

Chronic Rhinosinusitis with Nasal Polyposis and Biological Agents: The ARIA-ITALY Survey

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Abstract

Background: Chronic rhinosinusitis (CRS) is an inflammatory disease that affects the nasal mucosa and the paranasal sinuses. CRS can be associated by nasal polyposis (CRSwNP phenotype) in up to 30% of patients and it is frequently associated with bronchial asthma. CRSwNP shows predominantly an underlying activation of type 2 inflammatory pathways with the involvement of eosinophils, IgE, interleukin (IL)-4, IL-5 and IL-13. Biological drugs that target these inflammatory cytokines are currently a therapeutic option recognized by guidelines for the treatment of uncontrolled form of the disease. **Methods:** As part of the activity of the "ARIA-Italy" working group, a panel of 255 Italian Ear, Nose and Throat (ENT) specialists, pneumologists and immuno-allergologists actively participated in this national survey and answered a series of questions geared toward understanding the main criteria for patient characterization and therapeutic decision, highlighting multidisciplinarity, and the implementation of the management of CRSwNP patients, as a part of the precision medicine concept and the appropriate use of the biologicals. **Results:** Two hundred and fifty-five experts and specialists participated in the survey. **Conclusions:** The results of this survey obtained from an extensive number of active specialists throughout Italy allow some important concluding remarks to be drawn. The main points of agreement were that multidisciplinary care teams provide many benefits but that, once the team is established, meetings and communication between members must be coordinated. Finally, the dissemination of national disease registries and the continuous updating of guidelines and position papers related to CRSwNP and comorbidities should be encouraged.

Keywords. Chronic RhinoSinusitis with Nasal Polyposis phenotype, CRSwNP, bronchial asthma, multidisciplinarity, biological agents.

Impact statement

The results of this survey obtained from an extensive number of Italian specialists allow some important concluding remarks about biologicals and the treatment of CRSwNP and its impact on asthma.

Introduction

Chronic rhinosinusitis (CRS) is an inflammatory disease affecting the nasal mucosa and paranasal sinuses, with prevalence varying in different geographical areas. In Europe, it is estimated that CRS may affect more than 10% of the adult population (1). The prevalent signs and symptoms that define CRS are nasal obstruction and congestion, anterior/posterior rhinorrhea, facial pain, hypo/anosmia, and sleep disturbances. CRS can present without (chronic rhinosinusitis without nasal polyposis, CRSsNP) or with nasal polyposis (chronic rhinosinusitis with nasal polyposis, CRSwNP). Polyps are semi-transparent, light gray lesions resulting from inflammation and remodeling of the mucosa of the sinuses or nasal cavity (2). Up to 30% of patients with CRS may present with the phenotypic form with nasal polyposis (3). From the patient's perspective, CRSwNP has a significant impact on the quality of life (QoL) (4). Patients with CRSwNP experience higher symptom scores and greater severity of the clinical disease if compared with patients with CRSsNP. From a pathophysiological point of view, CRSwNP is characterized by the activation of specific inflammatory pathways that define its endotype and influence its severity, course and response to treatments (1). In the majority of patients, the CRSwNP is associated with the activation of type 2 inflammatory pathways, with an increase in the concentration of eosinophils (systemic and/or local), IgE (systemic or even just local) and interleukin (IL)-4, IL-5 and IL-13 (5). Patients with CRSwNP frequently present with comorbidities, such as bronchial asthma, including late-onset and often severe forms, also characterized by a type 2 inflammation pattern, suggesting the existence of common immunological pathways between the two diseases (6). The chronicity characteristic of the disease and comorbidities imply frequent treatments to control recurrent symptoms including medical therapies (intranasal corticosteroids, oral steroids, antibiotics) and surgical approach (7). The high frequency of the use of systemic corticosteroids, however, is associated with complications and adverse events and that make the management of these patients complex (8). Today, only about 35-40% of patients with CRS are well controlled after conventional treatment (9). Comorbidities also require patients to be followed by different specialists, with an increasing need to coordinate interventions, to optimize their timing and effectiveness. In light of what has been highlighted on the diagnostic and treatment clearly emerges the importance of multidisciplinary as the most appropriate tool for the management of the complex patient with CRSwNP. The introduction of biologic agents (monoclonal antibodies directed against molecules involved in inflammatory mechanisms such as IgE, IL-5, IL-4 and IL-13) as a therapeutic option for the treatment of CRSwNP has helped to improve significantly outcomes in patients with uncontrolled disease, improving QoL, and providing the basis for the achievement of personalized treatment targeted to the peculiar phenotypic and endotypic characteristics of each patient. However, the introduction of the new therapies raises new questions in clinical practice, such as the correct definition of the target patient type, the timing of intervention and the definition of the best biological agent for the specific patient phenotype/endotype, to ensure a personalized therapy while optimizing the cost/effectiveness of treatment (6). In particular, for the use of biologic drugs, there is a need for skills appropriate specialists who take into account the different components of the pathology (involvement of the upper and/or lower airways, allergies, drug hypersensitivity, recurrent infections, assessment of nasal structures and QoL of the patient). In real life clinical experience, complex situations are common, with patients with a long-standing history of

pathology, undergoing different treatments including for the comorbidities, for whom the therapeutic decision is complicated and not clearly defined by the national and international Guidelines. For these patients, the multidisciplinary approach is crucial and mandatory.

Methods

As part of the activities of the ARIA-Italy working group, a survey was organized with the participation of experts and specialists in allergology-immunology, pulmonology, and otolaryngology active throughout the Italian country. The survey was based on the completion of a questionnaire consisting of 17 items (table 1). The questions focused on the following points: 1) management of the patient with CRSwNP in clinical practice; 2) factors to be considered for therapeutic decision-making (comorbidities, previous surgery, etc.); 3) criteria for characterizing the patient to undergo the treatment and choice of biological agent; and 4) role of multidisciplinary for personalized patient management. Starting from literature evidence and the indications for treatment reported in the Guidelines, the participants answered the questions anonymously and taking into account the clinical practice in relation to the different regional realities. The opinions were collected during the period 2022-2023 and were discussed in a webinar coordinated by the authors of this article.

Results

Two hundred and fifty-five experts and specialists (age range: 26-77 years; M:56%; F:44%) participated in the survey. Participants came from all regions of Italy, with predominance for those from Lombardy; this region is the most populous in Italy with about 10 million people). Regarding the type of activity performed, the following distribution was observed: 130 hospital practitioners (51%); 84 freelancer practitioners (33%), 41 university professors and researchers (16%). Regarding the participant's specialty branch the distribution was as follows: 80 ENT specialists (31%), 71 immuno-allergologists (28%), and 104 pneumologists (41%) (figure 1). Although a wide distribution of responses was found, more than 64 of the respondents (25%) believed that the presence of asthma in their patients with CRSwNP was between 20 and 30% of the total cases; while on the other hand, more than 30% of the respondents believed that the presence of CRSwNP in patients with asthma was between 20 and 30% (figure 2). Finally, 250 participants (98%) thought it was important to assess the presence of an atopic condition in CRSwNP patients (figure 2). Regarding CRSwNP therapeutic aspects, only 82 participants (32%) believe that endoscopic surgery should be the first choice in the treatment of CRSwNP today (figure 3). Regarding the use of systemic steroids in the treatment of CRSwNP, 68% of participants use them in cycles, 31% never use them, and only 2% use them continuously (figure 3). Some questions were specifically asked to assess participants' treatment behavior regarding the use of biological agents in CRSwNP. As can be seen from the results shown in figure 4, the participants believe that the preference among the various biological agents available in Italy today for the therapy of CRSwNP should be given to dupilumab (75% of responses); however, it should be pointed out that dupilumab was the first to be introduced for the treatment of polyposis and experience with omalizumab and mepolizumab in Italy was limited at the time the survey was conducted. When choosing the biological agent for the treatment of polyposis, asthma comorbidity is largely (98% of responses) taken into account. The use of biological agents is also being considered in other complex diseases characterized by the presence of comorbidities, such as N-ERD. Seventy percent of respondents

believed that the use of biological agents in CRSwNP should not necessarily be postponed to polypectomy. Regarding the following specific question: AFTER STARTING THERAPY WITH BIOLOGICAL AGENT TO CURE CRSwNP WHEN DO YOU CONSIDER THE PATIENT RESPONDER OR NON-RESPONDER? Participants answered : 3 months, 6 months, 9 months, and 12 months in 13%, 59%, 9%, and 19%, respectively; therefore, most of the participants believe that a 6-month observation is the most appropriate for evaluating the efficacy of CRSwNP biological therapy. The following question was then formulated: IN CASE OF NASAL POLYPOSIS, WHICH OF THESE TESTS (SNOT-22, VAS, NPS) DO YOU USE FOR MONITORING THE RESPONSE TO THERAPY WITH BIOLOGICAL AGENTS OVER TIME? Participants answered : 22% SNOT-22, 6% VAS, 5% NPS, and 67% all of the above, respectively. From this response can be inferred the focus on making the assessment of response to biological agents using multiple rating scales at the same time. The last part of the survey focused on opinions regarding the multidisciplinary approach to CRSwNP. While it is true that almost all participants (83%) confirm that they relate to other specialists in the management of this pathology, particularly when it is associated with other comorbidities (such as asthma); it is also true that only in a limited number of Centers (45%) has a multidisciplinary working group been established with facilitated diagnostic-therapeutic pathways for patients (figure 5).

Discussion and Conclusions

The results of this survey obtained from an extensive number of active specialists throughout Italy allow some important concluding remarks to be drawn. The course of the patient with CRSwNP is made complex by the numerous symptoms and comorbidities that contribute to the definition of disease severity. The current availability of biological agents represents a potential improvement in the treatment and QoL of patients; but the use and choice of the biologic agents needs to be optimized in clinical practice through discussion among specialists, so that it can be targeted to those patients who can benefit most from it, to reduce therapeutic inappropriateness and economic burden. In the context of CRSwNP and comorbidities the patients' point of view or patient perspective can be viewed through two different but related lenses: 1) the individual's perspective as it relates to each patient's individual situation and 2) the aggregate perspective of the CRSwNP population, i.e. a perspective of common denominators despite unique individual variations. Recognition of the importance of the individual patient's perspective regarding their experience of CRSwNP is exemplified by the evolving patient/healthcare providers clinical interaction. Indeed, increasing recognition of the complexity of CRSwNP and comorbidities diagnosis and its treatments, requires a "bidirectional exchange" of opinions and objectives between patients and healthcare providers, in order to promote integration of the patient perspective into the patient/healthcare providers relation-ship. Treatment focused on the underlying disease often fails to address the ripples of impact provoked by CRSwNP with comorbidities which may become the main source of concern to the patient. For the patient perspective to be valid, it must be informed by an adequate comprehension by the patient of the facts of the clinical situation (10,11). Furthermore, the application of narrative medicine methodology could prove useful (12). Because patients with CRSwNP have had only limited occasions to unite to have their voices heard, hence missing the opportunity to contribute to the improvement of CRSwNP care, it was recently published a Patient Advisory Board Statement of the European Forum for Research and Education in Allergy and Airways diseases (EUFOREA) (13). The aim of this initiative was to identify unmet needs in

CRSwNP from the perspective of CRSwNP patients. Semi-structured interviews were conducted individually with European patients with CRSwNP and a panel of 30 members of the Patient Advisory Board reviewed the interview report and provided further input. Along with a loss of smell and continuous nasal secretions, most patients reported poor sleep quality and psychological impact as the most bothersome symptoms. Patients' frustrations relate primarily to the underestimation of the disease burden, the lack of coordination of care and the limited treatment options available to them. Treatment options with systemic steroids and/or nose surgery both have positive and negative aspects, including the lack of long-lasting efficacy. Better coordination of care, more patient-centered care, greater public awareness, increases in the disease mechanisms and better therapeutic options would be warmly welcomed by CRSwNP patients. The multidisciplinary approach, organization into networks, and the use of registries are identified as the key strategies for establishing a common language between the specialists and the patient, to implement the connection between specialist centers and the territory, diagnosis and management of the patient, with the goal of personalization of care. CRSwNP is certainly a "cross-cutting" condition that needs, in both the diagnostic and therapeutic phases, the contribution of multiple specialized expertise (14). Pharmacotherapy often may fail to treat CRSwNP and endoscopic sinus surgery (ESS) is often required. However, the synergistic use of pharmacotherapy and surgery often does not achieve disease control in the most severe cases. Furthermore, CRSwNP is associated with greater morbidity compared with CRSsNP, due to repeated exposure to OCS and surgery. The results of the present survey highlighted these contradictions. In particular, the response to question 8 concerning the use of OCS in CRSwNP, prompts a noteworthy observation: one-third of the surveyed specialists refrain from utilizing OCS, despite its established utility in controlling CRSwNP and assessing disease severity, along with its implications for biological therapy eligibility and for the potential excessive OCS use on CRSwNP management. These contradictory behaviors also emerge from the answers to question 13 about the sequencing of surgery and biological therapy; the striking revelation that 70% of respondents initiate biological therapy irrespective of prior surgical intervention suggests a prevailing inclination toward a medically-oriented approach to CRSwNP. This deviation from established guidelines advocating surgical intervention as the cornerstone of CRSwNP management, invites scholarly discourse and collaborative exploration. Furthermore, the significant economic and clinical burden of CRSwNP highlights the need for better treatment options and reorganization of the current care pathways (13). In this context, a multidisciplinary approach may improve CRSwNP management in patients with comorbidities, but currently there are only sparse examples of shared management model. Recently, an Italian panel of clinicians with different clinical expertise (pulmonologists, ear, nose and throat specialists, immunologists and allergy physicians) identified three different profiles of patients with coexisting asthma and nasal symptoms and discussed the specific tracks to guide a comprehensive approach to their diagnostic and therapeutic management: (1) Patient with severe asthma who needs to start a biologic therapy at the Allergy/Pulmonary Unit complaining about nasal symptoms; (2) Patient with severe asthma with ongoing biologic therapy at the Allergy/Pulmonary Unit complaining about nasal symptoms; and (3) Patient with Severe CRSwNP at the ENT Unit Complaining about Asthma Symptoms (15). Based on these different types of patients with comorbidities and different clinical and therapeutic presentation characteristics, it seems clear that there is a need to define a multidisciplinary approach by at least ENT specialist, allergist-immunologist and pulmonologist in order to evaluate symptoms and clinical history,

confirm diagnoses and to identify the best treatment strategy aimed at controlling both diseases and preventing clinical exacerbations. Regarding the preponderance of respondents' choice of dupilumab (question 9), it should be pointed out that, because the opinions in the present survey were collected in the period 2022-2023, the use of mepolizumab and omalizumab is probably underestimated because these biologics have been introduced in Italy for the treatment of CRSwNP as of March 2023. To improve the management aspects of this clinical-pathological area, a study was recently published that has summarized the outcomes of a Delphi process involving a multidisciplinary panel of ENT specialists, pulmonologists, and allergist-immunologists involved in the management of CRSwNP, who attempted to reach consensus on key statements relating to the diagnosis, endotyping, classification and management (including the right placement of biologic agents) of CRSwNP patients (3). On the following points, we think we can agree that there are many theoretical benefits of a multidisciplinary approach, which include the reduced need for documents to make referrals, access to services and treatments that would otherwise be inaccessible (e.g., radiological examinations, new biological treatments), optimized flow of patients from primary to secondary to tertiary care, management of adverse events, and obtaining a detailed overview of the management of multiple therapies for more than one pathology (16). Indeed, multidisciplinary care teams assure patient centrality, improvement of direct and indirect outcomes, cost reduction, and more appropriate therapeutic decisions (17,18,19). Once a multidisciplinary team is created, there is a need for coordination of meetings and communication between the various members. Among the effective and efficient planning tools capable of linking all phases of diagnosis-care-assistance are, along with the Individual Therapeutic Plan (ITP) and Individualized Care Plan (ICP), the Diagnostic Therapeutic Care Pathways (DTCP). Other additional factors were considered to be useful, as theoretical-practical multidisciplinary training events on diagnosis and therapy, which will attract considerable interest from ENT specialists, pulmonologists, and immuno-allergists. Educational events were also considered to be important since the approach to CRSwNP and comorbidities is evolving rapidly, and the number of treatment options is expanding. Finally, the use and dissemination of national disease registries and the continuous updating of guidelines and position papers related to CRSwNP and comorbidities should be encouraged.

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Contributions

CL, GP, FM, GWC contributed equally to this work; the other authors participated in the survey, reviewed and approved the manuscript.

Conflict of interests

The authors declare that they have no conflict of interest to declare with the current article.

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Table I - Survey ARIA CRS with polyposis & biologics: questionnaire.

(1)	Age (yrs) Sex (M/F)
(2)	Specialty: 1) Allergology 2) Pneumology 3) ENT 4) Internal Medicine 5) Pediatrics
(3)	REGION of your Country (Italy):
(4)	Employment status: 1) University 2) Hospital Physician 3) Freelancer Practitioner
(5)	Approximately in how many of the patients with nasal polyposis do you find asthma? 5-10% 11-20% 20-30% 30-50% > 50%
(6)	Approximately in how many of the patients with asthma do you find nasal polyposis? 5-10% 11-20% 20-30% 30-50% > 50%
(7)	To patients with nasal polyposis, do you make endoscopic surgery the first choice? YES NO
(8)	In patients with nasal polyposis, do you use systemic steroids? YES, in cycles YES, continuously NO, never
(9)	In case of using biological agent (according to indications) which one do you give preference to? Dupilumab Mepolizumab Omalizumab
(10)	When choosing a biologic agent to treat CRSwNP, do you take into account the presence of asthma comorbidity? YES NO
(11)	Do you think it is important to assess the presence of atopy in patients with CRSwNP? YES, always NO, never
(12)	For patients with N-ERD, who are difficult to treat and frequently have recurrence of polyposis, do you consider them suitable for therapy with biologic agents? YES NO
(13)	Where there is an indication, do you always initiate biologic agent therapy after polypectomy? YES, always NO, not necessary
(14)	How long after starting therapy with biological agent to treat CRSwNP do you consider the patient responder or non-responder? 3 months 6 months 9 months 12 months
(15)	In case you are an ENT specialist or pulmonologist/allergist, do you always have the referring counterpart specialist? YES NO

(16)	Does the facility where you work have a multidisciplinary team for the management of patients with CRSwNP? YES NO
(17)	In case of nasal polyposis, which of these tests do you use for monitoring over time? NPS SNOT-22 VAS total symptoms all of the above

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Figure 1: Typology of work activity and specialty branch of the Survey participants.

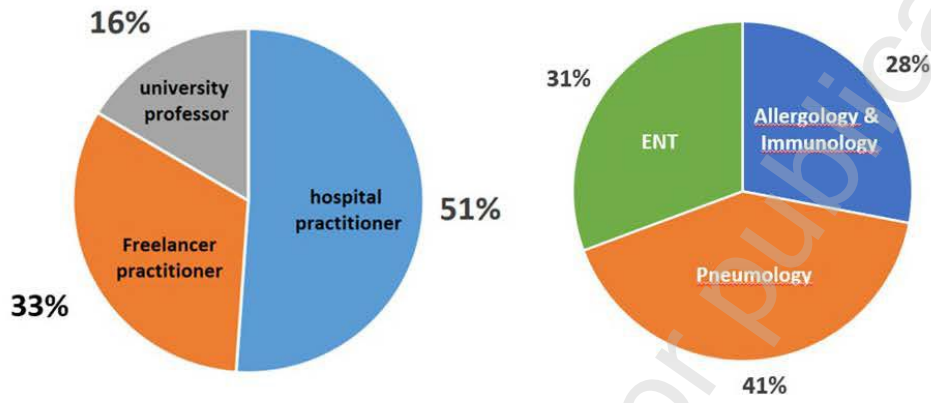


Figure 2: Items regarding the presence of comorbidities in the SRCwNP setting.

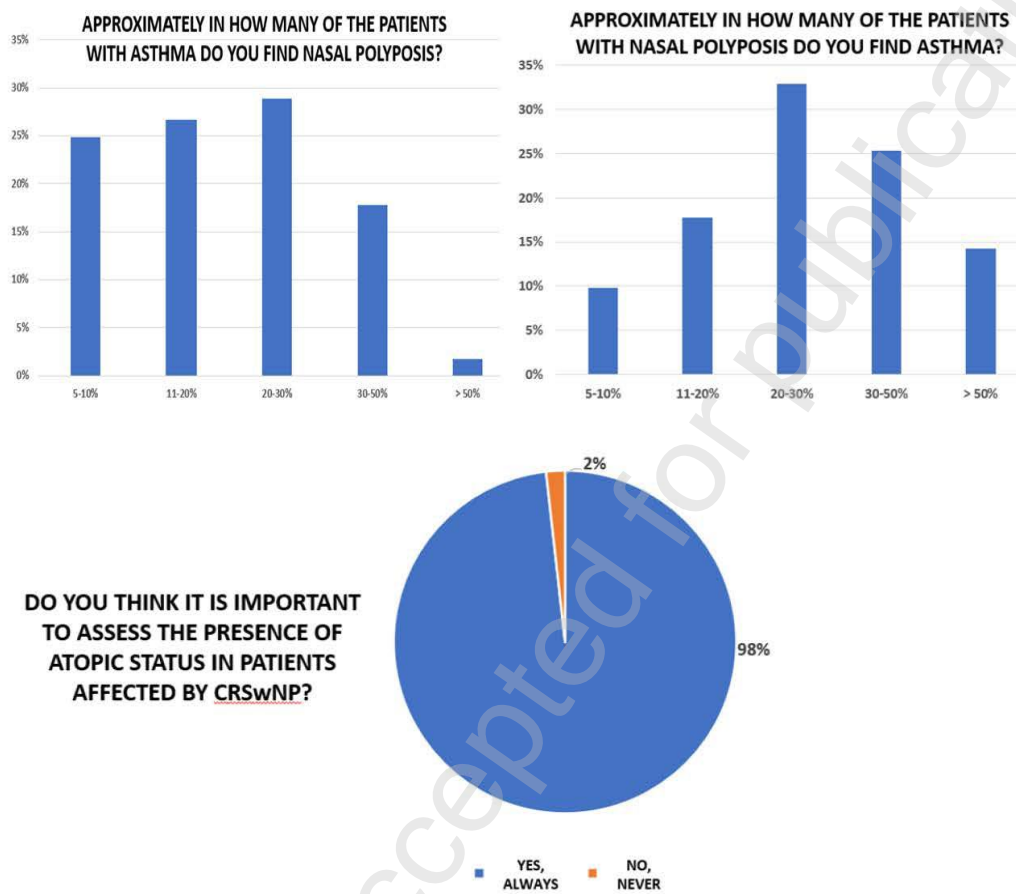
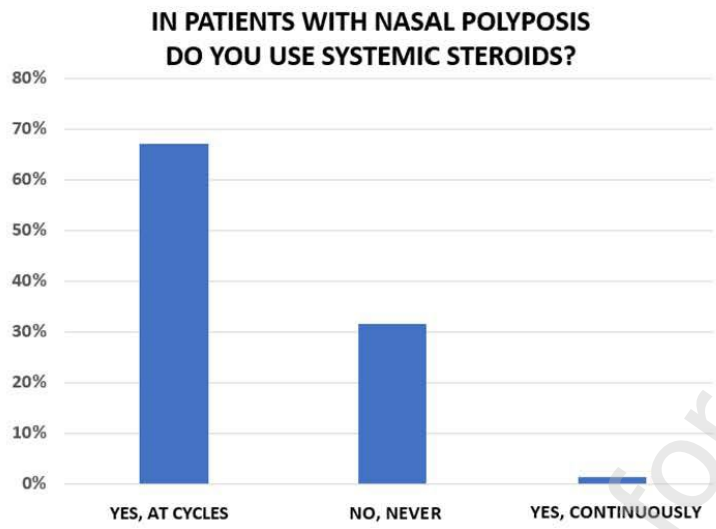


Figure 3: Items regarding the choice of endoscopic surgery and the use of systemic steroids.



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Figure 4: Specific questions and answers (%) about the approach to use of biological agents in patients with CRSwNP.

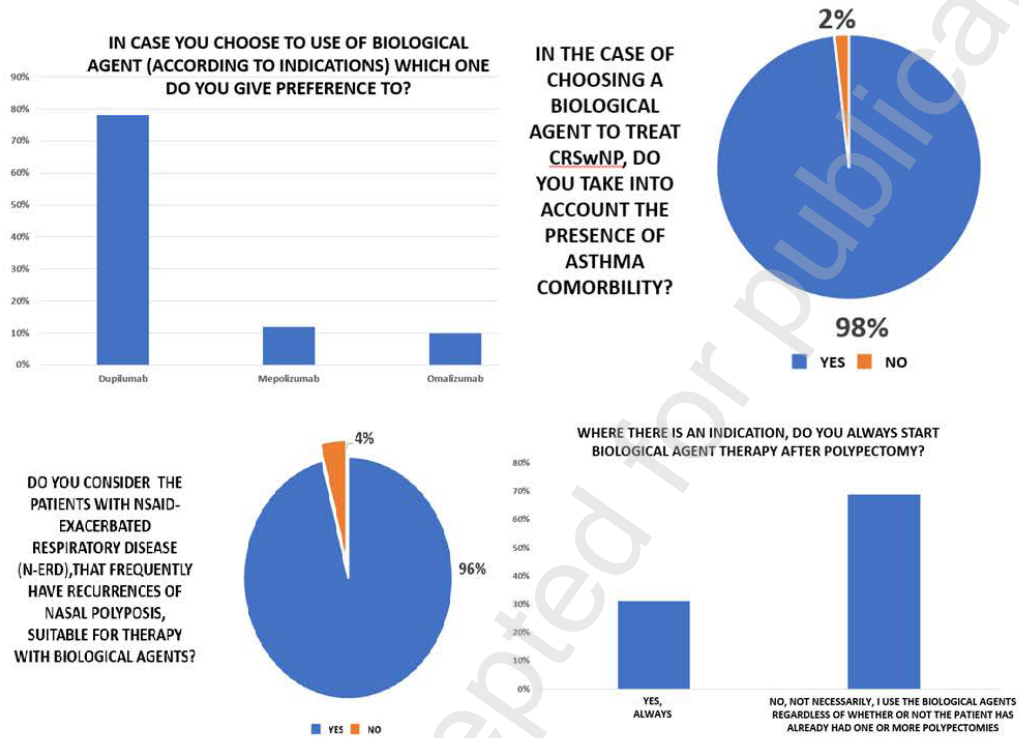
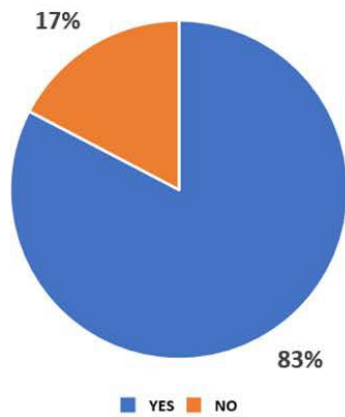


Figure 5: Specific questions and answers (%) about the organizational and multidisciplinary dynamics in patients with CRSwNP.

IN CASE YOU ARE AN ENT SPECIALIST OR PULMONOLOGIST/ALLERGIST DO YOU ALWAYS HAVE THE COUNTERPART REFERRAL SPECIALIST?



IS THERE A MULTIDISCIPLINARY TEAM IN THE STRUCTURE IN WHICH YOU WORK FOR THE MANAGEMENT OF PATIENTS WITH CRSwNP?

