

The potential role of biological treatment of chronic rhinosinusitis with nasal polyps: a nationwide cohort study*

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Abstract

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) can be a challenge to treat despite appropriate pharmacological therapy and endoscopic sinus surgery. With the introduction of biological treatment, costs will increase. In this study, we determine the number of patients with CRSwNP treated with endoscopic sinus surgery and revision surgery and thereby fulfil the main criterion for treatment with biologics in the newest European guidelines. Furthermore, we estimate a potential number of recipients of biologics nationwide.

Methods: All adult patients registered in the Danish National Patient Registry as having undergone first endoscopic sinus surgery for CRSwNP from 2012–2018 were included. The number of operations, surgery dates, and comorbidities were extracted. The Kaplan-Meier method was used to calculate the revision rate over time. Revision surgery was used as a surrogate to determine the pool of potential recipients of biologics, as these would fulfil the eligibility criteria and ensure the necessary cost-effectiveness.

Results: A total of 4667 operated patients with CRSwNP were included out of a population of 4.7 million adults (incidence 14/100,000 person-years). Approximately 18% (120 per year) was estimated to have revision surgery within seven years. The median time to revision surgery was 22 months. Of all analysed patients, 21% had registered asthma and/or allergic rhinitis, while these diseases were registered in 34% of patients treated with revision surgery.

Conclusion: In Denmark, an average of 120 operated patients annually will have revision surgery within seven years and may benefit from treatment with biologics as an alternative option to revision surgery.

Key words: paranasal sinus disease, nasal polyps, monoclonal antibodies, asthma, allergic rhinitis

Introduction

Chronic rhinosinusitis (CRS) is a chronic inflammatory disease, which can present with nasal polyps (CRSwNP) ⁽¹⁾. The overall prevalence of CRS varies according to geography and study methodology. European estimates are about 11% for CRS and 2% for CRSwNP ^(2,3). CRSwNP can be challenging to treat, with a high symptom burden and a high recurrence rate despite appropriate medical therapy ⁽¹⁾. CRSwNP is an impairing disease with broad negative consequences. Direct healthcare costs for

medication, hospitalisation, specialist visits and surgery – as well as indirect costs due to debilitating symptoms leading to absenteeism from the workplace – have an economic impact both for the individual patient and society ^(1,4). In addition, CRSwNP is associated with negative psychological consequences and a decrease in the quality of life for patients ⁽⁴⁾. Current European guidelines for CRS treatment (European Position Paper on Rhinosinusitis and Nasal Polyps 2020 [EPOS 2020]) recommend nasal irrigation with saline solution, topical/systemic steroids,

and antibiotics – and as a last resort endoscopic sinus surgery. Furthermore, biological treatment is now recommended for recalcitrant CRSwNP ⁽¹⁾.

Over the last decades, drugs targeting immunological triggers such as immunoglobulin E, interleukin-5, and interleukin-4/-13 have improved the treatment of severe asthma ⁽⁵⁾. These triggers have also been investigated extensively in studies on immunotherapy for refractory CRSwNP, showing promising results for patients with severe treatment-refractory disease and leading to FDA-approval of both Dupilumab (interleukin-4/-13-inhibitor) and Omalizumab (IgE-inhibitor) in 2019 and 2020, respectively ^(6,7).

The aim of this study was to determine the incidence of patients with CRSwNP treated with endoscopic sinus surgery and revision surgery in Denmark in order to estimate the potential pool of patients for whom biologics might be suitable and to inform healthcare policy-makers of the potential use of this new and costly treatment option based on high-quality, reliable registry data.

Materials and methods

This study is a nationwide, population-based, retrospective, cohort study. Data was obtained from the Danish National Patient Registry (DNPR), which contains information on all inpatient consultations and outpatient hospital consultations after 1995, registered according to the ICD-classification. Surgical procedures performed in Denmark are also registered in the DNPR by procedure-specific codes, see supplementary.

This population-based study design was possible due to access to a centralised, tax-funded, universal healthcare system for all residents in Denmark, which reduces selection bias. All Danish residents have a unique personal identification number used across all Danish national registries, which enable the combination of data on an individual level ^(8,9).

Patients

To assess the potential pool of suitable recipients of biologics in accordance with the main treatment criterion of having surgery for CRSwNP stated in the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS2020), we analysed all patients above the age of 18 who were registered in the DNPR with a primary diagnosis of CRS and who had at least one operation under general anaesthesia as determined by procedure-specific codes, in either the public or private sector, and within the specified time period, i.e. from January 2012 through December 2018.

We extracted information on the number of times the patient had undergone endoscopic sinus surgery, date of surgery, and time from initial surgery to revision. Patients having undergone endoscopic sinus surgery two years before the start of inclusion were excluded; this was done to avoid registering a revision surgery as a patient's first surgery. We did not record endoscopic sinus surgery with less than 14 days apart as revision surgery because these patients, with a high probability, did not undergo revision surgery due to the recurrence of CRSwNP but more likely due to post-operative bleeding, infection, and/or other complications from surgery. Furthermore, we excluded patients with diffuse secondary CRS such as cystic fibrosis and primary ciliary dyskinesia by their associated diagnosis codes, as these patients do not portray the general population's need for revision surgery, see supplementary.

We extracted information on hospital-registered asthma and allergic rhinitis for all the included patients at any visit to a medical department nationwide.

Patients ever registered as having nasal polyps were categorised as having CRSwNP for all hospital contacts, assuming inadequate registration.

The race of the study population was presumed to be Caucasian due to the largely homogeneous population of Denmark.

Statistical analysis

All statistical analyses were performed in R version 3.6.3 (Stanford University, Stanford, CA, USA). Kaplan-Meier analysis was used to assess the likelihood of revision surgery over time, as this model takes the staggered entry of the patients into account. The calculations and figure for the Kaplan-Meier survival curve were performed with the 'survival' R-package ⁽¹⁰⁾. The number of eligible patients was calculated as the revision surgery rate multiplied by the number of patients being operated for CRSwNP divided by the duration of the study period.

Results

Study population

In the entire Danish population of 4.7 million adult residents, from January 2012 through December 2018, a total of 9,603 patients had their first endoscopic sinus surgery for CRS. Of the analysed patients, 4,667 (48.6%) were categorised as having CRSwNP: This is the group that constitutes the study population and is the subject of all analyses and discussions in this paper.

Patient characteristics

Of the 4,667 patients included for analysis, the male/female-ratio in the study population was 2:1, and the mean age was 53 (SD 14.6) years. A concurrent diagnosis of asthma was recorded in 21%, and 3.9% were registered as having allergic rhinitis (Table 1).

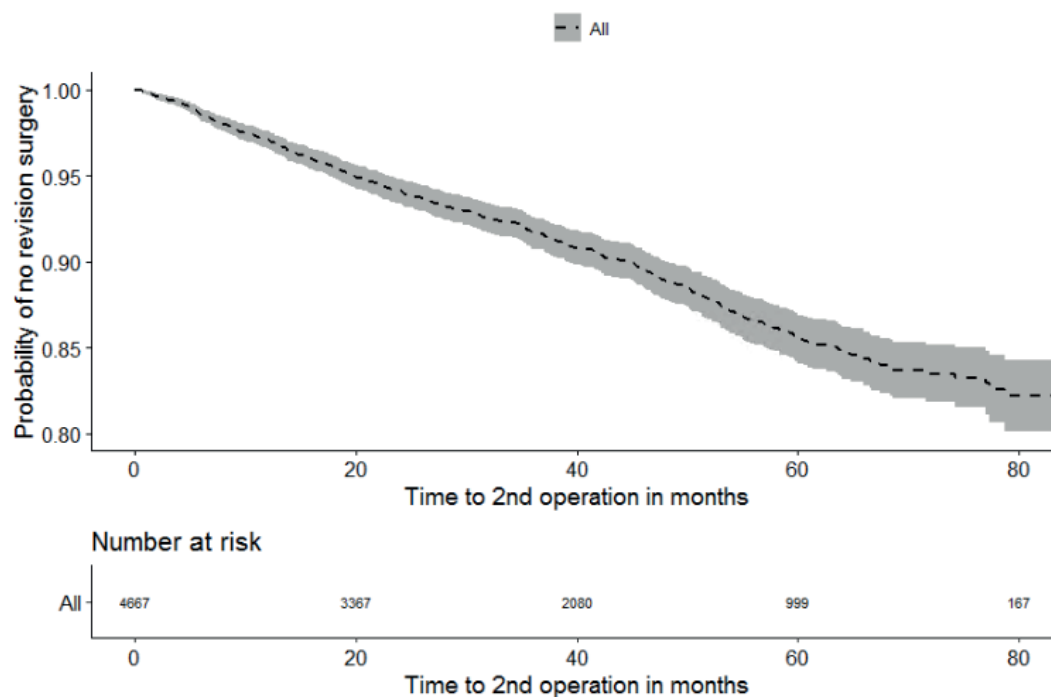


Figure 1. Kaplan-Meier curve for overall proportion of patients without revision sinus surgery over time, considering each patient's different time at risk. The shaded area indicated the 95% confidence interval for survival estimates.

Revision surgery

Based on the analysed 4,667 patients with CRSwNP, which had one or more surgical procedures according to surgical codes for endoscopic sinus surgery, an incidence of approximately 14/100,000 person-years for being operated for CRSwNP was calculated in accordance with the adult population divided by the study period. Seven years after the initial operation, approximately 18% would have had revision surgery (Figure 1).

Of the 441 patients who had revision surgery, 284 (64%) were men, 150 (34%) were registered with asthma, and 36 (8.2%) with allergic rhinitis.

Most of the patients (84.8%) who underwent revision surgery had only one revision surgery within the study period. Of the 67 patients with more than one revision surgery, 25 patients (37.9%) were registered with asthma and six patients (9%) with allergic rhinitis (Table 2).

Of all patients having received revision surgery, the median time to revision was 22 months (Table 1). Based on the assumption that patients receiving multiple surgeries for CRSwNP would have a sufficiently high symptom burden to be eligible for biologics, we calculated the average annual pool of patients that would go on to be potential recipients.

From the Kaplan-Meier analysis, we derived that about 18% of patients operated for CRSwNP would undergo revision surgery

within seven years (Figure 1), which calculates to an average of 120 patients annually (4,667 patients x 0.18 / 7 years).

Discussion

Endoscopic sinus surgery should be viewed as a symptom-alleviating procedure that optimises pharmacological disease control, as it facilitates the medication reaching the desired sinonasal targets. Consequently, revision surgery should be regarded as an indicator of poor disease control, though other factors such as patient adherence and radicality of the initial endoscopic sinus surgery may play a role^(11,12). If current guidelines are followed, failure to improve a patient's condition and symptoms leads to an additional work-up investigating the patient's type of immunological response and the histological subtype of the surgically excised tissue. Depending on the type of inflammation, biologics may be an option if medical treatment and endoscopic sinus surgery fail to alleviate symptoms. Furthermore, biologics could be an alternative for patients experiencing side effects from systemic corticosteroids or feeling hesitant about surgery. In the latest European guidelines (EPOS 2020), treatment with biologics is reserved for patients with CRSwNP who have already undergone endoscopic sinus surgery or who are not fit for surgery and also fulfil three of the following criteria: evidence of type 2 inflammation, need for systemic corticosteroids or a contraindication to systemic steroids, a significantly impaired quality of life, anosmia, and/or concurrent asthma needing regular steroid inhalations. The gui-

Table 1. Baseline characteristics of patients with CRSwNP and a history of a minimum of one endoscopic sinus surgery in Denmark from January 2012 through December 2018 by year of initial endoscopic sinus surgery.

Inclusion year	n	Mean Age (SD)	Sex (M) (%)	Asthma (%)	Allergic Rhinitis (%)
2012	560	53.1 (14.4)	393 (70.1)	127 (22.7)	21 (3.8)
2013	608	53.0 (14.8)	420 (69.0)	144 (23.7)	31 (5.1)
2014	695	52.6 (14.6)	490 (70.5)	143 (20.6)	27 (3.9)
2015	725	53.0 (14.5)	503 (69.3)	157 (21.7)	34 (4.7)
2016	736	53.0 (14.1)	525 (71.3)	133 (18.1)	27 (3.7)
2017	685	54.1 (15.0)	470 (68.6)	128 (18.7)	20 (3.0)
2018	658	52.6 (14.9)	462 (70.2)	123 (18.7)	21 (3.2)
Total	4667	53.1 (14.6)	3263 (69.9)	955 (20.5)	181 (3.9)

Table 2. Number of revision sinus surgeries within the study period from 2012 through 2018 and patient comorbidities. The overall number of patients analysed was 4667.

Revision surgery - count	Overall (% of total)	Asthma	Allergic rhinitis
1	374 (84.9)	126 (28.6)	33 (7.4)
2	55 (12.4)	20 (4.5)	6 (1.4)
3	9 (2.1)	5 (1.1)	0
4	2 (0.5)	0	0
7	1 (0.2)	0	0
Total (% of total)	441 (100%)	151 (34.0%)	39 (8.2%)

delines do not contain a temporal criterion, consequently there is no time limit from surgery to an evaluation of other eligibility criteria⁽¹⁾. A treatment algorithm in line with the one specified in the EPOS2020 ensures that only patients with an objectively verified need for a change in treatment strategy receive this costly treatment option.

It is quintessential when considering treatment with biologics to compare its cost and efficacy with that of the standard treatment. In a Dutch study from 2020, it was estimated that patients with CRSwNP cost an average of € 7,500 a year in direct and indirect costs, but the authors were unable to stratify patients according to the severity of the disease⁽¹³⁾. Patients undergoing multiple surgeries for CRSwNP are undoubtedly more likely to lead to higher indirect and direct costs than the typical patient with CRSwNP. Also, patients with a history of multiple operations would likely have received several courses of corticosteroids, a treatment which has been shown to increase the risk of diabetes, osteoporosis, gastric ulcers, and cataracts, potentially raising costs even further^(14,15).

In 2020 the efficacy of biologics for CRSwNP was investigated in a Cochrane review. The authors concluded that Dupilumab (anti-IL4/13) showed significant results, increasing the quality of life and reducing the extent of disease with minimal adverse events

in a group of patients with severe CRSwNP. This systematic review did not contain the newest data on Omalizumab (anti-Ig-E), which show significant improvement of patient-reported and clinical outcomes in patients with severe CRSwNP⁽¹⁶⁾. Biologics have not been compared with standard treatments such as revision surgery or other treatments such as systemic steroids, and for this reason we must reserve treatment with biologics for a highly selected patient group to ensure a cost/effectiveness balance.

In addition, both CRSwNP and comorbid asthma can be treated with biologics, depending on the subtype. Thus, patient-specific predictive and responsive biomarkers (e.g., blood eosinophils) and the severity of the patient's disease should be considered^(1,17). Therefore, a close interdisciplinary collaboration with pulmonologists on the optimisation of disease control should be established before starting a specific biological treatment to make sure cost-effectiveness is guaranteed, especially as surgery for CRS has been shown to improve asthma control⁽¹⁾.

It is our opinion that patients receiving multiple surgeries for CRSwNP are very likely to fulfil the eligibility criteria for biological treatment stated in the EPOS2020 and that treatment with biologics in this group would likely result in an acceptable cost/effectiveness ratio. Calculating the national average of patients

that would go on to receive revision surgery will give policy-makers an indicator of the number of eligible patients when deciding on a national implementation strategy for biological treatment for CRSwNP. We base the assumption of these patients being a surrogate for eligible patients on the generally accepted fact that patients with CRSwNP are characterised by type 2 inflammation^(17,18) and that high rates of verified comorbid asthma as high as 65% have been reported in operated patients⁽¹⁹⁾. Moreover, with a prevalence of 74–100% in re-operated patients when tested with more sophisticated tests, loss of smell is described as a major symptom, with between 76–98% of re-operated patients having anosmia^(20–22). Lastly, patients who had surgery for CRSwNP are highly associated with a SNOT-22-score of 40 and above^(4,23). In addition, biologics could be a suitable option for patients with contraindications to steroid treatment and patients who are not fit for surgery, although these patients were not included in our study.

In our nationwide population-based retrospective study of 4,667 patients having undergone initial endoscopic sinus surgery for CRSwNP at any time from January 2012 through December 2018, we showed that with a high degree of confidence about a fifth of the patients would go on to have revision surgery during the next seven years (Figure 1) and that half of these revision surgeries would occur within about two years of the initial operation. This is well in line with prior follow-up studies on revision surgery for CRSwNP^(11,24).

The association between asthma and CRSwNP in patients who have had surgery is widely acknowledged⁽¹⁾. In our study, both the overall group and the group of patients who underwent revision surgery had higher rates of registered asthma (21% and 34%, respectively) than the general prevalence seen in Denmark of about 10%⁽²⁵⁾. However, our rates were below those reported in the literature^(1,26). A previous study conducted in our department showed that 65% of patients operated for CRSwNP had comorbid asthma when tested and that half were undiagnosed prior to the study⁽¹⁹⁾. Our low figures may very well be due to unregistered and undiagnosed mild or moderate disease, as severe disease is more likely to be registered or diagnosed in a hospital setting (e.g., patients referred to a department of pulmonology). Thus, our figures can only verify the association between asthma and CRSwNP, especially in patients who have had revision surgery, but cannot be used to assess whether these patients fulfil the eligibility criterion of having comorbid asthma and needing corticosteroid inhalations, as this would require data on prescribed medication.

Based on our assumption and the calculated revision rate, we estimate that an average of 120 patients per year (18% of the 4,667 analysed patients divided by seven years) will become eligible for biological treatment.

The strength of this study is that Denmark has a free-of-charge tax-financed universal healthcare system, which decreases selection bias. Data in this study was derived from the DNPR, which contains a high-quality record of all medical conditions together with an extended follow-up. A limitation of the study could be the underrepresentation of concurrent type 2 inflammatory diseases in the study population as registration is based on the severity in a hospital setting. This means that moderate asthma and allergic rhinitis treated in a primary care setting is underrepresented in the data. Therefore, we were only able to use the data on registered asthma and allergic rhinitis as a marker for increased comorbidity in patients with revision surgery compared to patients who only had one endoscopic sinus surgery and the general population.

Furthermore, because of the study set-up, we could not extract data on the severity of symptoms (e.g., SNOT-22), loss of smell (e.g., Sniffin' Sticks TDI-score) or the use of systemic or inhaled corticosteroids. Thus, we can only refer to the current literature on patients operated and re-operated for CRSwNP to support our assumption of revision surgery being a surrogate marker for treatment eligibility. This should be considered when drawing conclusions based on the calculated incidence.

Conclusion

In conclusion, our large, highly reliable, nationwide, registry-based study found that annually in Denmark an average of 120 new patients operated for CRSwNP will become eligible for costly biological treatment within seven years, as this could be an alternative to the current strategy of revision surgery.

Authorship contribution

PRGE: Conception and design of the paper, data analysis, drafting of the manuscript; KKJ: Acquisition of data, drafting of the manuscript; KA: Conception and design of the paper, expert revision of the manuscript; VB: Expert revision of the manuscript; CvB: Expert revision of the manuscript and design. All authors read and approved the final manuscript.

Conflict of interest

Patrick Eriksen received grant support from Sanofi Denmark totalling USD 50,000.

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Supplementary data

CRS:

ICD-10: J320, J321, J322, J323, J324

CRSwNP:

ICD-10: J330, J331, J338, J339

Cystic Fibrosis

ICD-10: E840, E841, E848, E849

Ciliary Dyskinesia

ICD-10: J988a, Q103c

Operation codes:

Patients were included if they were registered as having undergone one of the following procedures as well as having CRSwNP as the indication for the operation.

KDHB20 – Surgical removal of nasal polyposis; KDHB40 - Concomitomy; KDMB20 - Endoscopic opening of the maxillary sinus, KDMW00 - Drainage of the maxillary sinus, KDMW99 – Operation on maxillary sinus, miscellaneous; KDMB10 - Radical resection of maxillary sinus; KDNB20 - Endoscopic ethmoidectomy; KDNW99 - Surgery of the ethmoid sinus or ethmoid bone, miscellaneous; KDPW00 - Drainage of frontal sinus; KDPW10 - Drainage of the sphenoidal sinus; KDPW99 - Operation on the frontal sinus or sphenoidal sinus; KEEB00 - Resection of the maxillary bone; KEEB99 – Resection of the maxillary bone, miscellaneous.