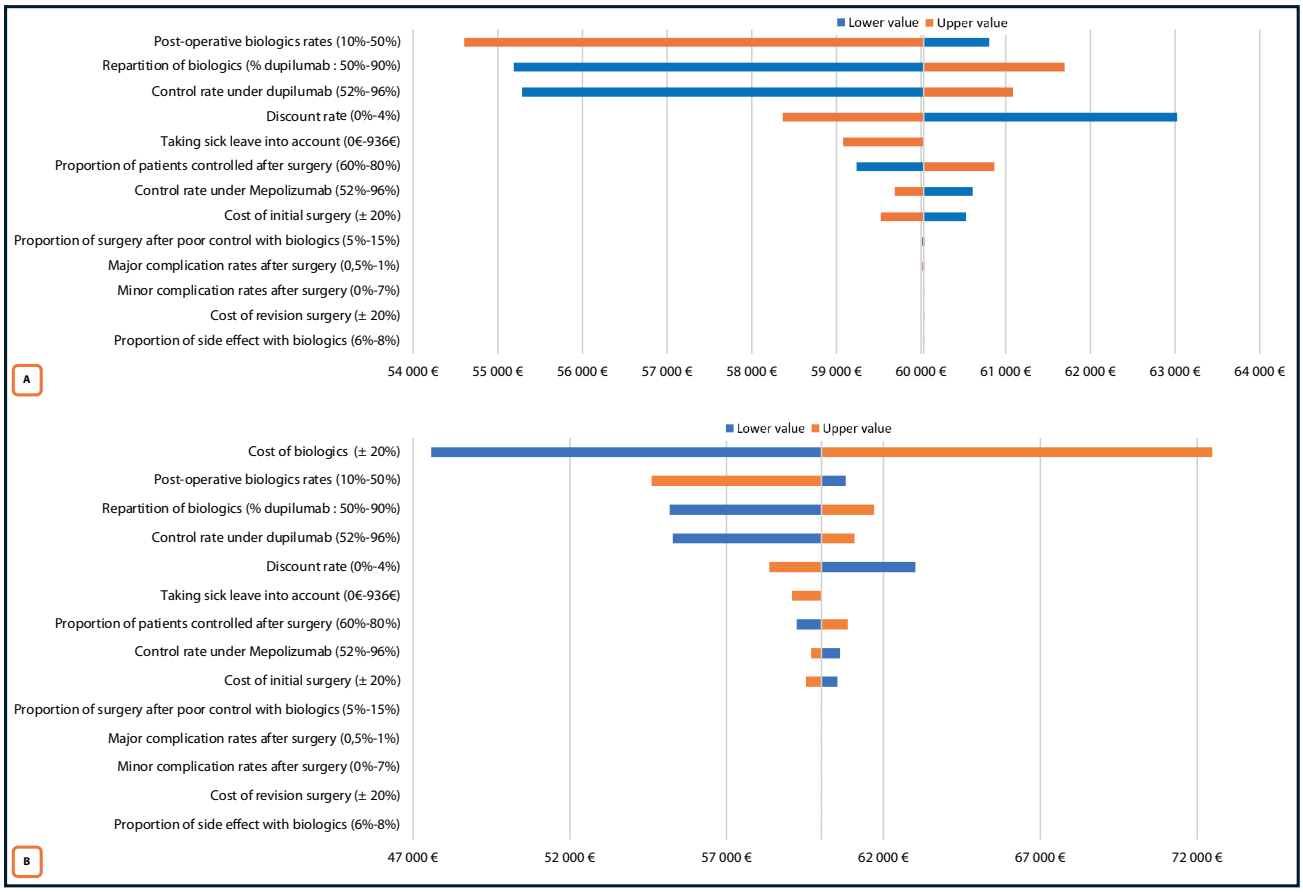


Figure 3. Change in objective olfactory function from baseline to post-treatment per olfactory test score and olfactory training group. A. Combined TDI scores. B. Odor detection threshold scores. C. Odor quality discrimination scores. D. Odor identification scores. In all panels, dots represent individual values (scores slightly jittered for visualization purposes) and solid bars depict group means. Dashed lines indicate 0. Note the difference in scale between panels A and B-D. Note that p-values in figure originates from ANCOVAs with baseline score as covariate.

budget impact of the biological approach would therefore be 666,775,955€ for the PHIS and 357,992,684€ for PPHI; hence, the overall difference would be 1,024,768,639€ (+1048% more costly than the reference situation). Direct costs are shown in Figure 4.

Discussion

Over 5 years, the estimated mean direct cost per patient was significantly lower in the surgical approach than in the biological one (- 60,000€). According to scenario 1 of the BIA, the overall 5-year direct cost to society would be 108,000,000€ in the surgical approach and 199,000,000€ in the biological one, representing an overall incremental net budget impact of 91,000,000€ for the biological approach (+184%). According to scenario 2, the overall incremental net budget impact of the biological approach would be more than 1,000,000,000€ (+1048%).

Over 5 years, the estimated mean direct cost per patient was significantly lower in the surgical approach with a 5-year control rate at 77% compared to the biological approach with an 88.8% control rate. Parasher et al. found similar results showing that a surgical strategy as first-line treatment was less costly but less effective than a strategy based on dupilumab [12]. Conversely, Scangas et al. found that a surgical approach was less costly but more effective than dupilumab [14]. The difference in effectiveness of the strategy could be explained by the short follow-up (less than 2 years) chosen in the latter study, which could overestimate the effectiveness of surgery. To the best of our knowledge, no economic study has yet compared mepolizumab with surgery. The differences in effectiveness reported from one study to another are likely related to a variability in the criteria used to define effectiveness.

In the present study, the surgical control rate was set at 69.7% [60%-80%] at 5 years. The study by deConde et al. found that, at 18 months, 60% of patients did not have a polyp recurrence while Hopkins et al. reported that, at 5 years, 79.6% of patients did not undergo revision ESS [6,7]. However, the first study only considered post-surgical polyp recurrence but did not report disease control, although the two may be independent. Moreover, the second study did not consider uncontrolled patients who had not undergone revision ESS. Thus, a compromise had to be made to enable valid estimations. Assuming that this

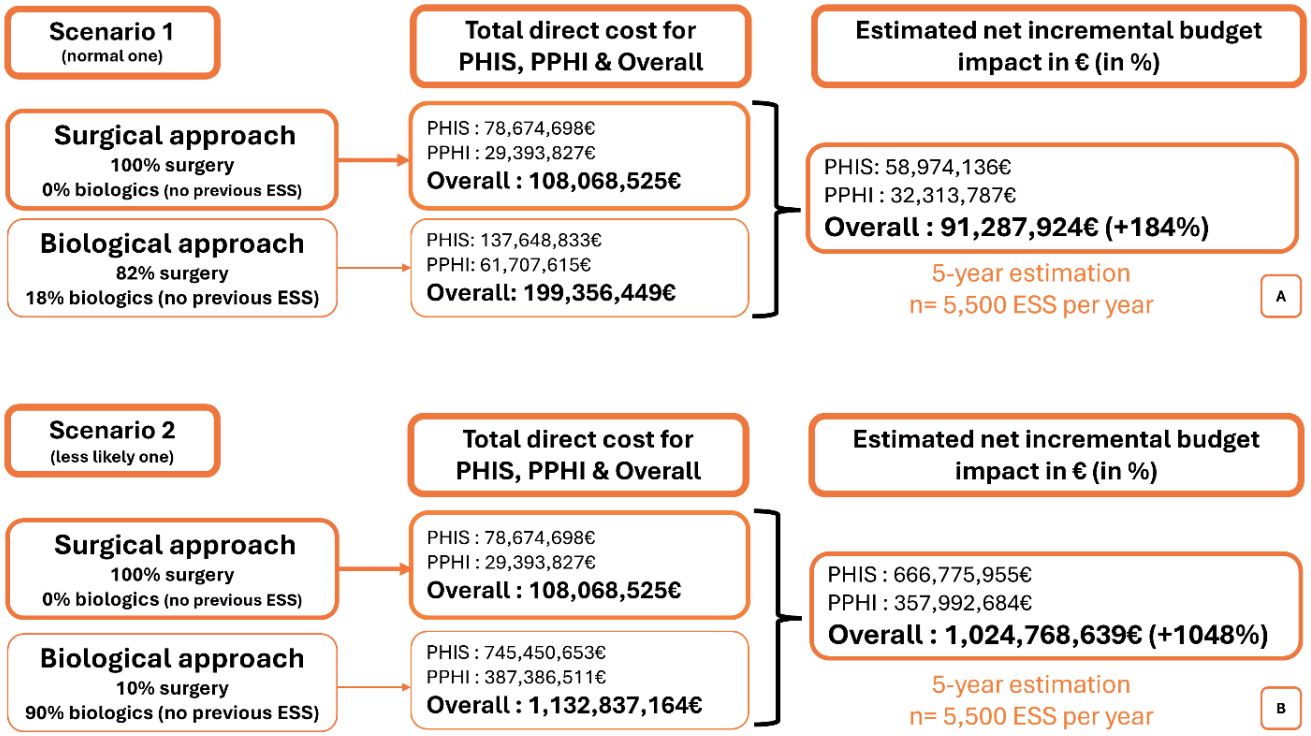


Figure 4. Schematic representation of the direct costs for scenario 1 (A) and 2 (B) of the budget impact analysis. In both scenarios, estimations were made on a 5-year time horizon, considering 5,500 ESS per year. Abbreviations: PHIS, public health insurance system; PPHI, patients and private health insurers; Overall: PHIS + PPHI; ESS, Endoscopic Sinus Surgery.

compromise overestimates the surgical control rate, and that a lower rate (60%) would probably lead to a substantial increase in the prescription rate of biologics (up to 90% in the worst-case scenario), a sensitivity analysis was carried out. Using these parameters, the analysis showed that the surgical approach remains the least costly for a similar 5-year control rate, reinforcing the robustness of the main analysis. While recommendations for the use of biologics vary among western countries [4,23–25], it appears that prescribing ESS as first-line and biologics only as second-line treatment (surgical approach), would provide both good control and cost optimization. The present results are of particular interest given the gradual decline recently observed by Low et al. in the annual rate of ESS in CRSwNP since the advent of biologics [41]. The extent of ESS needs to be taken into account as well, as a limited approach is not adequate for a typical endotype 2 CRSwNP and only extensive functional or radical ethmoidectomy should be considered as appropriate surgery before considering biologics [4,40]. One could argue that the price of biologics may decline in the next few years [45]. The sensitivity analysis herein showed that, even if the price of biologics decreases by 20%, the estimated mean direct cost per patient would still be significantly lower in the surgical approach than in the biological one (5,222€ vs 47,000€); this would still remain if the price fell by 50% (5,222€ vs 30,000€)

In the first scenario considered herein (i.e. the normal one), the estimated overall incremental net budget impact was about 91,287,924€ at 5 years (the biological approach being the most expensive; + 184%), indicating that a progressive increase in the proportion of patients treated with biologics would lead to a major augmentation of the overall direct cost for the treatment of uncontrolled CRSwNP. In the second scenario (i.e. the the less likely one one), the estimated overall incremental net budget impact was 1,024,768,639€ at 5 years (the biological approach being the most expensive, +1048%), indicating that if 90% of patients with uncontrolled CRSwNP were treated with biologics as first-line treatment (no previous ESS), the cost would be overwhelming from all perspectives. One could argue that excess hospitalization fees (greater than state-regulated prices) in private hospitals and indirect costs (per sick leave) were only included in the sensitivity analysis and not the main analysis. Nevertheless, if the price of the surgery was increased by 200% to simulate excess hospitalization fees, the direct cost of the biological approach would remain overwhelming with an estimated overall incremental net budget impact of about 83,011,115€. To our knowledge, several authors examined the cost-effectiveness of biologics for patients with CRSwNP [12–20], but only one other BIA regarding CRSwNP has been published, in which revision surgery was compared to the use of steroid-eluting sinus implant during the first surgery in uncontrolled CRSwNP. The authors found that revision surgery is more costly

than implanting stents during the first surgery [46], highlighting the significance of this first surgery in uncontrolled CRSwNP. The main strength of the present study was the type of analysis performed as it is important to understand if adopting a new technology is affordable. This BIA was built on a literature review, data from a healthcare database, as well as expert opinion; sensitivity analyses were also performed and confirmed the robustness of the conclusions. Nevertheless, this study has limitations. Statistical models are simplifications of the real world, and their objective herein was to grasp the financial complexity underlying the treatment of patients with CRSwNP. However, the type of surgery (polypectomy, partial or complete ethmoidectomy) performed for a CRSwNP may result in different recurrence rates [47]. In addition, we were unable to take into account the effect of steroid irrigation after ESS. This would allow better control of the disease post-operatively, but the size of the study was insufficient to include this type of data in the model [48]. Similarly, depending on a patient's biological profile, it has been shown that some patients respond better to one biologic or another (https://ginasthma.org/gina-reports/). Recent studies have also highlighted the need for earlier use of biologics in CRSwNP with aspirin-exacerbated respiratory disease [20,49]. Also, the present study is based on a 5-year time horizon, and effectiveness results used in this study come from short-term evaluation based on clinical trials [9,10], with a one- or two-year maximum follow-up. Moreover, CRSwNP is a chronic disease, and some patients are likely to remain on biologics for longer; indeed, the duration of treatment with biologics is not yet clearly established by international guidelines [4,23]. In addition, these findings apply to the French healthcare system, but are not necessarily generalizable to other healthcare systems, including the USA. Further studies are therefore needed to estimate the economic impact of these treatments worldwide, over the longer term and in case of biologics tapering in responders [50].

Conclusion

At current costs, if biologics were used as a first-line treatment (no previous ESS) in patients with uncontrolled CRSwNP, the extra direct cost would be overwhelming.

Acknowledgements

We thank Véréna Landel (Direction de le Recherche en Santé, Hospices Civils de Lyon) for her help in manuscript preparation. MF is supported by the Foundation of the Hospices Civil de Lyon fellowship and wishes to acknowledge the support of the Fondation Edmond Roudnitska (grant awarded), the Philippe Foundation (grant awarded), the France-Stanford Center (grant awarded) and the Association Française de Rhinologie (grant awarded).

Authorship contribution

Conceptualization: MF, TS, JM; data curation: TS; formal analysis: JM; methodology: MF, JM; project administration: MF, JM; resources: MF; software: JM; supervision: VF, SB, FC, MF; validation: MF, SB; visualization: FC, VF; writing-original draft: MF, TS, ST; writing-review and editing: MF, FC, PH, ZP, MC, VF, SB, ST. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

MF, FC, ZMP, and VF report personal fees as expert consultant for Sanofi and GlaxoSmithKline. All other authors have no competing interests in relation to this work.

Funding

None.

Availability of data and materials

Not applicable.

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Rhinology 63: 4, 0 - 0, 2025
https://doi.org/10.4193/Rhin24.418

Received for publication:
October 1, 2024
Accepted: March 25, 2025

Associate Editor:
Sietze Reitsma

This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

This supplemental material has been provided by the authors to give readers additional information about their work.

Appendix A. Supplementary material and methods

Time horizon

The rate of patients controlled in each approach was then estimated at 5 years. To simulate the patient pathways over time, a deterministic Markov approach was used. The Markov model is an analytical framework frequently used in decision analysis that accounts for events over time. Markov models use disease states to represent all possible consequences of an intervention of interest. At each period called "cycle", a cohort of patients moves between the disease states according to different probabilities. Cost and health outcomes are associated to each disease state. Finally, these results are aggregated over successive cycles to provide the total expected direct cost and outcome, which can be compared with the aggregated results of a similar cohort receiving another intervention. In the present analysis, during each 1-year cycle, the patient could either be controlled or uncontrolled, in which case the patient would be proposed a different treatment depending on the treatment previously received (either start a biologic, undergo a revision ESS, or receive the standard treatment (Figure 1); each state is associated with a cost. Duration of use of biologics were also considered over a 5-year period in the model as, according to recently published data [28–30], it is unlikely that patients who achieve disease control will discontinue treatment or switch therapies. Conversely, when disease control is not reached after 6 months, patients may switch biologics once and then discontinue them if disease control is still not reached (Figure 1). Two experts in CRSwNP were consulted for the review and validation of all inputs and key economic modeling assumptions (FC and VF). Economic modeling was then developed to simulate the 5-year mean direct cost per patient in each approach.

Measurement and valuation of resources and costs

For both approaches, two ENT consultations in the first year and then one each year, CT scans, and long-term topical treatments (nasal irrigation with high-volume saline solution and nasal corticosteroid spray) were included. In the surgical approach, the cost of two post-operative consultations and those associated with possible complications were also included. To identify the type of hospital stay (outpatient or inpatient), the "ScanSanté" website, which lists all hospitalizations in private and public centers, was consulted using the CCAM code LAFA018 (bilateral ethmoidectomy). In the biological approach, the cost of an initial injection by a nurse and that of any complication were also considered. The cost of hospitalization and that of any revision ESS, and their distribution according to DRG was obtained from the French hospital discharge database (ScanSanté website for 2023, accessed May 1st, 2024; link: https://www.scansante.fr). The cost of standard care, surgical procedures, biologics, consultations, and imaging examinations was set on French healthcare tariffs. Full details are available in Table S2 and Table S3.

Approach to engagement with patients and others affected by the study

Contrary to guidelines recommending a single perspective [31], we considered direct costs from three perspectives, namely PHIS, PPHI, and overall (PHIS + PPHI). Healthcare systems vary between western countries: for example in France, the costs of surgery are often covered in large parts by the PHIS, whereas the costs of biologics are largely covered by PPHI. In the USA, surgery and biologics are largely covered by PPHI. Moreover, an overall perspective is more internationally relevant. The BIA was modeled over 5 years using a multicohort approach. In the first year, only incident cases were considered, whereas in subsequent years, new cases were added to those already included. The annual number of incident patients was estimated at 5,500 (see methods above). As recommended, for the BIA, the costs were not discounted [18]. Excess hospitalization fees (greater than state-regulated prices) in private hospitals were not considered. Indirect costs (per sick leave) were excluded from the reference case analysis but included in the sensitivity analysis as recommended [31] (French guidelines accessed at https://Www.Has-Sante.Fr/Jcms/R_1499251/Fr/Choix-Methodologiques-Pour-l-Evaluation-Economique-a-La-Has). BIA and cost analysis were performed using Excel. Results were considered statistically significant at $P < .05$, and all tests were 2-tailed.

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Please see references from the complete manuscript.

Table S1. Demographics obtained from the French Hospital Discharge Database.

Hospital stay	n = 11 750
Age (years)	49,5 [10-90]
Sex (Female)	4217 (35.9%)
Comorbidities	
High Blood pressure	661 (5.6%)
Asthma	563 (4.8%)
Obesity (BMI >25)	308 (2.6%)
Obstructive Sleep Apnea	292 (2.5%)
Hospital stay types	
Day-case	4381 (37.3%)
1 night	4687 (39.9%)
2 nights	1850 (15.7%)
3 nights	476 (4.1%)
4 nights or more	356 (3.0%)

Values correspond to numbers (proportions) for categorical variables and means [minimum-maximum] for quantitative variables. *The data presented concerning the distribution of hospital stay types concern a sub-group of 1162 patients. This is the subgroup of patients having undergone 2 operations for whom data were available. The center mentioned corresponds to the center of their first operation.

Table S2. Clinical course and associated direct costs for patients in the surgical approach.

	Regulated fee	Reimbursement rate	Source: French DRG code
Pretreatment workup			
General practitioner appointment	26.50 €	70%	GS - CS
One ENT specialist consultation with nasal endoscopy	85.30 €	70%	APC-GCQE001
Standard care (nasal irrigation and nasal corticosteroid spray)	26.76 €	70%	
CT scan	26.02 €	70%	LAQK002+YYYY600+FT
One ENT specialist consultation with nasal endoscopy	55.30 €	70%	CS + MPC + GCQE001
Pre-anesthetic appointment	27.00 €	70%	CS + MPC+ MCS
Subtotal workup	**246.88 €**	**172.816€**	
Surgery (+ hospitalization fee*)			
Outpatient sinus surgery	1,915.62 €	80%	03C07J
Sinus surgery, level 1	1,915.62 €	80%	03CO71
Sinus surgery, level 2	3,952.14 €	80%	03C072
Post-operative follow-up			
Five ENT appointments with nasal endoscopy (at 1 month, 6 months, and every year)	331.80 €	70%	(CS + MPC + GCQE001)
Costs of minor complications (6.5%)**	110.60 €	70%	(CS + MPC +GCQE001)
Costs of major complications (0.7%)			
One ENT specialist consultation with nasal endoscopy	55.30 €	70%	CS + MPC + GCQE001
CT scan	25.27 €	70%	LAQK009
Orbital decompression, level 2	3,952.14 €	80%	03C072
Orbital decompression, level 3	10,155.70 €	80%	03C072
Osteomeningeal breach closure, level 2	5,503.13 €	80%	02C032
Drainage of intracranial infection, level 4	27,625.80 €	80%	01C044
Two ENT specialist consultation with nasal endoscopy (at 1 week and 1 month)	110.60 €	70%	CS + MPC + GCQE001
Total	**4,170.07 €**	**3,314.26 €**	
Sick leave, €/day***	267.68 €		
Sick leave, €/day from the gross domestic product***	936.00 €		

*The hospitalization fee is paid by patients or their private health insurance. **We assumed that a minor complication would require an average of two ENT consultations. ***Sick leave is usually 8 days; therefore the total extra-cost would be (33.46€/d)*8 and (177€/d)*8 from the gross domestic product, respectively. Abbreviations : Level 1 to 4 corresponds to the complexity of the procedures based on factors such as the duration of the intervention, the procedure's complexity, associated risks, and expected outcomes. It is important to note that this classification may vary depending on case specifics and the medical decisions made by healthcare professionals. For example, a level 1 orbital decompression is a minor or low-complexity orbital procedure, typically involving only the soft tissues of the orbit. Conversely, a level 4 procedure is a very high-complexity orbital procedure, often involving deep orbital tissues and carrying significant risks or complications.

Table S3. Clinical course and associated direct costs for patients in the biological approach.

	Regulated fee	Reimbursement rate	Source: French DRG code
Pretreatment workup			
General practitioner appointment	26.50 €	70%	GS - CS
One ENT specialist consultation with nasal endoscopy	85.30 €	70%	APC-GCQE001
Standard treatment (nasal irrigation and nasal corticosteroid spray)	26.76 €	70%	
CT scan	26.02 €	70%	LAQK002+YYYY600+FT
One ENT specialist consultation with nasal endoscopy	55.30 €	70%	CS + MPC + GCQE001
Subtotal workup	**219.88 €**	**153.92 €**	
Biologics			
Cost of dupilumab, per month	1 333.2 €	70%	
Cost of mepolizumab, per month	947.1 €	70%	
First injection by nurse	10.57 €	70%	AMI+MAU+IFD+IK
Cost of follow-up			
Five ENT specialist consultations (one per year)	276.50 €	70%	CS + MPC + GCQE001
Cost of minor complications (7%) *	110.60 €	70%	(CS + MPC + GCQE001)

* We assumed that a minor complication would require an average of two ENT consultations.

Table S4. Lower and upper estimates for the variables considered in the sensitivity analysis.

Variable	Lower estimate	Upper estimate
Surgery control rate	60%	80%
Rate of biologics as second-line treatment	10%	50%
Cost of initial surgery (± X%)	-20%	20%
Cost of revision surgery (± X%)	-20%	20%
Major complication rate after surgery	0.5%	1%
Minor complication rate after surgery	0%	7%
Biologics control rate under dupilumab	52%	96%
Biologics control rate under mepolizumab	52%	96%
Rate of surgery as second-line treatment	5%	15%
Biologics complication rate	6%	8%
Discount rate	0%	4%
Taking sick leave into account	0 €	936 €
Repartition of biologics, % of dupilumab	50%	90%
Cost of biologics (± X%)	-20%	20%