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Management of patients with chronic rhinosinusitis with nasal polyps (CRSwNP): Results from a survey among allergists and clinical immunologists of the North-west and Center Italy Inter-Regional Sections of SIAAIC and otorhinolaryngologists of National IAR

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TO THE EDITOR,

Chronic rhinosinusitis with nasal polyps (CRSwNP) is one of the most common medical conditions worldwide, characterised by chronic inflammation of the paranasal sinuses lasting for >12 weeks and the presence of nasal polyps. Its estimated prevalence is about 4% of the general population.[1] Symptoms, such as loss of smell, anterior or posterior rhinorrhoea, nasal congestion, and facial pressure, may be severe and often disabling. In particular, CRSwNP is often associated with comorbidities, including asthma and aspirin/nonsteroidal anti-inflammatory drug exacerbated respiratory disease (AERD). Although the pathogenesis of CRSwNP is not completely understood and significant heterogeneity is found at macroscopic and microscopic levels, type 2 inflammation and eosinophils are thought to play a role.[2] Along with this treatment of CRSwNP involves a combination of both surgical and medical approaches, including the recent introduction of biologic therapeutic drugs. In Italy monoclonal antibodies for CRSwNP can be prescribed by both allergists/immunologists (AIs) and otorhinolaryngologists (ENTs). Three monoclonal antibodies are now authorized for CRSwNP: anti-IL-4/IL-13 (dupilumab), anti-IgE (omalizumab), and anti-IL-5 (mepolizumab).

Two Inter-Regional Sections of SIAAIC (Italian Society of Allergology, Asthma and Clinical Immunology) including Tuscany, Emilia-Romagna, Republic of San Marino, Umbria, Marche,

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Piedmont, Liguria and Valle d'Aosta, and national IAR (Italian Academy of Rhinology) carried out a survey amongst their respective members to screen how AIs and ENTs manage CRSwNP. The aim of the survey was to collect opinions, insights, and clinical practice of the participants to identify areas of similarities or differences between AIs and ENTs and to emphasize possible improvements in the management of CRSwNP. A team of experts selected from both the aforementioned scientific societies and GlaxoSmithKline (GSK) designed and implemented the project to identify the management workflow of the patients affected from CRSwNP. To this aim, the survey entitled "CRSwNP Management: the point of view of the Otorhinolaryngologist and the Allergist-Immunologist" was anonymously delivered via a web platform to the members of both societies, between May 16 and July 3, 2022. A shared body of 20 questions was administered to both AI and ENT specialists with 2 additional questions exclusively directed to ENTs and 1 exclusively to AIs, anonymous to each other. Questions were structured to identify areas of similarities or differences in the points of view of 2 differently oriented specialists (medical and surgical specializations, respectively).

Questions were uploaded to an electronic platform developed by GSK's Knowledge Center at WNS Global Services Limited. No personal data were required of the participants. The questions did not have open fields but only 1 answer was allowed. The results were collected and processed by GSK Knowledge Center and reported in an aggregated form. The results were reported as a descriptive analysis.

One hundred and eleven AIs belonging to SIAAIC and 83 ENT specialists belonging to IAR completed the whole questionnaire. Questions and obtained results are summarized in Table 1.

The survey could be divided into four different macro topics: (A) general awareness of CRSwNP, (B) burden of systemic steroids intake and related side effects, (C) disease impact on patient quality of life, (D) use of biomarkers and biologic therapy, with special focus on patient management, timing of biologics and expected outcomes.

In the first group of questions (Table 1 Q1-3) both specialists jointly agreed to use multiple parameters to assess severity of CRSwNP with a single parameter chosen by a minority (8%). Almost all were also concordant about the frequent association between asthma and CRSwNP. This shared vision about the burden of asthma and CRSwNP is indeed the prerequisite to creating multidisciplinary teams to better manage severe forms of both diseases.

Q4 and Q6 were focused on the burden of orally (OCS) or parenterally administered (PCS) steroids (Table 1). In general, prednisolone/prednisone are the most used oral steroids, and prednisolone for injection. AIs and ENTs partially disagree on this point. It is well known that OCS therapy is used or overused both in asthma and CRSwNP, with the consequence of side effects and serious economic repercussions in the form of high healthcare resource utilisation.[3] A previously neglected point, i.e. the influence of OCS on the ACTH-cortisol axis, has been recently focused. Indeed, normal adrenal homeostasis and hypothalamic-pituitary-adrenal axis can be affected by steroid therapy even in case of limited drug amounts or short duration.[4,5] In this field differences can be appreciated between the two groups of specialists. OCS effects are evaluated by both specialists in 53% of cases (Table 1 Q4), on the basis of visible hypocorticosurrenalism exclusively, without any help from the laboratory especially by AIs (56%) rather than ENT (48%). Assessment of adrenocorticotropic hormone (ACTH) and blood cortisol levels is more prevalently used by AIs (36%) than ENTs (13%) (Fig. 1A). The difference between the two groups of specialists might reside in the greater medical experience of IAs about the reduction of OCS overuse allowed by biologic therapies in asthma and other diseases, such as Eosinophilic Granulomatosis with Polyangiitis (EGPA), Lupus or urticarial.[5–7] CS administration is the most common cause of adrenal suppression, which may challenging in patient care and potentially underdiagnosed. In this regard, an increased awareness about a safe withdrawal of OCS has also been recommended in other diseases and a recent overview how to diagnose adrenal insufficiency in rheumatologic practice is now available.[8] Thus, despite the attention to the side effects of OCS, only a minority (26%) of clinicians effectively assess the function of the adrenal gland, and, actually, 39% ENTs versus 8% of AIs only do not assess steroid overuse at all thus contributing to the underestimation of this problem.

		ENTs	AIs	Tot
Q1	**How do you assess CRSwNP disease severity?**			
	Measuring polyps dimension using NPS	4%	1%	2%
	Considering CT scans (sinus opacification)	0%	0%	0%
	Use of steroids by the patient (amount, number of courses, ..)	1%	4%	3%
	Measuring polyps dimension together with CT scans (sinus opacification)	4%	3%	3%
	By combination of SNOT-22, NPS, ACT, eosinophilia, olfactometry, radiological evaluation, use of systemic corticosteroids	91%	92%	92%
Q2	**Which is the percentage of patients with CRSwNP also suffering from severe asthma?**			
	<10%	13%	12%	13%
	10-30%	50%	43%	46%
	30-50%	27%	33%	30%
	>50%	10%	12%	11%
Q3	**In patients with CRSwNP and Asthma do you evaluate possible AERD?**			
	Yes, in all the patients by medical history	97%	96%	96%
	Yes, but only in severe patients	2%	1%	2%
	Yes, through the use of specific tests	1%	3%	2%
	Never	0%	0%	0%
Q4	**How do you evaluate the overuse of oral corticosteroid?**			
	Evaluating hypercorticism related effects by visual inspection	48%	56%	53%
	Evaluating cortisol levels and ACTH	13%	36%	26%
	I do not evaluate it	39%	8%	21%
Q5	**In your opinion which is the item mostly affecting the health-related quality of life of patients with CRSwNP ?**			
	Potential risk of surgery	6%	3%	4%
	Side effects of oral or parenteral corticosteroids	7%	18%	13%
	Total/partial olfactory loss	23%	24%	24%
	Sleep disorders	12%	12%	12%
	Nasal obstruction	50%	43%	46%
	Nasal discharge	2%	0%	1%
Q6	**Which is the percentage of patients with CRSwNP who may have developed side effects from OCS/ PCS? (e.g.: Increased blood pressure, diabetes, osteoporosis, cataracts, glaucoma, mood alterations, modification of body look, ...)**			
	<5%	45%	15%	28%
	5-10%	36%	37%	37%
	10-30%	14%	32%	24%
	>30%	5%	16%	11%
Q7	**In patients with CRSwNP and asthma do you use questionnaires listed below ?**			
	No, never	5%	6%	6%
	Yes, I use SNOT-22	37%	5%	19%
	Yes, I use ACT	1%	5%	4%
	Yes, I use both SNOT-22 and ACT	57%	84%	72%

Q8	**In case of CRSwNP and asthma do you assess eosinophilic status? If yes, how?**			
	No, never	4%	0%	2%
	Blood test, independently of systemic steroids in the last month	11%	10%	10%
	Blood test, before the use of oral/ parenteral steroids	6%	30%	20%
	Blood test, after washout from oral/ parenteral steroids	25%	22%	23%
	Blood test, in addition to nasal cytology or polyp biopsy	54%	38%	45%
Q9	**In your opinion which is the most appropriate test to assess eosinophilia in patients with CRSwNP?**			
	Nasal cytology	36%	39%	38%
	Polyp biopsy	33%	48%	41%
	Blood test	31%	13%	21%
Q10	**In your opinion, which is the proportion of patients with severe uncontrolled CRSwNP eligible for biologic therapy?**			
	<10%	20%	7%	13%
	10-20%	23%	27%	25%
	20-35%	29%	25%	27%
	>35%	28%	41%	35%
Q11	**When do you take into account biologic therapy?**			
	Since the first visit	9%	13%	11%
	After at least 3 months follow-up after the beginning of adequate topical therapy	12%	36%	26%
	After at least 6 months follow-up after the beginning of adequate topical therapy	23%	41%	34%
	Only after surgery	52%	9%	27%
	It is not the main therapy for CRSwNP	4%	1%	2%
Q12	**In case of patients with CRSwNP eligible for biologic therapy, do you use a multidisciplinary board evaluation?**			
	Yes, for all patients	33%	53%	44%
	Yes, but only in patients with asthma	35%	18%	25%
	Yes, but only in patients with severe asthma	21%	15%	18%
	No, never	11%	14%	13%
Q13	**In relation to surgery, which is the correct timing to introduce biologic therapy in patients with severe CRSwNP?**			
	Only after a sino-nasal surgery	2%	1%	2%
	Only after a complete sino-nasal surgery (full FESS)	42%	20%	29%
	After corticosteroid therapy (not considering surgery)	16%	55%	38%
	After corticosteroid therapy, after surgery	40%	24%	31%
Q14	**In your opinion, which it the most important outcome to obtain with biologic therapy in severe CRSwNP?**			
	Reduction of nasal polyp score (NPS)	13%	6%	9%
	Reduction of sino nasal symptoms (obstruction/discharge)	23%	23%	23%
	Reduction into need of surgery	19%	7%	12%
	Reduction into need of oral/systemic steroids	12%	45%	31%
	Increase of sense of smell	4%	1%	2%
	SNOT-22 score amelioration	29%	18%	23%

Q15	**In your opinion, which is the most important outcome that patients with severe CRSwNP expect from biologic therapy?**			
	Reduction in nasal polyp score (NPS)	1%	2%	2%
	Reduction in sino nasal symptoms (obstruction/discharge)	48%	61%	56%
	Reduction into need of surgery	16%	12%	13%
	Reduction into need of oral/ parenteral steroids	4%	6%	5%
	Increase of sense of smell	11%	8%	9%
	SNOT-22 score amelioration	20%	11%	15%
Q16	**Which is the best time-point to assess the efficacy of biologic therapy in CRSwNP?**			
	After 1 month since the beginning	18%	5%	10%
	After 3 months since the beginning	35%	53%	46%
	After 6 months since the beginning	45%	42%	43%
	After 12 months since the beginning	2%	0%	1%
Q17	**Which is the most important parameter to consider when assessing the efficacy of biologic therapy in CRSwNP?**			
	Total Nasal Endoscopic Score	26%	16%	20%
	Nasal obstruction	13%	12%	12%
	Recovery of the sense of smell	11%	7%	9%
	Reduction in the oral/ parenteral steroids use	10%	29%	21%
	SNOT-22	40%	36%	38%
Q18	**In your opinion, to what extent are GPs informed about novel therapeutic options for patients with CRSwNP?**			
	Information are not up to date and GPs cannot properly advise on novel therapeutic options	66%	50%	57%
	Information are not up to date but GPs can refer patients to a network of specialists	24%	33%	29%
	Information are up to date but the GPs do not have an available network of specialists as referral	6%	13%	10%
	GPs are informed about the value of biologic therapy and have a network of specialists	4%	4%	4%
Q19	**Which should be the role of GPs in the management of patients with CRSwNP ?**			
	To promptly uncover the disease	23%	35%	30%
	To increase adherence to therapy	10%	3%	6%
	To monitor and manage comorbidities if present	8%	7%	8%
	To refer patients to specialist centers when first line therapy is not sufficient	59%	55%	56%
Q20	**Which might be the first line of action for a Scientific Society to improve patients' awareness about CRSwNP and therapeutic management?**			
	To improve collaboration and promote activities with groups of patients or patient associations to ameliorate disease awareness	7%	3%	5%
	To favor GP training focused on the management of CRSwNP to support emersion and referral	39%	53%	47%
	To collaborate and create multidisciplinary shared approaches specific for CRSwNP patients	40%	31%	35%
	To create multidisciplinary training events for GPs (and patient association groups)	14%	13%	13%

	FOR ENTs ONLY	
Q21	**Do you assess comorbid allergic status in patients with CRSwNP ?**	
	No, never	1%
	Yes, I perform tests by myself otherwise I refer patients to the allergists	71%
	Yes, but only in case of severe CRSwNP and I refer patients to allergists	7%
	Yes, only when medical history is evocative for allergy	21%
Q22	**In patients with CRSwNP do you assess comorbidity of asthma?**	
	No, never	1%
	yes, by medical history and, if doubtful, I refer patients to Pulms/AIs	76%
	yes, but only in the case of severe CRSwNP	2%
	yes, by medical history and ACT and then I refer patients to Pulms/AIs	21%
	ONLY FOR AIs ONLY	
Q23	**In a patient with asthma do you assess the comorbidity CRSwNP ?**	
	No, never	0%
	Yes, always by medical history	54%
	Yes, only in case of severe CRSwNP	2%
	Yes, by medical history, CT scans and ENT visit	44%

Table 1. (Continued) Questionnaire purposed to the specialists. *Percentage(s) of responders are shown. Ear, nose and throat specialists (ENTs) in pale blue; immunoallergologists (AIs) in orange, all the specialists (Tot) in green.* ***Abbreviations:*** *ACT asthma control test; ACTH AdrenoCorticoTropic Hormone; AERD Aspirin Exacerbated Respiratory Disease; AI(s) immunoallergologist specialist(s); CRSwNP chronic rhinosinusitis with nasal polyps; CT computerized tomography; ENT(s) ear, nose and throat specialist(s); FESS functional endoscopic sinus surgery; GPs general practitioner(s); NPS nasal polyp score; OCS oral corticosteroids; Pulms pulmonologists; PCS parenteral corticosteroids; SNOT-22 sino-nasal outcome test 22*

OCS/PCS-related side effects (Table 1 Q6) are expected by the majority of ENTs (81%) in less than 10% of patients while about two-thirds of AIs (69%) estimate that 5–30% develop some undesired effects from steroids (Table 1 and Fig. 1B). This difference may reside in both a prevalent medical (rather than surgical) approach by AIs versus ENTs and, secondly, in the longer experience in steroids withdrawal following the use of biologicals.[5] Data from the Optimum Patient Care Research Database and British Thoracic Society Difficult Asthma Registry, clearly show that almost all the severe asthmatics (93%) do exhibit 1 or more side effects due to systemic corticosteroids, in particular type II diabetes, osteoporosis, dyspeptic disorders, and cataract.[9] Thus, the overuse of OCS (or PCS) is not only of clinical relevance but also reflects an economic problem. The economic impact of CRSwNP on the healthcare system is less known than in asthma and national and international registers on nasal polyposis will be the way to provide data from the real world.

The third crucial point of interest of the survey was to understand the impact of nasal polyposis on patient quality of life (Table 1 Q5) and the expected outcomes of the biologic therapy, by clinicians and patients (Q14 and 15). Similar proportions of ENTs and AIs recognized that nasal obstruction represents the most impacting symptom of CRSwNP, followed by loss of smell and sleep disorders, but it is notable that AIs put side effects of OCS/PCS as third (Table 1). About the outcomes of the biologic therapy, the reduction of nasal symptoms was recognized as a goal by both clinicians with a reduction of surgical interventions (19%) and SNOT-22 improvement (29%) preferred by ENTs. Vice versa, opinions between ENTS and AIs deeply differ about 2 different items: the importance of the polyp volume measured by Total Nasal Endoscopic Score (NPS) (13% ENTS vs 6% AIs) and the reduction of OCS/PCS (12% ENTs vs 45% AIs) (Fig. 1C). Globally considered, NPS, need for surgery, and SNOT-22 amelioration were chosen by 61% ENTs versus 21% AIs (Table 1).

The last section of the questionnaire focused on the use of biomarkers and biologics, with the aim to explore possible differences between specialists in the management of monoclonal antibodies in

CRSwNP. Biomarkers are predictors of efficacy and are necessary for precision/personalized medicine.[10,11] In addition to peripheral blood, as detected in asthma, eosinophils in CRSwNP can also be assessed in nasal fluid (by nasal cytology) or in polypoid tissues (by histology in biopsies) (Table 1 Q9). ENTs equally selected the 3 choices (36%, 33%, and 31%, respectively). On the contrary, AIs were confident that the better choice should be a polyp biopsy (48%). It is indeed true that direct observation of *in situ* inflammation might be superior than assessing circulating eosinophils. However, in randomized clinical trials, blood eosinophilia has been used as a surrogate. In the SYNAPSE study, a greater clinical benefit was indeed obtained in patients with baseline blood eosinophil levels $\geq$150/μL than <150. Similarly, better results were found when eosinophils were greater, versus less, than 300/μL.[12] This finding supports the concept that circulating eosinophils may be suitable biomarkers for responsiveness in CRSwNP as already described in severe asthma. Further data from the real-world studies will further clarify this relationship, whereas in recent observations nasal biopsy and cytology were comparably accurate.[13]

Interestingly enough, striking differences between ENTs and AIs were found about selection criteria (Q10-11), goals (Q14-15), timing (Q13), and management (Q16) of the biologic therapy (Table 1). First, steroids withdrawn was considered as the primary achievement by AIs (45% vs 12%, Table 1 Q14), whereas amelioration of SNOT-22 is the principal result for ENTs (29%), but both agree about the importance of clinical improvement from the patient point of view (Table 1 Q15, 48% ENTs and 61% AIs). Second, and possibly related to the above item, the timing to introduce the biologic therapy (Table 1 Q13) is strongly influenced by CS use for 55% of AIs versus persistent symptoms despite conventional therapy for 40% of ENTs (Fig. 1D). The prescription of the authorized monoclonal antibodies for CRSwNP) is timely regulated by the Italian Medicines Agency (AIFA) as based on NPS>5 or SNOT22 > 50, failure/adverse events of CS therapy or endoscopic sinus surgery (ESS) intervention and limited to recognized Centers. Third, although both specialists recognized that patients eligible for biologics may exceed 30% (Table 1 Q10), more than two-thirds (77%) of AIs gave importance to the failure of topical therapy while one-half of ENTs (52%) took into account this option only after surgery (Table 1 Q11). This

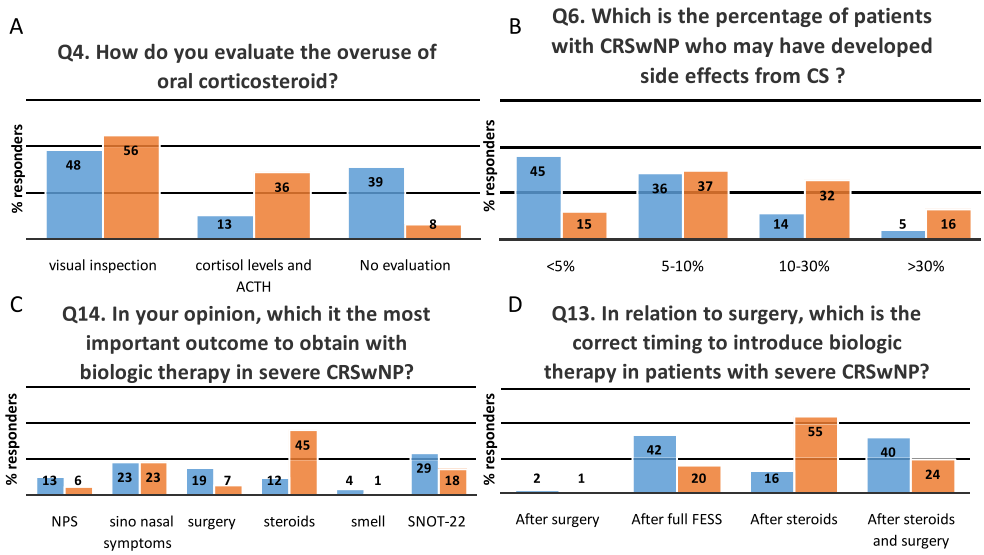

Fig. 1 Most relevant differences in the viewpoints of ENTs (ear, nose and throat specialists) and AIs (allergists/immunologists) about the management of CRSwNP. A selection of 4 questions of the survey among the 20 administered to both otorhinolaryngologists (ENTs) and allergists/immunologists (AIs) is reported. Columns depict the percentages (y-axis) of ENTs (in blue) and AIs (in orange) giving the corresponding answers indicated on the x-axis. Punctual values of the percentages are depicted within the individual columns. Abbreviations: ACTH AdrenoCorticoTropic Hormone; CRSwNP chronic rhinosinusitis with nasal polyps; FESS functional endoscopic sinus surgery; NPS nasal polyp score; CS corticosteroids (oral or parenteral); SNOT-22 sino-nasal outcome test 22

difference might be a crucial point. Both specialist groups are aware of the need for better disease control when the standard of care fails and are supported by the results of the available clinical trials and real-life evidence. The propensity to a more conventional therapy might indeed reside in limitations about prescription of biologics, but this appears to be unlikely. Albeit anonymous, members of the societies participating in the survey mostly belong to the academic community. Thus, only marginal (or no) influence due to private-exclusive medical activity or North/Central Italy-limited geographical affiliation could be envisaged. On the other hand, the 2 groups of specialists could be differently worried about costs. Actually, objective outcome measures instead of patient-reported outcomes should be hopefully applied in combination to better assess "responders" to biologic therapies, especially in the view of the direct costs of these drugs. This opinion is indeed shared by both ENTs and AIs who almost homogenously replied with the appreciation of NPS and SNOT22 as the most important parameters to assess efficacy of biologics (Table 1 Q17). Biologic therapy is indeed more expensive, almost initially, than the standard of care. However, it then turns out to be more virtuous as able to lower indirect costs in the long term. Further, it highly reduces additional costs due to comorbidities, ie, because of the chronic use of corticosteroids.[14,15] As a conclusion, questions about when to start biologic therapy and who is the ideal candidate are still open, and regardless of the strict indications from regulatory agencies the different specialist groups might operate further selection base on personal views, prevalently nasal symptoms for ENTs, mainly CS use for AIs.

Finally, the survey had to point out the desirable organization to manage CRSwNP patients (Table 1 Q18-19). Both groups of specialists agreed that General Practitioners (GPs) should identify patients with CRSwNP and refer them to a hub center. Along with this, the unanimous (>90%) opinion was to favor the collaboration with GPs to support the emersion of the disease and facilitate the access to tertiary centers for severe patients. In addition, independently of the specialty all promote joint working and coordination of the different complementary skills in multidisciplinary teams for a properly accurate management, not differently from oncologic or lung fibrotic diseases. This aim is also recognized as a line of action of scientific societies (Table 1 Q20) by about one-third of the specialists. In addition, although not specifically addressed in the present survey, academia may play a leading role to provide a better awareness to future specialists about the different therapeutic opportunities in CRSwNP.

Summing up, this survey highlights the different viewpoints of the 2 groups of specialists usually managing patients affected by nasal polyps and points out their different clinical practice approaches (ie, medical vs surgical) and their attitude to address biological therapy. If the aim of a modern therapeutic management of CRSwNP is the reduction of steroids, this survey underlines how there is still a need to increase awareness about the risks of a prolonged use of these drugs especially in the surgical speciality. However, the shared opinion to strengthen collaboration and set up multidisciplinary teams paves the way towards a true holistic approach to these patients based on rational and reasoned considerations about the pro-and-cons of surgical and medical therapies.

Abbreviations

ACTH, AdrenoCorticoTropic Hormone; **AIs**, allergists/immunologists; **CRSwNP**, chronic rhinosinusitis with nasal polyps; **CS**, corticosteroids; **ENTs**, otorhinolaryngologists; **ESS**, Endoscopic Sinus Surgery; **FESS**, functional endoscopic sinus surgery; **GP(s)**, General Practitioner(s); **IAR**, Italian Academy of Rhinology; **IL**, interleukin; **NPS**, Nasal Polyp Score; **OCS**, oral CS; **PCS**, parenterally administered CS; **SIAAIC**, Società Italiana di Allergologia, Asma ed Immunologia Clinica; **SNOT-22**, Sinonasal Outcome Test 22.

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Availability of data and materials

Available on request.

Author's contribution

All the authors contributed to the protocol development. BD wrote the paper. BD, BL, PP, CFRM, RM and SC concepted the design, interpreted the data and revised the manuscript. All the Authors read and approved the final manuscript.

Ethics approval
This study was based on an anonymous survey; therefore, it did not require formal approval by an institutional review board nor written informed consent. Participation was voluntary and data remained anonymous.

Author consent for publication
All authors reviewed and approved the final version of the paper and gave their consent for publication in World Allergy Organization Journal.

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