

Rhinology Future Debates 2017 by EUFOREA: Novel treatments and surgical solutions in rhinology

1. INTRODUCTION

The *Rhinology Future Debates* is a unique clinician-orientated initiative organised by the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA). EUFOREA (www.euforea.eu) is an international non-profit organisation aiming at reducing the prevalence and burden of chronic respiratory diseases. EUFOREA brings together specialists from the entire healthcare system to create opportunities for innovative thinking and development of new techniques, devices, protocols and concepts for a patient-centred approach in prevention and optimal care.¹ Advocacy for integrated care pathways and implementation of precision medicine in respiratory diseases are key priorities of the EUFOREA team.^{2,3}

The Rhinology Future Debates have been organised for the first time in 2016 and aim at filling the gap between industry-investor meetings and clinicians working with patients affected by upper respiratory diseases. The debates deal with topics of innovation in diagnostic and therapeutic approaches, including novel devices, molecules and e-health tools and other innovative solutions.

The second Rhinology Future Debate took place in Brussels in December 2017 and brought together key experts in the field of respiratory diseases, industrial partners and patients for a discussion forum in the respiratory field. Debate topics in 2017 included (a) Real World Evidence data in AIT—What does it bring to us?, (b) Positioning Dymista in Allergic Rhinitis treatment (a separate report is available for this debate), (c) Nasal turbinate as therapeutic target in patients with turbinate-induced nasal symptoms, and (d) Lessons from biologicals in asthma for ENT physicians.

The debates were fully recorded and are available online (www.euforea.eu; www.rhinology-future.com) (Figure 1). This report summarises the key messages from each debate and further consolidates the discussion by providing additional evidences of the current state of the art in the field through literature reviewing.

2. REAL WORLD EVIDENCE DATA IN AIT—WHAT DOES IT BRING TO US?

Allergic diseases are still on the rise and represent a serious socioeconomic health problem. It is estimated that billions Euros may be saved annually with better and earlier intervention.⁴ Various symptomatic treatments such as antihistamines, leukotriene receptor antagonists and glucocorticoids are prescribed in allergic diseases. Despite their efficacy and symptom relief, these treatments have not proven to change the course of the disease. To date, allergen immunotherapy (AIT) holds curative potential for allergic diseases and therefore represent an important treatment strategy to tackle the global rise of allergies.

Allergen immunotherapy is based on the administration of slowly increasing doses of an allergen (eg grass, birch, HDM, etc), either subcutaneous (SCIT) or sublingual (SLIT), and which, after repetitive exposures, will desensitise the body and reduce the allergic response.⁵ The main mechanisms of desensitisation reside in the induction of peripheral T-cell tolerance, the promotion of the formation of

regulatory T cells, the change of antibody isotypes, among others.⁶ The promise of AIT is multiple and resides in its ability to control symptoms and modify the course of the disease, for instance by reducing new sensitisations, preventing the development of comorbidities, and by providing efficacy even after treatment cessation.⁷

Different Real World Evidences (RWE) studies on grass tablets and birch SLIT were presented to the panellists of the *Rhinology Future Debates*^{8,9} (Figure 2). These retrospective studies, included data from the German and French national health insurance system. The data consisted of the purchase history of AR symptomatic drugs and anti-asthmatic drugs in AIT group compared to non-AIT group.^{8,9} Although discrepancy was observed in absolute values, results from across all studies were associated with an increase in allergic rhinitis (AR) and asthma (AA) control, assessed by medication usage, as well as a decrease in asthma onset in patients undergoing AIT.^{8,9} The prevention of asthma with AIT is a promising achievement, acknowledged by all panellists, and which is in-line with the concept of precision medicine (PM) for airway diseases.¹⁰

2.1 The value of Real World Evidence (RWE) versus Randomised Controlled Trials (RCT) data for AIT

The panel further discussed the impact and relevance of RWE compared to RCT. All agreed that RCT are essential for the registration of new drugs, to determine both its efficacy and safety. However, the panel also admits that randomised controlled trials, with their high exclusion criteria, do not always reflect real-life conditions (eg patients with bad habits, non-adherent to treatment, smokers, comorbidities, etc).¹¹ On the other hand, RWE studies consist of large patient cohorts with long follow-up, reflecting real world conditions and thus overcoming RCT limitations in terms of demographics, lifestyle, compliance and comorbidity.¹² The panel agrees that RCT and RWE studies generate different type of data, with different aims, hypothesis and research question, which allow investigators to tackle a problem from very different perspectives. Because of the novelty of RWE studies, the panel also recognises that developing new standards for the evaluation RWE data would be highly needed.

An important part of the debate highlighted that current guidelines were based solely on RCT, and therefore on patients who are not representative of the global population. Indeed, a previous study showed that only 7.4% of patients seen in general practices could be enrolled for RCT.¹³ The same picture was reported in asthma¹⁴ and in severe asthma, with less than 10% of patients from the French COBRA cohort being eligible to RCTs.¹⁵ The guidelines should therefore be revised, to include the latest information obtained from RWE studies and the specific questions answered, in order to better meet the needs of patients with allergic diseases in real life.

2.2 Integration of mHealth for RWE studies

We are living in a new technological era, where each individual carries a powerful computer with themselves, that is a mobile phone. The mobile technology has the power to revolutionise the health system as we know it, by providing better integrated care path- way,¹⁶ by improving disease management³ and by generating large RWE data.¹⁷ The *Allergy Diary* app. is a good example of such mobile technology. With currently 18 000 users from 23 countries, the app was designed to monitor AR level of control and treatment (including AIT), and has already generated large amount of data.¹⁷⁻¹⁹ The future integration of new tools to the *Allergy Diary* app., such as the levels of local pollen and air pollution, will permit more in-depth analyses and precise correlation of the RWE data.

2.3 The future of AIT and RWE

The panellists expressed the need for better product characterisation. Indeed, many allergen formulations for AIT are currently available on the market, and a product-specific evaluation of products' efficacy is strictly recommended.^{7,20,21} The determination of reliable biomarkers to identify good AIT responders and to measure the success of AIT should be also further investigated.²²

Delivering personalised AIT to reduce the burden of allergy in each patient is the way forward. In that sense, RWE studies will help further stratifying patients, giving rise to new phenotypes, which in turn will permit to find the right treatment for the right patient, one of the pillar concepts of Precision Medicine. Finally, as AIT is sometimes perceived as expensive, RWE data could provide essential evidences to objectively evaluate the cost-effectiveness of the therapy.

FIGURE 1 Impressions of the debates



FIGURE 2 Summary of the debate: Real World Evidence data in AIT—What does it bring to us?

Summary

Real World Evidence data in AIT - What does it bring to us?

Real World Evidence (RWE) vs Randomised controlled trials (RCT)

- RCT are essential for the registration of new drugs, but do not reflect real-life conditions
- RWE provide complementary data that should be considered for future guidelines
- New standards should be created for the evaluation of RWE studies

Integration of mHealth for AIT

- Digital technologies such as mobile app. are excellent tools to obtain additional RWE data

Unmet needs in AIT

- Better characterization of the different AIT products available on the market (focus on efficacy)
- Identification of reliable biomarkers for the selection of AIT responders
- Additional evidences are needed to reveal the cost-effectiveness of AIT

3. NASAL TURBINATE AS THERAPEUTIC TARGET

The obstruction of the nasal cavity is, for many patients with allergic and idiopathic rhinitis, a problem which greatly affect their quality of life (eg sleeping disorders, snoring and sleep apnoea).^{23,24} The causes of the obstruction can be multiple, but often occurred from the swelling of the inferior turbinate which, when in contact with the nasal septum, create a blockage of the nasal airflow. In addition, the mucosa of the nasal turbinate might release mediators that are considered important in both allergic and non-allergic rhinitis.^{25,26} Different treatment strategies are currently available for reducing nasal congestion.²⁷

Depending on the aetiology of the congestion, medical treatments such as nasal steroid sprays, decongestant sprays or tablets, or other anti-inflammatory nasal or oral treatment might be effective. However, a significant percentage of patients with nasal turbinate hypertrophy might experience uncontrolled disease despite currently available medical treatment.²⁸

During the debates, two methods aiming at long-term efficacy were presented to the panel (Figure 3): the Medtronic microdebrider-assisted inferior turbinoplasty, which is a surgical technique to reduce the size of the turbinates,²⁹ and the Chordate Kinetic Oscillation Stimulation (KOS) system, which is a non-surgical technique filling the gap in between medical treatments and surgery.^{30,31}

The KOS system is a patient-friendly technique, described as easy, rapid and a safe procedure which does not require anaesthesia. After placing the catheter in the nostrils, a balloon will expand and generate kinetic oscillation. First results published with the KOS system have shown reduction in idiopathic rhinitis symptoms following the treatment, as determined by questionnaire symptom score (RQSS),³⁰ with effects lasting for at least 6 months, as determined by total vasomotor rhinitis score (TVRSS).³¹ The underlying mechanism of action still needs to be further explored, but it was suggested to be mediated, at least in part, through the modulation of the autonomic nervous system (ANS) (due to its effect on Heart Rate Variability³²). As previously described, the neurogenic inflammation plays an important role in the pathogenesis of idiopathic rhinitis.³³ Although promising, the panel agreed that more clinical data should be obtained to understand better the mechanisms behind KOS-driven relief of symptoms.

The microdebrider-assisted inferior turbinoplasty is a minimally invasive surgical technique with almost 20 years of clinical experience. This technique can be performed under local or general anaesthesia. It is used to directly reduce the volume of the submucosal vascular stromal tissue without damaging the overlying respiratory epithelium.²⁹ Therefore, mucociliary flow patterns are not disturbed, and protection, filtration and humidification processes continue postsurgery. Data from clinical studies have shown that 91% of patients remain symptoms-free (based on VAS score) 10 years after the surgery.³⁴ No major post-operative complications, such as bleeding, crusting, or atrophic rhinitis, were observed in adults or children.^{35,36} Using this technique, the long-term effect appears to be high, most likely due to the thorough removal of submucosal tissue and inflammatory cells.

3.1 Positioning KOS-system and microdebrider- assisted inferior turbinoplasty in the treatment of chronic nose congestion

It is worth emphasising that the two techniques presented target different types of patients at very different stages of disease development. If proven efficient, Chordate KOS-system would be positioned in the early phase of treatment of idiopathic rhinitis. However, additional studies are required to determine the phenotypes of patients that are more susceptible to respond positively to the treatment. Powered turbinoplasty surgery represents an efficient method to reduce oedematous tissue and provide relief to the patient, and as most surgical techniques, should be considered once most medical treatments in isolation have failed to reduce symptoms.

3.2 Towards patient-friendly approaches

The panellists recognised the effort of both companies to provide patient friendly approaches for the treatment of turbinate inflammation, which minimise the risks of post-operative adverse events like bleeding after a classic turbinectomy or the risk of excessive surgical removal of the inferior turbinate. Indeed, radical resection of the turbinates may lead to severe functional disturbances, and the development of a secondary atrophic rhinitis.³⁷ The patients from the panel were also very enthusiastic about the development and improvement of new patient-friendly approaches such as those techniques presented during this debate.

FIGURE 3 Summary of the debate: Nasal turbinate as therapeutic target

Nasal turbinate as therapeutic target

Treatment of chronic nose congestion Methods presented

- **Kinetic Oscillation Stimulation (KOS)-system** - *from Chordate*

- Non-surgical technique filling the gap between medical treatments and surgery

- Does not require anaesthesia

- Reduction of idiopathic rhinitis symptoms (>6 months)

Positioning: Early phase of idiopathic rhinitis treatment. Additional studies are required to determine the phenotypes of responders

- **Microdebrider-assisted inferior turbinoplasty** - *from Medtronic*

- Minimally invasive surgical technique

- Local or general anaesthesia

- 91 % of idiopathic rhinitis patients remain symptoms-free (+10 years after the surgery)

Positioning: Should be considered once most medical treatments in isolation have failed to reduce symptoms

- **Towards patient-friendly approaches**

Patients from the panel truly appreciated the development and improvement of new patient-friendly approaches such as those stated above

4. LESSONS FROM BIOLOGIC DRUGS IN ASTHMA FOR ENT DOCTORS

Several monoclonal antibody therapies (Figure 4), mainly targeting type 2 inflammation (in particular IgE or IL-5 for those on the market), have been shown to be effective in substantially reducing asthma exacerbations, be corticosteroid-sparing, improve lung function and/or improve quality of life in patients with severe asthma³⁸ that is resistant to optimal standard treatment based on inhaled corticosteroids and add-on drugs such as Long-Acting Beta-Agonists (LABAs) or leukotriene receptor antagonists. Evidence is accumulating that also in upper airway disease, such as chronic rhinosinusitis with nasal polyps (CRSwNP), these therapies are effective and can reduce nasal polyp (NP) size, improve the patients' QoL and positively impact lower airway outcome parameters.³⁹⁻⁴² Type 2 inflammation is seen in at least half of the severe asthma patients and is the predominant endotype in CRSwNP in Europe.⁴³ Different molecules such as immunoglobulin (Ig)E, IL-4, IL-5 or IL-13 are involved and have both specific or overlapping downstream effects on mast cell degranulation, eosinophil maturation and activation, goblet cell hyperplasia and others. Anti-IgE or omalizumab was the first approved biological treatment for patients with severe allergic asthma and is positioned at step 5 of the stepwise treatment approach according to the Global Initiative for Asthma (GINA).⁴⁴ For the IL-5 pathway, three different molecules have been evaluated in phase III clinical trials for patients with severe eosinophilic asthma: mepolizumab, reslizumab and benralizumab.⁴⁵⁻⁵¹ The first two monoclonal antibodies are targeting IL-5, and the latter one is targeting the IL-5 receptor alpha. All three reduce exacerbation rates and improve asthma control whereas only reslizumab (through intravenous route) showed clinically relevant changes in lung function parameters after 1 year of treatment.⁴⁹ As outlined in GINA 2017, mepolizumab is now available to treat severe eosinophilic asthma in the USA and

across Europe through monthly subcutaneous injections, while reslizumab is currently registered only for the intravenous administration. Benralizumab is the next anti-IL5 strategy that will be available, with very promising results upon subcutaneous injections every 8 weeks.⁵¹ The anti-IL-4R α or dupilumab also showed very significant effects notably on asthma exacerbation rate and improved lung function were observed.^{52,53}

FIGURE 4 Summary of the debate: Lessons from biologic drugs in asthma for ENT doctors

Summary

Lessons from biologic drugs in asthma for ENT doctors

Monoclonal antibodies for CRSwNP and/or asthma

Omalizumab (anti-IgE)

Mepolizumab (anti IL5)

Reslizumab (anti-IL5)

Benralizumab (anti IL5R α)

Mepolizumab (anti-IL4R α)

Need for biological treatments

- A significant number of patients with CRS and/or asthma suffers from uncontrolled disease
- Recurrence of NPs following surgery is common
- Long-term use of systemic corticosteroids can lead to potential side effects
-

Comorbid diseases

- Asthma and CRSwNP are two chronic respiratory diseases that often co-exist
- Treating simultaneously asthma and CRSwNP is needed to achieve optimal control of both diseases

Biomarkers as tools to identify the target population

- Because of the high cost of monoclonal antibodies, clinically applicable biomarkers are needed to identify the target population for each of these biologicals
- Potential biomarkers for type 2 inflammation includes: peripheral or local eosinophils, serum total IgE, serum periostin, fraction of exhaled nitric oxide (FeNO)

Positioning biologicals in daily treatment algorithms

- The position of biologicals into the CRSwNP treatment algorithms is still subject to debate
- Biologicals could be positioned after failure of maximal medical treatment including a course of oral corticosteroids. This implies that the patient should not have had necessarily a sinus surgery before

4.1 Need for biological treatment

The need for biological treatment is underlined by the fact that a significant number of patients with asthma and/or CRSwNP suffers from uncontrolled disease despite optimal standard management.^{54,55} A

separate phenotype of frequent asthma exacerbations among patients with severe asthma has been reported.^{56,57} A joint European-Canadian study showed high proportions of patients with asthma who report the need for acute treatment that can be either seeing a doctor for worsening of symptoms (38%-52%), emergency room visits (9%-36%) or overnight hospitalisation (3%-10%).⁵⁸ In line, approximately 40% of patients reports uncontrolled disease upon maximal medical and surgical treatment in a tertiary centre.⁵⁵ In addition, a study in the UK showed that the mean number of surgeries per patient (in the revision group) was 3.3 (range 2-30),⁵⁹ thus indicating that recurrence of NP following surgery is common. These studies clearly demonstrate the need for superior novel treatment strategies for both asthma and CRSwNP.

From the patient perspective, not only efficacy of a treatment is important but also its associated changes in quality of life. During the debate, one of the patients, who received biological treatment before, experienced a drastic improvement in quality of life but also acknowledged that likely not all patients respond to the same extent. Moreover, patients are very aware of potential side effects of the use of systemic corticosteroids, often their only option.⁶⁰ In general, most biologicals that were tested for asthma or CRSwNP showed improved disease control.³⁸

4.2 Co-morbid disease concept

Asthma and CRSwNP are two chronic respiratory diseases that often co-exist, hence called co-morbidities. Asthma is found in 70% of CRSwNP patients, and sinus disease is reported in 35%-60% of severe asthma patients according to European and American wide studies^{43,54,61} and chronic rhinosinusitis severity is associated with the need for asthma-related systemic corticosteroids.⁶² Therefore, there is the need to treat both conditions simultaneously to achieve optimal control of both asthma and CRSwNP. Recently, one study reported that half of uncontrolled asthmatics improved after sinus surgery.⁶³ CRSwNP patients with comorbid asthma were also assessed in the phase II trial with dupilumab. Asthma control significantly improved after dupilumab treatment and a modest but significant effect was observed on lung function (FEV1%pred).⁴¹ During the debate, it was highlighted that more effort is needed on evaluating upper and lower airway outcome parameters in clinical trials involving biologicals for, respectively, asthma and CRSwNP. Moving from local (inhalers) to systemic (biologicals) treatment again allows targeting of the “united” airways in patients with comorbid disease, which is the patient population that might benefit the most from these novel therapies.

4.3 Biomarkers as tools to identify the target population

In general, all panel members acknowledged that there is the need for clinically applicable biomarkers that identify the target population for each of these biologicals, especially because of the high cost of those therapies. Different candidate biomarkers for type 2 inflammation exist such as peripheral or local eosinophils, serum total IgE, serum periostin, fraction of exhaled nitric oxide (F_ENO).^{43,64,65} For patients with both allergic and eosinophilic phenotypes defined by increased serum total IgE (and specific IgE against at least one perennial allergen) and increased blood eosinophils, no data are available to decide which biological will be most effective: anti-IgE, anti-IL5 or anti-IL4Ralpha. During the debate, it was stated that a Belgian initiative (called “Predictumab”) was recently launched to investigate patients who fit the reimbursement criteria for both omalizumab and mepolizumab, in order to decide upon the best therapeutic strategy and to compare “face-to-face” these two biologicals in this prevalent subgroup of severe asthma patients. This kind of academic, randomised pragmatic trial, which is also considered in other European countries, should bring important information on theragnostics (predicting the therapeutic response) in severe asthma and should be developed for CRS and comorbid diseases.

Alternatively, patients might have increased eosinophils with normal total IgE levels and the other way around. For these patients, it is easier to choose the right biological treatment based on the blood eosinophil counts or serum total IgE levels. However, total IgE is helpful in deciding whether or not to give anti-IgE treatment (patient with low serum IgE responding less frequently), but for those with increased

total IgE, the level itself does not predict the impact of the treatment. Another interesting subgroup of patients who has not been studied in much detail yet are those patients with increased serum total IgE without clearly elevated serum-specific IgE levels against common aeroallergens. These non-atopic asthmatics might also benefit from anti-IgE treatment. One proof of concept study with omalizumab could already confirm this real-life observation,⁶⁶ as well as a study in CRSwNP and comorbid asthma showing no difference in the response rate between allergic and non-allergic asthmatics.³⁹

FeNO also has the potential of being a clinically applicable biomarker for prediction of the response to biological treatment due to its non-invasive nature.⁶⁷ A meta-analysis has shown that implementing FeNO in the management of adult asthmatics can reduce the frequency of asthma exacerbations.⁶⁸ It, however, did not affect day-to-day clinical symptoms and inhaled corticosteroid dose thereby limiting the universal use of FeNO to guide treatment decisions in asthmatics. Several studies have evaluated nasal NO in patients with CRS.^{67,69} The potential of this biomarker to guide disease management needs to be analysed in larger cohorts of patients.

Lastly, it was highlighted during the debate that even the presence of specific symptoms or comorbid disease, such as nasal polyps or asthma can be a biomarker to predict response to type 2 targeted therapies.

4.1 Positioning biologicals in daily treatment algorithms

It is important to clearly define what is considered as severe disease in asthma and CRSwNP. A clear distinction is made between difficult-to-treat asthma and severe asthma.⁷⁰ Difficult-to-treat asthmatics have uncontrolled disease that might be attributed to lack of patient adherence, improper use of medication or sustained exposure to allergens or pollutants among others.^{71,72} A similar reasoning was proposed when considering reasons for uncontrolled disease in upper airway disease, which might be due to patient-related, diagnosis-related or treatment-related factors.²⁸ Only when these factors are properly dealt with and uncontrolled disease remains, then a patient is classified as severe. It has been reported that severe disease is present in 3%-5% of asthma patients but it accounts for a disproportionate high amount of healthcare expenses.^{61,73,74} Exact numbers for CRSwNP have not been published but it is estimated that severe disease accounts for 5%-10% of CRSwNP patients.²⁸

The position of biologicals into the CRSwNP treatment algorithms will be subject to debate of the upcoming years. It was proposed that biologicals for CRSwNP could be positioned after failure of maximal medical treatment including a course of oral corticosteroids. This implies that the patient should not have had necessarily a sinus surgery before. Comparative studies are needed to provide more evidence for this concept. One study already showed that the need for surgery is reduced after treatment with mepolizumab at week 25 in CRSwNP patients requiring sinus surgery.⁷⁵

When deciding upon the right timing of surgery versus conventional medical or biological treatment, it is important to realise that timely sino-nasal treatment also impacts lower airway outcomes. A prospective study in UK showed that the prevalence of asthma is lower in patients who had sinus surgery within the first year after onset of the first CRS symptoms compared to patients who are operated after 5 years.⁷⁶ The same concept may also apply to biological treatment. Finding a consensus on the positioning of surgery and biologicals will be key in the near future, and different trials (eg the PolypESS in the Netherland and MACRO in the UK) are currently being conducted to provide this evidence.

4.2 Joining forces for a better respiratory health of the patient

Several proposals and initiatives that require joint action between different healthcare providers and academics were identified during the debate:

- There is the need for gaining more insights into the clustering of different type 2 airway diseases. A registry of patients with comorbid type 2 disease (including CRSwNP and asthma) containing clinical and biological information, including which patient respond to which treatment, is needed, and

EUFOREA might be ideally suited to coordinate such initiative. This will help to convince regulatory authorities of the united airway concept when imposing criteria for outcomes of clinical studies in patients with chronic respiratory diseases.

- Advocacy at different levels (geographical, political, multi-disciplinary) is needed. The patients' voice will be very helpful in identifying and describing the burden of chronic respiratory disease. This will assist the process of convincing regulatory authorities about the need for reimbursement for biological therapies. In addition, also pharmaceutical companies will have to put effort on bringing these therapies available at affordable prices.
- When thinking out of the box, one might imagine that for the patient, it is more attractive to have a monthly injection with a biological than the need to take inhaled or nasal corticosteroids twice a day. More data and drastic reductions in price are required before such a system can become reality in clinical practice.⁷⁷
- Globally still hundreds of patients with asthma die every day of asthma, although therapy with inhaled steroids can prevent asthma deaths. Making these "cheap" drugs accessible to every patient with asthma on a global scale should go hand in hand with precision medicine initiatives that are currently mainly focusing on patients with severe disease.

CONCLUSION

For the second time in Rhinology, a peer-to-peer scientific exchange with key experts in the field of rhinology and key medical colleagues from leading industries led to a brainstorming and discussion event on a number of hot issues in Rhinology. All panellists felt the discussions were extremely valuable, and a follow-up will be organised in September 2018.

CONFLICT OF INTEREST

C. Bachert is part of the advisory board and PI for Sanofi, Novartis, and Astra-Zeneca. J. Bousquet is on the advisory board for and/or has received consultancy fees from and/or has received honoraria for meeting lectures from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Sanofi-Aventis, Takeda, Teva, and Uriach; and has shares in Kyomed. G. Joos reports grants and personal fees from AstraZeneca, grants from Boehringer Ingelheim, grants from Chiesi, grants and personal fees from GlaxoSmithKline, grants and personal fees from Novartis, personal fees from Teva, outside the submitted work. All fees were paid to the Ghent University and Ghent University Hospital. O. Pfaar reports grants and personal fees from ALK-Abelló, grants and personal fees from Allergopharma, grants and personal fees from Stallergenes Greer, grants and personal fees from HAL Allergy Holding B.V./HAL Allergie GmbH, grants and personal fees from Bencard Allergie GmbH/Allergy Therapeutics, grants and personal fees from Lofarma, grants from Biomay, grants from Nuvo, grants from Circassia, grants and personal fees from ASIT Biotech Tools S.A., grants and personal fees from Laboratorios LETI/LETI Pharma, personal fees from Novartis Pharma, personal fees from MEDA Pharma, grants and personal fees from Anergis S.A., personal fees from Mobile Chamber Experts (a GAZLEN Partner), personal fees from Pohl-Boskamp, personal fees from Indoor Biotechnologies, grants from Glaxo Smith Kline, all outside the submitted work. D. Price has board membership with Aerocrine, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Mundipharma, Napp, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals; consultancy agreements with Ammirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Napp, Novartis, Pfizer, Teva Pharmaceuticals, Thera-vance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from Aerocrine, AKL Research and Development Ltd, AstraZeneca, Boehringer Ingelheim, British Lung Foundation, Chiesi,

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AUTHORS' CONTRIBUTION

BP, SS, WF and PWH have written the manuscript. CB, JB, PWH, OP, DP, EP and GS have contributed to the debate "Real World Evidence data in AIT—What does it bring to us?" CB, WF, PWH, EP, GS, AS and AW have contributed to the debate "Nasal turbinate as therapeutic target." PWH, CB, WF, GJ, RL, CP, GS and DP have contributed to the debate "Lessons from biologicals in asthma for ENT physicians." All authors have reviewed the manuscript.

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