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This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/158524> since

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Received: 2014.06.17
Accepted: 2014.07.22
Published: 2014.11.04

A Survey of Clinical Features of Allergic Rhinitis in Adults

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Data Interpretation D
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Source of support: Self financing

Background: Allergic rhinitis (AR) has high prevalence and substantial socio-economic burden.

Material/Methods: The study included 35 Italian Centers recruiting an overall number of 3383 adult patients with rhinitis (48% males, 52% females, mean age 29.1, range 18–45 years). For each patient, the attending physician had to fill in a standardized questionnaire, covering, in particular, some issues such as the ARIA classification of allergic rhinitis (AR), the results of skin prick test (SPT), the kind of treatment, the response to treatment, and the satisfaction with treatment.

Results: Out of the 3383 patients with rhinitis, 2788 (82.4%) had AR: 311 (11.5%) had a mild intermittent, 229 (8.8%) a mild persistent, 636 (23.5%) a moderate-severe intermittent, and 1518 (56.1%) a moderate-severe persistent form. The most frequently used drugs were oral antihistamines (77.1%) and topical corticosteroids (60.8%). The response to treatment was judged as excellent in 12.2%, good in 41.3%, fair in 31.2%, poor in 14.5%, and very bad in 0.8% of subjects. The rate of treatment dissatisfaction was significantly higher in patients with moderate-to-severe AR than in patients with mild AR ($p < 0.0001$). Indication to allergen immunotherapy (AIT) was significantly more frequent ($p < 0.01$) in patients with severe AR than with mild AR.

Conclusions: These findings confirm the appropriateness of ARIA guidelines in classifying the AR patients and the association of severe symptoms with unsuccessful drug treatment. The optimal targeting of patients to be treated with AIT needs to be reassessed.

MeSH Keywords: **Administration, Sublingual • Desensitization, Immunologic • Patient Compliance • Rhinitis, Allergic, Seasonal**

Full-text PDF: <http://www.medscimonit.com/abstract/index/idArt/891206>

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Background

Allergic diseases show a continuous increase worldwide, with a major role for allergic rhinitis (AR), which currently has a prevalence up to 40%, but with significant differences in urban and rural environments (higher in rural areas) [1–3]. Among the possible explanations of such increase, childhood infections and exposure to certain microbial antigens seem to present a strong negative correlation with allergies, giving birth to the “Hygiene Hypothesis” as a possible cause of the rise of the allergic burden in Western countries [4]. The importance of AR is further highlighted by its substantial social and economic costs [5,6], and to the impairment of patient’s daily activities and productivity [7–9]. AR was long classified as seasonal or perennial according to its duration, related for the former to sensitization to pollens or moulds and for the latter to house dust mites or animal epithelia, but the Allergic Rhinitis and its Impact on Asthma (ARIA) document, endorsed by the World Health Organization and published in 2001, introduced a new classification of AR based on duration and severity of symptoms [10]. ARIA distinguished intermittent AR (IAR), defined by symptoms occurring for <4 days/week for <4 consecutive weeks, from persistent AR (PER), defined by symptoms occurring for >4 days/week for >4 consecutive weeks. Moreover, a severity scale of mild to moderate-severe symptoms (based on the AR impact on activities and quality of life) was proposed [10]. The ARIA classification was validated in 2003 [11] and is currently widely used worldwide. A multicenter study, named SURF (Survey of Rhinitis Features), was aimed at addressing the phenotypes of AR in a large population of children and adults. The results in children were already reported [12] and here we present the data concerning the adult population.

Material and Methods

The SURF study included 35 centers throughout Italy, recruiting a total of 3383 adult patients presenting with rhinitis (48% males, 52% females, mean age 29.1 years, range 18–45 years). For each patient, the attending physician had to fill in a standardized questionnaire, which was previously validated by the Federazione delle Società Italiane di Immunologia, Allergologia e Immunologia Clinica (IFIACI). The issues assessed by the questionnaire were: ARIA classification of rhinitis, kind and duration of symptoms, results of skin prick tests (SPT), allergen identified as clinically relevant, co-morbidities, treatment plan, response to treatment, satisfaction with the treatment, and feasibility of allergen immunotherapy (AIT). The continuous parameters (based on numeric values) were reported as mean, median, and standard deviation, while the categorical parameters (based on values that function as categories) were reported as contingency tables. Data were statistically analyzed by the chi-squared test for 2 data tables and by

Table 1. Allergens eliciting a positive skin prick test (SPT) and their clinical relevance.

Allergen	Number of positive SPT	% of total according to clinical relevance
Grass pollen	1470	42.6%
House dust mites	1266	32.2%
Parietaria pollen	845	23.9%
Olive pollen	706	10.4%
Cypress pollen	625	11.4%
Betulacee pollen	560	10.2%
Animal epithelia	432	4.7%
Compositae pollen	318	3.6%
Other pollens	191	1.6%
Alternaria spores	127	1.5%
Foods	23	0.5%
Other allergens	798	9.3%

log-linear models for more than 2 data tables. A *p* value lower than 0.05 was considered significant. Correlations were analyzed by linear regression.

Results

Out of the 3383 patients with rhinitis, 2788 (82.4%) had AR: of these, 311 (11.5%) had a mild intermittent, 229 (8.8%) had mild persistent, 636 (23.5%) had moderate-severe intermittent, and 1518 (56.1%) had moderate-severe persistent form; in 130 cases the data was missing. The rate of patients with persistent rhinitis was significantly higher than that of intermittent rhinitis ($p < 0.01$). There were 595 (17.6%) patients who had other kind of rhinitis, the most common being idiopathic rhinitis (251 cases), non-allergic rhinitis with eosinophilia (NARES, 123 cases), occupational rhinitis (68 cases), and infective rhinitis (58 cases). The mean duration of rhinitis was 7.0 ± 7.2 years.

Concerning the sensitization, Table 1 shows all the allergens eliciting positive SPT and their clinical relevance as assessed by patient history. Table 2 reports the identified co-morbidities. Patients with no co-morbidities had a higher frequency of mild AR, while patients with 2 or more co-morbidities had a higher frequency of moderate-to-severe AR. The most frequently used drugs were oral antihistamines (2150 patients, 77.1%) and topical corticosteroids (1695 patients, 60.8%), followed by anti-leukotrienes (412, 14.8%), anti-asthmatic drugs (392 patients, 14.1%), topical antihistamines (354, 12.7%), oral

Table 2. Reported co-morbidities in patients with AR.

Co-morbidity	Number of cases (%)	
Conjunctivitis	1496	(53.7%)
Asthma	1053	(37.8%)
Sinusitis	382	(13.7%)
Sleep disturbances	228	(8.2%)
Nasal polyps	129	(4.6%)
Oral allergy syndrome	52	(1.9%)
Adenoids/tonsils hypertrophy	48	(1.7%)
Urticaria	43	(1.5%)
Dermatitis	36	(1.3%)
Cough	37	(1.3%)
Anosmia	7	(0.3%)
Recurrent respiratory infections	13	(0.5%)
Other	318	(11.4%)

corticosteroids (177, 6.3%), nasal decongestants (117, 4.2%), chromones (78, 2.8%), and others (587, 21.1%). Response to treatment was available in 2760 completed questionnaires; it was judged as excellent in 304 cases (12.2%), good in 1027 (41.3%), fair in 775 (31.2%), poor in 359 (14.5%), and very bad in 19 (0.8%). Satisfaction with treatment was judged as very satisfactory in 340 cases (13.7%), satisfactory in 1425 (57.3%), unsatisfactory in 703 (28.3%), and very unsatisfactory in 18 (0.7%). The rate of dissatisfaction was significantly higher in patients with moderate-to-severe AR than in patients with mild AR ($p < 0.0001$). Figure 1 shows the correlation between response to treatment and patient satisfaction; this correlation was significant ($p < 0.01$). Data on the viability of AIT showed that in 2024 cases (73.8%) the treatment was considered indicated. This concerned 144 patients (46.5%) with mild intermittent, 412 patients (65.4%) with mild persistent, 201 patients (85.2%) with moderate-to-severe intermittent, and 1200 patients (80.8%) with moderate-to-severe persistent AR. Indication to AIT was significantly more frequent ($p < 0.01$) in patients with severe than with mild AR. Considering the 2 major causes, AIT was viewed as feasible in 28.6% of patients allergic to grass pollen and in 22.7% of patients allergic to dust mites.

Discussion

The introduction of the concept of disease phenotyping was very important, because phenotypization may significantly

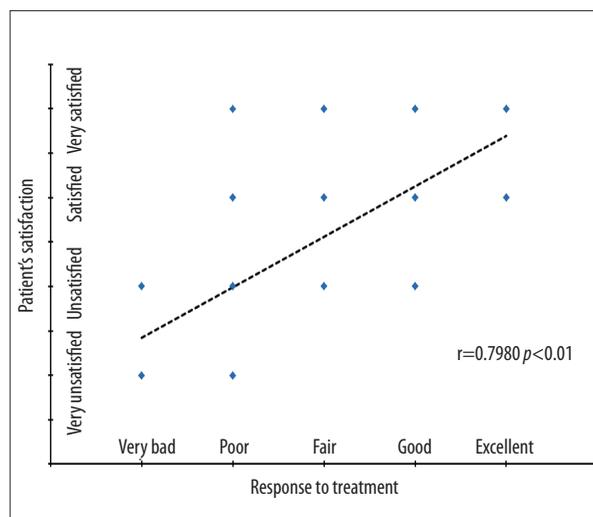


Figure 1. Correlation between patient satisfaction and response to therapy.

influence the choice of diagnostic tests, predict the response to specific treatments, and suggest the long-term prognosis [13]. In the past, different clinical phenotypes were proposed, based on the period of occurrence of symptoms, defining the 2 forms of seasonal (the old “hay fever”) or perennial rhinitis [14], and on the predominance of sneezing and nasal discharge (sneezer/runners) or nasal blockage (blockers) [15]. However, the ARIA classification redefined the criteria for identifying the phenotype of patients with AR, by the duration – intermittent or persistent – regardless of the season, and the severity of symptoms with their impact in daily life, classified as mild and moderate-to-severe [9]. Recent studies showed that the ARIA severity classification clearly discriminates the impact of AR in all domains of quality of life and categorized symptom score [16], and that the ARIA classification was correlated with the nasal cytology, which showed different cell types and counts according to different severity, with higher counts of mast cells and lymphocyte/plasma cells in moderate-to-severe AR [17]. The SURF study was aimed at investigating the features of AR in a large population of children and adults. Several issues were assessed for their possible association with AR feature, including the results of SPT, the allergen identified as clinically relevant, the co-morbidities, the kind of treatment, the response to treatment, the satisfaction with the treatment, and the feasibility of immunotherapy. Immunotherapy is the only available treatment working on causes of allergy, being able to reduce the immunological and clinical reactivity to the responsible allergen [18]. The findings must be discussed with the data, when available, from the literature. Concerning the culprit allergens, grass pollen and house dust mites were confirmed to be the 2 major causes of AR [19,20], with prevalence of moderate-to-severe disease and of persistent forms. This confirms the suitability of the ARIA classification, because the previous classification in seasonal and perennial forms would

have missed the clinical importance according to the duration for grass-pollen. Co-morbidities were more common in patients with moderate/severe AR, with the highest rate for conjunctivitis, which was present in 54% of subjects, defining the picture of rhinoconjunctivitis, which occurs very frequently in patients with AR [21]. According with the literature, the other 2 most common co-morbidities were asthma (~38%) and sinusitis (~14%) [22–26]. In treatment of AR, the most frequently used drugs were oral antihistamines (77%) and topical corticosteroids (61%), in accordance with the ARIA guidelines, which state the adequacy of these treatments based on the evidence from controlled trials [10,22]. In contrast, patient satisfaction with prescribed treatments is scantily investigated, despite its importance in compliance to treatment [27]. A study on adult allergic patients assessed satisfaction with antihistamines, showing that the second-generation agents were considered by both the patients and the physicians to be effective and well-tolerated [28]. However, a recent survey on adult patients with AR, mostly treated with antihistamines and nasal corticosteroids, found that only 33.5% were satisfied with treatments; female gender, presence of co-morbidities, and severity of AR were factors significantly associated with treatment dissatisfaction [29]. In the present study, the response to treatment, as assessed by the physician, was judged as excellent in 12%, good in 41.3%, fair in 31.2%, poor in 14.5%, and very bad in 0.8% of cases. Satisfaction with treatment was judged as very satisfactory in 14%, satisfactory in 57%, unsatisfactory in 28.3%, and very unsatisfactory in 0.7% of cases. Response to treatment and satisfaction were significantly correlated. As expected, dissatisfaction was significantly higher in patients with moderate-to-severe AR than in patients with mild AR ($p < 0.0001$). This raises the issue of severe AR uncontrolled by drug treatment, which includes the form currently defined as severe chronic upper airway disease (SCUAD) [30]. In this clinical form, a multifactorial etiology may underlie the development of sinus-nasal inflammation not responsive to drugs [31].

Concerning the feasibility of AIT, our data show that in 2024 cases (74%), the treatment was considered increasingly indicated according to severity, ranging from 46% in mild intermittent to 81% in moderate-to-severe persistent AR. Focusing on the 2 major causes of AR, AIT was viewed as feasible in 28% of patients allergic to grass pollen and in 23% of patients allergic to dust mites. Comparing the findings from the present study with those from the previous part of the SURF study on children [12] is of clear interest. Resulted of all the examined features were comparable, with the exception of the presence of adenoids/tonsils hypertrophy, which was significantly more frequent in children than in adults (6.6% vs. 1.7, $p < 0.0001$). This is quite obvious, because this pathology is typically pediatric, but recent immunological data suggest the need to reconsider the approach to hypertrophy of adenoids/tonsils (which are immunological organs belonging to the Waldeyer's ring),

which is mostly based on surgical removal. In fact, it was reported that hypertrophic adenoids of allergic children undergoing sublingual immunotherapy (SLIT) have the typical response to the specific allergen administered by the treatment, thus suggesting we reconsider their immunological role [32].

Conclusions

AIT was judged as appropriate in 28.6% of patients allergic to grass pollen and in 22.7% of patients allergic to dust mites, while the ranking was reversed (31.3% of mite-allergic patients and 28.6% of grass pollen-allergic patients), but not significantly different, in the pediatric part of the SURF study [12]. The perception of a greater indication of AIT for the more severe AR is in agreement with specific studies demonstrating the ability of AIT to work in drug-resistant AR. In particular, in a controlled trial on 410 AR patients unresponsive to drug treatment, a good response to subcutaneous immunotherapy was reported [33], and such an outcome was recently confirmed in a real-life study using SLIT by 5-grass pollen tablets [34]. Therefore, targeting the patients with severe AR not controlled by drugs needs the attention of the specialists involved in diagnosis and treatment of AR to provide to patients with an effective therapy.

Acknowledgements

The authors acknowledge the Adult SURF Study Group: Monica Albano, Lucrezia Allegretti, Giorgia Altomonte, Andrea Antico, Antonio Arena, Renato Ariano, Pasquale Arigliano, Paola Arrigoni, Augusto Arsieni, Arianna Aruanno, Paola Bernardis, Adriano Berra, Lucia Billeri, Arrigo Boccafogli, Franco Borghesan, Linda Borgonovo, Paolo Borrelli, Marina Braga, Megan Bresciani, Guglielmo Bruno, Massimo Bruno, Domenico Bruzzese, Alessandro Buonomo, Gianni Cadario, Paolo Candi, Renato Cantone, Stefania Capretti, Anna Carabelli, Rino Caramazza, Annamaria Carbonara, Aurelia Carosso, Cristiano Caruso, Riccardo Caruso, Giuseppe Casino, Stefano Casotto, Francesco Castellano, Gloria Castiglioni, Lidia Cecchi, Francesca Chiarini, Fulvia Chieco Bianchi, Giuseppe Cinquepalmi, Massimo Cinquini, Silvia Cocchi, Caterina Colangelo, Giselda Colombo, Gabriele Cortellini, Stefano Crescioli, Nunzio Crimi, Francesco Cucinelli, Antonio Curcio, Marina Cutajar, Gennaro D'Amato, Raffaele de Palma, Giuseppe Del Pozzo, Fabrizio Della Torre, Pantalea Delle Donne, Fabio Di Claudio, Elisabetta di Leo, Gabriele di Lorenzo, Giuseppe Di Marco, Paola Di Rocco Cesinaro, Maria Distaso, Vito Ditta, Francesca Emiliani, Giuseppe Ermini, Susanna Facchetti, Alessandro Farsi, Elisabetta Favero, Ilenia Folletti, Maurizio Franchini, Enrico Gammeri, Sebastiano Gangemi, Federica Gani, Domenico Gargano, Francesco Giannoccaro, Giuseppina Giro, Dario Graceffa, Giacomo Greco, Gabriella Guarnieri, Antonino Ingrassia, Rossella Intravaia, Loredana

Iorno, Simona la Piana, Luigi La Rosa, Rocco Laddaga, Carlo Lamanna, Massimo Landi, Luigi Leonetti, Stefania Leto Barone, Gennaro Liccardi, Fabio Lodi-Rizzini, Laura Losappio, Giacomo Lucivero, Donatella Macchia, Francesco Madonna, Enrico Maffezzoni, Vincenzo Mancuso, Roberto Manetti, Giacomo Manfredi, Silvia Manzoni, Maria Marcotulli, Fulvia Marengo, Gianna Maria D'Ippolito, Simonetta Masieri, Andrea Matucci, Marina Mauro, Antonietta Melchiorre, Francesco Menzella, Corrado Micucci, Sabrina Mietta, Manlio Milanese, Stefano Minetti, Ambra Modiano, Stella Modica, Marcello Moinaghi, Michela Mondino, Maria Marcotulli, Giorgio Munno, Lionello Muratore, Francesco Murzilli, Rosalba Natoli, Franco Nebiolo, Eustachio Nettis, Elisa Olivieri, Alessandro Pannofino, Mauro Parpanesi, Vincenzo Patella, Angelica Petraroli, Silvia Peveri, Marta Piantanida, Maria Pietrafesa, Elena Pinter, Stefano Pizzimenti, Luana Pompilio, Valeria Porcaro, Paolo Prandini, Valerio Pravettoni, Salvatore Pugliese, Carlo Quarta, Cristina

Quecchia, Oliviero Quercia, Roberto Quilleri, Alberto Raie, Salvatore Randazzo, Erminia Ridolo, Giovanni Rolla, Antonino Romano, Federica Rota, Marina Russello, Annalisa Santucci, Eleonora Savi, Giovanna Scarantino, Sergio Scarpa, Domenico Schiavino, Angelo Rito Sciacca, Paolo Serra, Maurizio Severino, Alberto Sirena, Giuseppe Spadaro, Francesca Spina, Mario Sugamiele, Giordano Taddeo, Maria Teresa Ventura, Sergio Testi, Enrico Tombetti, Cinzia Tosoni, Massimo Triggiani, Salvatore Tripodi, Elisabetta Vallerani, Arnoldo Vargiu, Attilio Varricchio, Marcello Zambito, Mario Zanforlin, Giovanna Zanoni.

Conflicts of interests

Franco Frati and Ilaria Dell'Albani are employees of Stallergenes Italy. Cristoforo Incorvaia is a scientific consultant for Stallergenes Italy. The other authors have no conflicts of interest that are directly relevant to the content of the study.

References:

1. Asher MI, Montefort S, Björkstén B et al: ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet*, 2006; 368: 733–43
2. Schwindt CD, Settignano R: Allergic rhinitis (AR) is now estimated to affect some 1.4 billion people globally and continues to be on the rise. Editorial. *Am J Rhinol Allergy*, 2012; 26(Suppl.1): S1
3. Quercia O, Incorvaia C, Puccinelli P et al: Prevalence of allergic disorders in Italy: the Cotignola population study. *Eur Ann Allergy Clin Immunol*, 2012; 44: 5–11
4. Prokopakis E, Vardouniotis A, Kawauchi H et al: The pathophysiology of the hygiene hypothesis. *Int J Pediatr Otorhinolaryngol*, 2013; 77: 1065–71
5. Reed SD, Lee TA, McRory DC: The economic burden of allergic rhinitis: a critical evaluation of the literature. *Pharmacoeconomics*, 2004; 22: 345–61
6. Blaiss MS: Allergic rhinitis: direct and indirect costs. *Allergy Asthma Proc*, 2010; 31: 375–80
7. Stull DE, Schaefer M, Crespi S, Sandor DW: Relative strength of relationship of nasal congestion and ocular symptoms with sleep, mood and productivity. *Curr Med Res Opin*, 2009; 25: 1785–92
8. Engel-Yeger B, Engel A, Kessel A: Differences in leisure activities between children with allergic rhinitis and healthy peers. *Int J Pediatr Otorhinolaryngol*, 2010; 74: 1415–18
9. de la Hoz Caballer B, Rodriguez M, Fraj J et al: Allergic rhinitis and its impact on work productivity in primary care practice and a comparison with other common diseases: the Cross-sectional study to evaluate work productivity in allergic rhinitis compared with other common diseases (CAPRI) study. *Am J Rhinol Allergy*, 2012; 26: 390–94
10. Bousquet J, van Cauwenberge P, Khaltaev N, ARIA Workshop Group: World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol*, 2001; 108(Suppl.5): 147–334
11. Demoly P, Allaert FA, Lecasle M, Bousquet J, PRAGMA: Validation of the classification of ARIA (allergic rhinitis and its impact on asthma). *Allergy*, 2003; 58: 672–75
12. Zicari AM, Indinnimeo L, De Castro G et al: Pediatric SURF Study Group. A survey on features of allergic rhinitis in children. *Curr Med Res Opin*, 2013; 29: 415–20
13. Corren J: Asthma phenotypes and endotypes: an evolving paradigm for classification. *Discov Med*, 2013; 15: 243–49
14. Weeke ER: Epidemiology of hay fever and perennial allergic rhinitis. *Monogr Allergy*, 1987; 21: 1–20
15. Khanna P, Shah A: Categorization of patients with allergic rhinitis: a comparative profile of “sneezers and runners” and “blockers”. *Ann Allergy Asthma Immunol*, 2005; 94: 60–64
16. Valero A, Muñoz-Cano R, Sastre J et al: The impact of allergic rhinitis on symptoms and quality of life using the new criterion of ARIA severity classification. *Rhinology*, 2012; 50: 33–36
17. Gelardi M, Incorvaia C, Fiorella ML et al: The clinical stage of allergic rhinitis is correlated to inflammation as detected by nasal cytology. *Inflamm Allergy Drug Targets*, 2011; 10: 472–76
18. Bousquet J, Lockey RF, Malling HJ: WHO Position Paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. *Allergy*, 1998; 53(Suppl.44): 4–30
19. Valero A, Justicia JL, Antón E et al: Epidemiology of allergic rhinitis caused by grass pollen or house dust mites in Spain. *Am J Rhinol Allergy*, 2011; 25: 123–28
20. Izquierdo-Dominguez A, Valero AL, Mulla J: Comparative analysis of allergic rhinitis in children and adults. *Curr Allergy Asthma Rep*, 2013; 13: 142–45
21. Phipatanakul W: Allergic rhinoconjunctivitis: epidemiology. *Immunol Allergy Clin North Am*, 2005; 25: 263–68
22. Bousquet J, Khaltaev N, Cruz AA et al: Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update (in collaboration with the World Health Organization, GA2LEN and AllerGen). *Allergy*, 2008; 63(Suppl.86): 8–160
23. Kariyawasam HH, Rotiroti G: Allergic rhinitis, chronic rhinosinusitis and asthma: unravelling a complex relationship. *Curr Opin Otolaryngol Head Neck Surg*, 2013; 21: 79–86
24. Hellings PW, Prokopakis EP: Global airway disease beyond allergy. *Curr Allergy Asthma Rep*, 2010; 10: 143–49
25. Hellings PW, Fokkens WJ, Akdis C et al: Uncontrolled allergic rhinitis and chronic rhinosinusitis: where do we stand today? *Allergy*, 2013; 68: 1–7
26. Georgalas C, Vlastos I, Picavet V et al: Is chronic rhinosinusitis related to allergic rhinitis in adults and children? Applying epidemiological guideline for causation. *Allergy*, 2014; 69: 828–33
27. Pinto RZ, Ferreira ML, Oliveira VC et al: Patient-centred communication is associated with positive therapeutic alliance: a systematic review. *J Physiother*, 2012; 58: 77–87
28. De Vos C, Mitchev K, Pinelli ME et al: Non-interventional study comparing treatment satisfaction in patients treated with antihistamines. *Clin Drug Invest*, 2008; 28: 221–30
29. Ciprandi G, Incorvaia C, Scurati S et al: Satisfaction with allergy treatments depends on symptoms severity but not on allergen specificity in patients with allergic rhinitis. *Int J Immunopathol Pharmacol*, 2012; 25: 307–9
30. Bousquet J, Bachert C, Canonica GW et al: Extended Global Allergy and Asthma European Network, World Allergy Organization and Allergic Rhinitis and its Impact on Asthma Study Group. Unmet needs in severe chronic upper airway disease (SCUAD). *J Allergy Clin Immunol*, 2009; 124: 428–33

31. Prokopakis EP, Vlastos I, Ferguson BJ et al: SCUAD and chronic rhinosinusitis. Reinforcing hypothesis driven research in difficult cases. *Rhinology*, 2014; 52: 3–8
32. Masieri S, Trabattoni D, Incorvaia C et al: A role for Waldeyer's ring in immunological response to allergens. *Curr Med Res Opin*, 2014; 30: 203–5
33. Frew AJ, Powell RJ, Corrigan CJ, Durham SR, UK Immunotherapy Study Group: Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhino-conjunctivitis. *J Allergy Clin Immunol*, 2006; 117: 319–25
34. Pastorello EA, Losappio L, Milani S et al: 5-grass pollen tablets achieve control in patients with seasonal allergic rhinitis unresponsive to drug: a real-life study. *J Asthma Allergy*, 2013; 6: 127–33