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Chronic rhinosinusitis with nasal polyps management in the biologic therapy era: an international YO-IFOS survey

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Abstract

Purpose To investigate the consistency between the international guidelines recommendations and worldwide standard practices regarding diagnostic work-up and follow-up strategies for managing patients with Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) in the era of monoclonal antibodies.

Methods A questionnaire developed by the Rhinology section of the Young Otolaryngologists of the International Federation of Oto-rhino-laryngological Societies (Yo-IFOS) included items regarding the management of CRSwNP patients, monoclonal prescription, surgical and follow-up procedures, awareness of biologicals availability, and other relevant clinical practices. The online survey was directed to otolaryngologists and distributed in Europe, North America, South America, and the Middle East through otolaryngological and/or rhinological societies.

Results A total of 202 responses were analyzed; the mean participants' age was 45 ± 11 (73% men and 27% women), and 31% were from the United States, Canada 19%, Europe 45%, Middle East and South America 5%. Only 60% of the respondents declared using validated symptoms and endoscopic score systems in their clinical practice. Several practice discrepancies emerged in our cohort, including preferred surgical approach, prescription of preoperative oral steroids, and perioperative antibiotics (59% and 58%, respectively), as well as divergent awareness levels of available biologics for CRSwNP worldwide.

Conclusions CRSwNP needs a complex and time-consuming assessment, according to the latest guidelines. There seems to be a gap between these recommendations and the real-world data, which should draw more attention to bringing them into uniform clinical practice in the near future.

Keywords Biologics · Rhinosinusitis · Nasal polyps · Biological drugs · Guidelines · Rhinology

Introduction

The treatment of chronic rhinosinusitis with nasal polyps (CRSwNP), a condition that affects 2–5% of the population [1], has been profoundly changed with the introduction of monoclonal antibody therapy, which is now incorporated in the latest disease-specific guidelines recommendations [2–5]. Dupilumab (an anti-IL4Ra and anti-IL13Ra recombinant human IgG4 monoclonal antibody) was the first drug approved in Europe for clinical use in October 2019, followed by omalizumab in August 2020, and mepolizumab in 2021; more recently even benralizumab showed promising results [6–9].

These monoclonal antibodies have demonstrated an excellent efficacy and safety profile, yet they represent an important challenge for the healthcare system because of their high cost [10]. The duration of such therapy is also unknown, but it may become a lifelong treatment for CRSwNP [2–4]. Implementation of available patient-reported outcome measures and the need for multiple consultations with other specialists can be time-consuming in everyday clinical practice, though. It is, therefore, of the utmost importance that a rigorous process is used to identify ideal candidates for biologics,

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assess their effectiveness, and monitor their side effects [11]. The study aimed to assess the concordance between the currently available guidelines recommendations and the real-world clinical practice in the management of CRSwNP by ENT surgeons across different countries.

Materials and methods

An online survey was developed by the Rhinology section of the YO-IFOS group in accordance with the CROSS guidelines [12]. Ethics approval for surveying North American respondents was received from Western University Human Research Ethics Board (ID 120154) according to the principles of the Declaration of Helsinki. Approval or waivers were received from other countries as required. The survey, developed and written in English (available in its full version in the Appendix), was distributed in the period from December 2021 to May 2022 among Otolaryngologists in North America (Canada and USA), Europe (Spain, Italy, France, Portugal, UK, and Armenia), Central and South America (Colombia, Peru, Chile, and Mexico), and the Middle East (Israel and Egypt) through official National otolaryngological and rhinological societies and included questions regarding the management of CRSwNP patients, including monoclonal prescription and other clinical practices.

The first section included demographics and work-volume questions, such as age, sex, country of specialty, number of CRSwNP patients seen monthly, and monthly number of simple or extended endoscopic sinus surgeries. The second section investigated the practices in managing CRSwNP comorbidities, such as allergy, asthma, and cystic fibrosis. The third one comprised the use of validated questionnaires or scores when documenting patient symptoms during clinic follow-ups or during surgeries, such as the sinonasal outcome test SNOT-22/olfactory objective testing/the nasal polyp score/radiological scores such as the Lund–Mackay score/endoscopic scores such as the Lund–Kennedy score [13–15]; we also assessed if preoperative radiological checklists such as the CLOSE or ADCDEF systems were used [16, 17]. The fourth part evaluated the management of an initially diagnosed CRSwNP, timing of radiological investigations and related surgical interventions. Biologic therapy referral protocols were addressed in the fifth section, in which participants were asked about the monoclonal therapies available in their countries, the timing for prescribing biologic therapy, and different CRSwNP symptoms and comorbidities that would lead them to choose an upfront treatment of monoclonal antibodies over surgical treatment. In the sixth part, participants were presented with four real-life clinical scenarios of CRSwNP patients with distinct disease severity levels and were asked to choose their first surgical intervention from multiple-choice answers. (See Appendix, section 6, questions a–d) Surgical interventions ranged from simple procedures (Balloon sinuplasty, polypectomy, etc.) to more extensive sinonasal dissections (Frontal drill out or Draf III procedure, etc.). The last section investigated the initial management of CRSwNP patients and peri/post-operative management of CRSwNP; oral steroids and antibiotics usage, and the timing of postoperative intranasal steroid applications.

The questions were elaborated using the web-based platform SurveyMonkey (Momentive Inc., San Mateo, CA, USA). A permanent link to the survey was emailed three times during the study period. The link was sent directly to the respondent's email addresses, with IP verification allowing for a single survey answer submission per user. Responses were collected anonymously, and incomplete responses were excluded from the analysis.

Descriptive statistical analysis was performed using SPSS (v20.0). Results are expressed as percentage of respondents for each item. Multianswer questions are presented as a frequency of times each answer was chosen by respondents, therefore, not necessarily adding up to 100%.

Results

A total of 235 participants answered the questionnaire; 33 were incomplete and, therefore, excluded. Demographic data and geographic distribution are listed in Table 1. The countries with the highest percentage of fellowship-trained participants in rhinology and skull base surgery were; Mexico 4/5 (80%), Canada 27/38 (71%), the U.S.A 39/62 (63%), Egypt 2/4 (50%), Israel 4/9 (44%), Italy 7/23 (30%), and Spain 8/51 (16%).

Regarding the work volume, an average of 54 ± 57 (range 3–420) CRSwNP patient visits monthly was found, of which 34 ± 20 new patients, while 66 ± 20 were follow-up visits. The most common follow-up interval was once

Table 1 Demographic data and geographic distribution

Characteristic	Participants, no. (%) ($N=202$)
Age; mean (SD), y	45 (11)
Sex	
Women	55 (27)
Men	147 (73)
Country where participant practices Medicine	
North America	100 (50)
Europe	80 (40)
Middle East	13 (6)
South America	9 (4)

every 6 months (54%). Participants reported a yearly surgical volume of 60 ± 27 functional endoscopic sinus surgeries (FESS) and 31 ± 28 extended endoscopic sinus surgeries (EESS) (frontal drill out and rebooting techniques).

Most participants investigate the presence of asthma in CRSwNP adult patients (72%); however, only 24% refer them to a respirologist/pneumologist. One-half inquire about the presence of AERD, and 46% refer the patient for ASA challenge. 33% of the participants investigate the presence of atopic dermatitis, and 14% refer to a dermatologist. Around 66% investigate the presence of a possible allergic trigger (by skin and blood tests) in the case of CRSwNP, but only 28% refer to an allergologist. Regarding CRSwNP in pediatric patients, 50% investigate cystic fibrosis, and 58% refer to a pediatrician.

Only 69 (34%) participants have a multidisciplinary committee on respiratory diseases (single airway concept) at their institutions, which are constituted mainly by pneumologists (29%), otolaryngologists (29%), allergologists (29%), pediatricians (8%) and pharmacist (7%). Only 16% of participants have a special commission for the advanced management of CRSwNP in their hospital, formed mainly by otolaryngologists (93%), pneumologists (84%), and allergologists (75%); only 6% had a dermatologist.

Most respondents (61.4%) use questionnaires to evaluate CRSwNP symptoms. Among them, 67% are fellowship-trained specialists, and 33% are general otolaryngologists. SNOT-22 is the most commonly used questionnaire (57%), followed by NOSE (15%). Only 16% perform routine instrumental assessment olfactory testing.

The most common laboratory blood tests for CRSwNP work-up are eosinophils level (70%), total IgE (69%), specific IgE (46%), and ANCAs (13%). Moreover, tissue eosinophils count (41%) and nasal cytology (18%) were utilized.

Sixty percent of participants use validated score systems to report endoscopic nasal findings; Nasal polyp score (37%) and Lund–Kennedy score (31%) were the most common scoring systems reported. Just over half of respondents use a radiological reporting score, with 57% using Lund–McKay, 18% using CLOSE, and 14% using the ABCDEF system. Upon diagnosing CRSwNP, 62% of participants request a CT scan immediately. When participants were asked about re-imaging their patients, 4% would repeat the CT every year, and 94% would repeat it only in perioperative planning of revision surgery or in case of a suspected complication. 83% of participants discuss surgical options in case of medical therapy failure.

Most of the U.S.A and Italy participants recognized that dupilumab is approved in their countries for the treatment of CRSwNP (98% and 100%, respectively), while only 69% in Canada, 70% in Israel, and 43% in Spain. Regarding omalizumab, 80% in the US, 48% in Spain, 45% in Canada, and 40% in Israel were aware of its approval. While 72% of US participants recognized that mepolizumab is approved in their country, only 44% in Canada and 33% in Spain reported it being available in their country. A representation of respondents' awareness of currently available biologics is presented in Fig. 1.

The participants were asked about the timing of administering monoclonal antibodies, 77% indicated they would prescribe monoclonal therapy in case of topical therapy failure post-operatively, 24% would prescribe it post-operatively regardless of adjuvant topical therapy result, and 17% would prescribe it preoperatively. Grade 4 polyposis is the most common (87%) reason to favor upfront surgical therapy over biologic treatment, while others were: loss of smell accounts (24%), nasal discharge (15%), and facial pressure (23%). Moreover, factors favoring monoclonal therapy over endoscopic surgery were history of previous surgery (63%),

	Omalizumab			Dupilumab			Reslizumab			Mepolizumab			Benralizumab		
	Yes	No	Correct answers (%)	Yes	No	Correct answers (%)	Yes	No	Correct answers (%)	Yes	No	Correct answers (%)	Yes	No	Correct answers (%)
Canada	20	18	53	31	7	82	0	38	100	20	18	53	0	38	100
US	50	11	82	61	0	100	6	55	90	46	15	75	13	48	79
Israel	4	5	44	7	2	78	0	9	100	1	8	89	0	9	100
Spain	29	22	57	26	25	51	0	51	100	20	31	39	4	47	92
Italy	6	17	74	23	0	100	0	23	100	1	22	96	1	22	96

Fig. 1 Level of awareness of available biologics for CRSwNP by country. Correct answers are defined based on medication approved for use in Chronic Rhinosinusitis with Nasal Polyps as of May 2022 for each Country. At this time, Omalizumab was approved in Canada, United States (US), Israel, and Spain; Dupilumab was approved in all countries listed above; Mepolizumab was approved in Canada, US, and Spain; Reslizumab and Benralizumab were not approved in any of these countries. Colour code: Green = above 80% correct answers; Yellow = between 60% and 80%; Red = below 60%

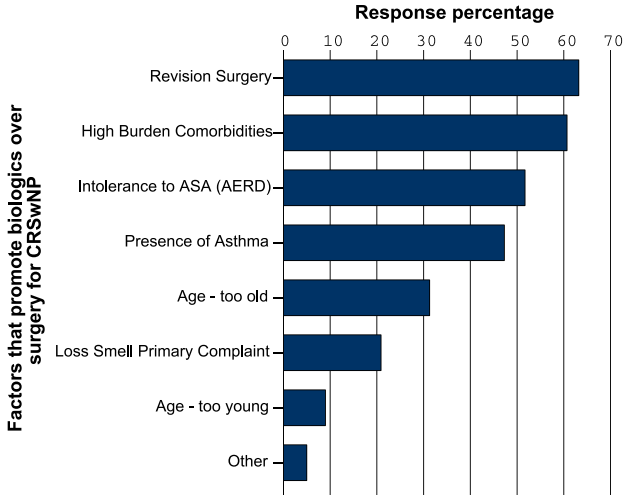

Fig. 2 Response percentage for the multiple choice question, "Which of the following factors would prompt you to consider commencing treatment with biologics rather than surgery for CRSwNP?"

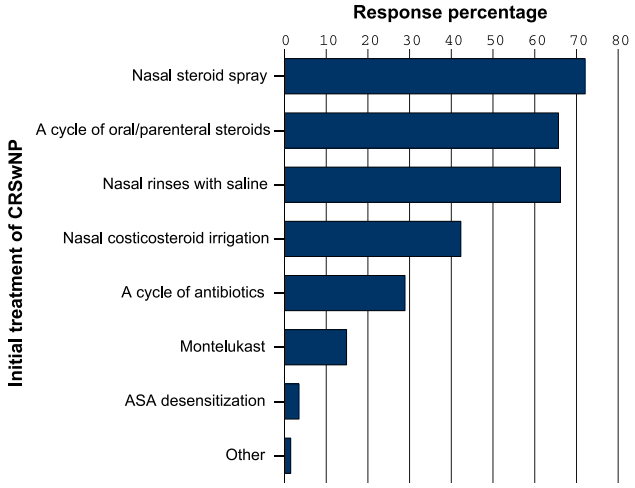

Fig. 3 Response percentage for the multiple choice question, "Which of the following drugs do you usually suggest for the initial medical treatment for CRSwNP?"

severe comorbidities (60%), N-ERD (51%), asthma (47%), young age (9%), elderly (31%), and loss of smell (21%), as demonstrated in Fig. 2. Interestingly, only 25% of participants refer their N-ERD patients for aspirin desensitization.

In the first clinical scenario question (section 6, question a, in the appendix), the most common answers were full house endoscopic surgery (66%) and Standard FESS (24%). The second question (section 6.b), Standard FESS (52%), Full House FESS (23%), and mini FESS (10%). In the third question (section 6.c), Full house ESS (36%), Extended ESS (31%), and standard FESS (14%). In the fourth question (section 6.d); Extended ESS (50%), Full house ESS (36%).

Figure 3 shows the response regarding CRSwNP initial management. Nasal steroid spray was the most common therapeutic option (72%), followed by nasal rinses with saline (66%), oral/intravenous cycle of steroid (65%), nasal corticosteroid irrigations (42%), antibiotics (29%) and Aspirin desensitization (3.5%). A total of 118 (59%) participants indicated they usually prescribe a preoperative dose of oral steroids, and 58% administer a dose of preoperative antibiotics. Moreover, 33% of participants use a dissolvable middle meatus spacer without steroids, and 22% use it with steroids; of the remainder, 15% use a non-dissolvable spacer.

Discussion

Our results highlight the gaps and the differences between how otorhinolaryngologists actually manage CRSwNP across many countries, a condition that has a worldwide estimated prevalence of around 5% [18]. The therapeutic management of this complex disease now includes different monoclonal antibodies that have been demonstrated to effectively improve QoL, reduce symptom burden, and delay the need for further surgeries in these patients [6–9]. Such drugs result from increased knowledge of the pathophysiology of CRS with and without nasal polyps, whose many distinct endotypes and corresponding phenotypes are now recognized [19]. For type 2 CRSwNP, even sub-phenotypes are being identified, which would explain the differences in clinical response to the same monoclonal antibody [20]. It is interesting to note that when "chronic rhinosinusitis" is used as a keyword in the PubMed search engine, more than 1000 articles are retrieved for 2021. Worldwide, many scientific societies have updated their guidelines to incorporate these latest medications and, despite some differences, they are pretty consistent in the diagnostic criteria and therapeutic indications [21].

From these premises, and because CRS currently requires a thorough work-up, it is disappointing that more than one otolaryngologist out of three did not use any questionnaire for its evaluation. All the guidelines agree that these tools are essential in the initial management of disease, because they capture the impact on quality of life, help decide to undergo sinus surgery, and permit evaluation of outcomes [2, 3]. Furthermore, without these questionnaires, it is impossible to correctly identify a candidate for biologics, since their cut-offs were used as inclusion criteria in the trials above [6–9]. What is surprising is that most of the respondents declared a fellowship or subspecialty in rhinology/skull base surgery. A simple explanation would be that PROMs are not easy to administer in everyday practice because of technical or time constraints (e.g., paper-based versus electronic PROMs) [22]. However, it is possible that many fellowship programs might often favor teaching advanced surgical techniques more than focusing on the medical management of CRS.

Regarding the work-up of the phenotype/endotype of CRS, most surgeons screen for type-2 inflammation by blood tests, such as eosinophil count and total IgE. As for the presence of comorbidities, only 24% of our respondents send their patients to a respirologist, a quite disappointing result if we consider that adult-onset asthma is present in 25% of CRSwNP and is often underdiagnosed [23, 24]. Nasal cytology is used rarely despite its promising prognostic results [25], and it remains a research tool more than an effective clinical adjunct [26]. The measurement of the group of antineutrophil cytoplasmic antibodies (ANCA) is also seldomly performed. For instance, the EPOS paper recommends it only for severe cases "not responding to conventional therapy [3]." In addition, while the IL-5-driven EGPA (formerly Churg–Strauss syndrome) may be ANCA-negative in about half of cases [27], it can be even triggered by anti-IL-4 drugs, such as dupilumab [28].

The majority of the interviewed participants agreed that massive (i.e., at least NPS = 6) CRSwNP was a strong indication for endoscopic sinus surgery, coherently with the fact that biologics have poorly performed in terms of polyps size reduction (ranging from 1 to 2 in terms of NPS) [29]. Instead, classic symptoms of CRS (discharge, loss of smell, or facial pain) were estimated to be less important in proposing upfront FESS, yet there is increasing evidence that preoperative symptom score or burden constitutes the best predictor for surgical success [30, 31].

Another point that deserves to be discussed is that while most participants recognized that dupilumab was approved in their country, this knowledge was less consistent when asked about omalizumab or mepolizumab. This might be due to the real-life experience of otolaryngologists worldwide with dupilumab, which had better results in CRSwNP patients than other monoclonal therapies, or a marketing emphasis reflected by the respective companies. As of this time, there is no published phase III trial yet with a head-to-head comparison of different monoclonal therapies; however, indirect comparisons such as the recent meta-analysis from Wu et al. would possibly favor dupilumab as the first choice for CRSwNP [32].

The currently accepted treatment algorithm, supported by several published papers [1, 3, 4], suggests prescribing biologic therapy in case of appropriate medical therapy (AMT) and surgery failure. Although specific subsets of patients are more likely to fail surgery and AMT, there are no sound demographic or serological markers that can preemptively identify these patients consistently at this time [33, 34].

Most participants (73%) would prescribe monoclonal therapy in case of failure of topical therapy post-operatively; however, 17% of them would consider prescribing biologic therapy preoperatively. This latter indication is at present off-label because of the absence of supporting data in the pre-FESS setting [35]. Then, while ESS and biologics are equivalent in reducing symptoms of CRSwNP [36], some authors have estimated the surgical upfront strategy to be more cost-effective than dupilumab for the initial treatment of CRSwNP [37]. Given the actual cost of biological therapies, this might be a substantial financial burden on public and private health care systems, and a recently published letter suggests a de-escalation trial of dupilumab in patients with well-controlled CRSwNP to help reduce this cost burden [10].

Our work is, to the best of our knowledge, the first to provide a snapshot of the current practice of CRS, but we are well aware that this is rapidly changing. Shortly, more attention will be drawn to the biological bases of CRS, and reasonably, otorhinolaryngologists will improve their knowledge. Future research should also identify which barriers or limiting factors prevent their correct implementation into clinical practice. In general, these obstacles are known to be very context-specific and depend on many variables such as the physician's and patients' attitudes, technology and materials available, and the organization, where we practice [38]. The only study published in the literature for the implementation of the 2007 American Academy guidelines for acute sinusitis [39], demonstrated that by using a Plan–Do–Study–Act cycle method, an increase in adherence up to 41–57% can be achieved [40]. While reassuring, these findings need to be also replicated for CRSwNP before any conclusion can be drawn.

There are also some limitations of the present study: fellowship-trained rhinologists were the majority of our respondents, and therefore, a selection bias exists, because "non-specialized" otolaryngologists may have answered differently. Then, as for every survey, there are factors that may have impacted the response rate. For instance, older surgeons tend to be less prone to answer [41]. Finally, accidental or even intentional response bias cannot be excluded.

Conclusions

Severe CRSwNP is a complex disease that has been treated surgically at the highest therapeutic level until the arrival of biological drugs. Despite the large amount of literature that has been published and the numerous guidelines available, much work remains to be done to bring them to a uniform clinical practice. Although the currently available position papers are helpful for otolaryngologists worldwide, their practical implementation still needs some refinements and modifications to be introduced in the near future.

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Availability of data and material The datasets generated during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest Juan Maza-Solano has received fees for participation in Advisory Boards (GSK and SANOFI), presentations (ALK, AMPLIFON, MSD-Organon, GSK, NOVARTIS and SANOFI) and participation in clinical trials (GSK, NOVARTIS, SANOFI and AstraZeneca). Leigh Sowerby has received clinical trial support from AstraZeneca, Roche, Optinose, Sanofi and GSK and speaking honoraria for GSK and Sanofi (Advisory board). Isam Alobid is consultant for Menarini, Novartis, Sanofi, GSK, MSD, Salvat, and Roche. All other authors declare they have no competing Interests.

Ethical approval Ethics approval for surveying North American respondents was received from Western University Human Research Ethics Board (ID 120154) according to the principles of the Declaration of Helsinki. Approval or waivers were received from other countries as required.

Informed consent Informed consent was obtained digitally from all individual participants included in the study.

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