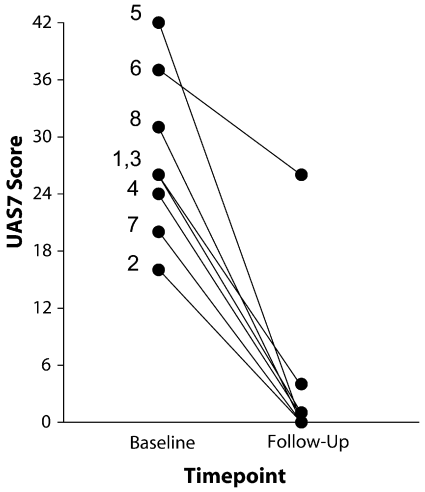

FIG 1. Response of patients (numbers from 1-8) to omalizumab therapy.

double-blind, cross-over, comparative effectiveness trials[11] are still needed to determine whether omalizumab works better than third-line and other fourth-line treatment options. Such research could possibly provide a sound scientific basis for promoting omalizumab to the level of a third-line recommendation in future evidence-based treatment guidelines.

We thank Michael Hanna, PhD, Mercury Medical Research & Writing, for providing medical writing and data visualization services.

Markus Magerl, MD[a]
Petra Staubach, MD[b]
Sabine Altrichter, MD[a]
Elena Ardelean, MD[a]
Karoline Krause, MD[a]
Martin Metz, MD[a]
Karsten Weller, MD[a]
Marcus Maurer, MD[a]

From [a]the Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité–Universitätsmedizin Berlin, Berlin; and [b]the Department of Dermatology, Universitätsmedizin Mainz, Mainz, Germany. E-mail: marcus.maurer@charite.de.

Disclosure of potential conflict of interest: M. Maurer is or recently was a speaker and/or advisor for Almirall Hermal, Bayer, Schering Pharma, Biofrontera, Essex Pharma, Genentech, JADO Technologies, Jerini, Merckle Recordati, Novartis, Sanofi Aventis, Schering-Plough, Leo, MSD, Merck, Shire, Symbiopharm, UCB, and Uriach M. Magerl is or recently was a speaker for Almirall, Essex Pharma, and Jerini/Shire. M. Metz has been a speaker for Uriach and Essex Pharma. M. Metz is or recently was a speaker for Essex, MSD, Uriach, Merckle Recordati, Novartis. S. Altrichter, E. Ardelean, K. Krause, P. Staubach, and K. Weller declare no conflict of interests.

REFERENCES

1. Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Giménez-Arnau AM, et al. EAACI/GA^{2}LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. Allergy 2009;64:1417-26.
2. Kaplan AP. Chronic urticaria: pathogenesis and treatment. J Allergy Clin Immunol 2004;114:465-74.
3. Gaig P, Olona M, Muñoz Lejarazu D, Caballero MT, Domínguez FJ, Echechipia S, et al. Epidemiology of urticaria in Spain. J Invest Allergol Clin Immunol 2004;14:214-20.
4. Maurer M, Ortonne J-P, Zuberbier T. Chronic urticaria: an internet survey of health behaviors, symptom patterns and treatment needs in European adult patients. Br J Dermatol 2009;160:633-41.
5. Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Giménez-Arnau AM, et al. EAACI/GA^{2}LEN/EDF/WAO guideline: management of urticaria. Allergy 2009;64:1427-43.
6. Barlow RJ, Black AK, Greaves MW. Treatment of severe chronic urticaria with cyclosporine A. Eur J Dematol 1993;3:273-5.
7. Scheinfeld N. Omalizumab: a recombinant humanized monoclonal IgE-blocking antibody. Dermatol Online J 2005;11:2.
8. Młynek A, Zalewska-Janowska A, Martus P, Staubach P, Zuberbier T, Maurer M. How to assess disease activity in patients with chronic urticaria? Allergy 2008;63:777-80.
9. Spector SL, Tan RA. Advances in allergic skin disease: omalizumab is a promising therapy for urticaria and angioedema. J Allergy Clin Immunol 2009;123:273-4.
10. Kaplan AP, Joseph K, Maykut RJ, Geba GP, Zeldin RK. Treatment of chronic autoimmune urticaria with omalizumab. J Allergy Clin Immunol 2008;122:569-73.
11. Sox HC, Greenfield S. Comparative effectiveness research: a report from the Institute of Medicine. Ann Intern Med 2009;151:203-5.

Available online August 5, 2010.
doi:10.1016/j.jaci.2010.05.047

Uncontrolled allergic rhinitis during treatment and its impact on quality of life: A cluster randomized trial

To the Editor:

The treatment of allergic rhinitis is now well established. Although the majority of patients present with controlled symptoms during treatment, many are still uncontrolled, leading to the concept of severe chronic upper airway disease (SCUAD).[1] Patients with SCUAD are likely to have an impaired quality of life affecting social functioning, sleep, school results, and/or work performance. However, this concept requires validation.

As a pilot study to investigate SCUAD, the prevalence of uncontrolled rhinitis after 2 weeks of treatment and its impact on quality of life and work productivity were assessed on the basis of a *post hoc* analysis carried out from a published pragmatic, cluster-randomized trial.[2]

Methods have been described[2] and are summarized in this article's Online Repository at www.jacionline.org. For the treatment of patients with allergic rhinitis during the grass pollen season, allergy or ears, nose and throat specialists were randomized to follow a strategy based on Allergic Rhinitis and its Impact on Asthma (ARIA)[3] or free-choice treatment, according to their practice. The study was performed in France.

Outcomes included a Rhinitis Total Symptom Score (RTSS4: nasal obstruction, pruritus, sneezing, and rhinorrhea) monitored daily for 14 days using a diary. The self-administered disease-specific Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ; 28 questions),[4] the Allergy-Specific Work Productivity and Impairment questionnaire (WPAI-AS),[5] and a visual analog scale (VAS) for the global evaluation of rhinitis[6] were measured at baseline and after 14 days of treatment. Ocular symptoms were assessed both by questionnaire and the RQLQ eye symptom domain (E-RQLQ).

An *a priori* definition of SCUAD was used: a VAS level for the global evaluation of rhinitis ≥5 cm (0-10 cm scale) and/or severe ocular symptoms defined by the occurrence of ocular symptoms in the diary and RQLQ (E-RQLQ ≥2.5, cutoff level at the 75th percentile of E-RQLQ).

The only patients considered for the analysis were those who completed the evaluation of all of the outcomes at baseline and after treatment. Because data were not normally distributed after treatment, medians 25th to 75th percentiles and nonparametric tests were used.

Patients were recruited between March 8 and July 15, 2002. A total of 399 physicians enrolled 796 patients. Two hundred ten patients (26.4%) were excluded from the analysis (see this article's Fig E1 in the Online Repository at www.jacionline.org).

At baseline, characteristics of the patients were similar and not clinically different between treatment groups (see this article's Table E1 in the Online Repository at www.jacionline.org). Most of the patients at baseline presented with moderate/severe allergic rhinitis as defined by ARIA (see this article's Fig E2 in the Online Repository at www.jacionline.org). Individual outcomes were normally distributed at baseline and skewed after treatment.

After treatment, symptom scores were reduced, and quality of life and productivity were improved. The differences between free-choice treatment and ARIA appear to be small, even if significantly different (see this article's Table E2 in the Online Repository at www.jacionline.org).

Eighty-two patients presented a VAS ≥5 cm, 52 (18.1%) in the free-choice treatment and 30 (10.3%) in the ARIA-based strategy. Patients with bothersome eye symptoms (ocular symptoms and E-RQLQ ≥2.5) corresponded respectively to 9.1% (26) and 9.0% (27). Overall, 111 (18.9%) patients presented an uncontrolled rhinitis after treatment (VAS ≥5 cm and/or bothersome eye symptoms): 58 with a VAS ≥5 cm, 29 with an E-RQLQ ≥2.5, and 24 with both VAS ≥5 cm and E-RQLQ ≥2.5. At baseline, patients in the SCUAD group were slightly younger ($P = .04$), but there were no differences in sex, tobacco-smoking habits, or asthma. They did not have more severe disease at baseline than controlled patients.

In the current study, it was found that SCUAD, a newly described phenotype of allergic rhinitis,[1] is present in around 10% to 20% of patients with allergic rhinitis. Patients with SCUAD present uncontrolled nasal and/or ocular symptoms and an impaired quality of life and work performance.

We used a cluster-randomized trial aiming to mimic real life. There was no exclusion of patients at randomization, as is often the case in clinical trials, because we wanted to study the whole range of patients regularly seen by physicians. Although the treatment was administered by specialists, it was found that the ARIA-based strategy was more effective than the free-choice treatment.[2]

Some limitations may exist in this article. Many methods assess the efficacy of a treatment for allergic rhinitis, but in outpatient clinics, there is no validated objective test.[7] Symptom scores and quality of life measurements have been used. These 2 methods assess the different characteristics of the patients. The VAS is a technique used to measure subjective phenomena, and changes in VAS within patients are more appropriate for study purposes than single measurements. This is why, in the current study, we used a cutoff level (≥5 cm) probably greater than needed to characterize uncontrolled rhinitis. In a recent article in the same population, we found that a cutoff level of 3 cm was sufficient when the VAS was measured at 2 intervals. There was no validated ocular symptom outcome, so we selected E-RQLQ in patients with ocular symptoms reported in a diary. The cutoff level was set at the 75th percentile.

In asthma, control is a key outcome, independent of asthma medications. A similar independent relationship was proposed in allergic rhinitis.[1] However, this concept had never been defined in a study. In this study, it has been shown that the SCUAD phenotype is a common problem, as suspected in clinical practice. SCUAD should apply only to patients who, despite adequate treatment, are still uncontrolled. It was found that SCUAD was present in around 10% to 20% of these patients when VAS and ocular symptoms were considered.

Impact on quality of life and work productivity is highly relevant in SCUAD. Although improved by comparison to pretreatment, patients with SCUAD had a significantly impaired quality of life (median RQLQ before treatment and during treatment, 2.77 and 2.04, respectively) whereas the median RQLQ of controlled patients was 0.58. Moreover, all RQLQ domains were significantly altered in SCUAD when compared with controlled patients. Similar results were observed for work productivity.

Patients with SCUAD require a more effective treatment since their quality of life and work productivity remain impaired. They may be ideal candidates for specific immunotherapy or novel treatments yet to be developed. Because the current study is a *post hoc* analysis, further studies are needed to confirm the concept.

*Philippe J. Bousquet, MD[a]**
*Claus Bachert, MD[b]**
*Giorgo W. Canonica, MD[c]**
Thomas B. Casale, MD[d]
*Joaquim Mullol, MD[e]**
Jean Michel Klossek, MD[f]
*Torsten Zuberbier, MD[g]**
*Jean Bousquet, MD[h]**

From [a]Département de Biostatistique, Epidémiologie Clinique Santé Publique et Information Médicale, Groupe Hospitalo-Universtaire Carémeau, Nîmes, France; [b]the Department of Otorhinolaryngology, Ghent University Hospital, Belgium; [c]the Allergy and Respiratory Diseases Clinic, DIMI, University of Genoa, Italy; [d]the Division of Allergy, Asthma, and Immunology, Creighton University Medical Center, Omaha, Neb; [e]the Rhinology Unit and Smell Clinic, Ears, Nose, and Throat Department, Hospital Clínic-IDIBAPS, Barcelona, Spain; [f]the Department of Ears, Nose, and Throat, Poitiers, France; [g]the Department of Dermatology and Allergy, Charité Universitätsmedizin Berlin, Germany; and [h]Service des Maladies Respiratoires, Hôpital Arnaud de Villeneuve, Montpellier, France, and INSERM CESP Centre for research in Epidemiology and Population Health, U1018, Villejuif, France. E-mail: jean.bousquet@inserm.fr.

*Members of Global Allergy and Asthma European Network (GA[2]LEN), supported by the Sixth EU Framework program for research, contract no. FOOD-CT-2004-506378.

Almirall Pharma supported the study, which was independently carried out and analyzed.

Disclosure of potential conflict of interest: T. B. Casale has received research support from Schering-Plough and Stallergenes and is on the Board of Directors for WAO. T. Zuberbier has performed industry consulting for Schering-Plough, Novartis, Leti, Stallergenes, Bayer Schering, Ansell, Kryolan, UCB, MSD, DST, Sanofi-Aventis, and Procter and Gamble; is on the Editorial Board of the Journal of Allergy, the Scientific Advisory Board of the German Society for Allergy and Clinical Immunology, and the Expert Commission "Novel Food" of the German Federal Ministry of Consumer Protection; and is Chairman of the European Academy of Allergology and Clinical Immunology, Dermatology Section, Head of European Centre for Allergy Research Foundation, a committee member of the WHO Initiative Allergy Rhinitis and its Impact on Asthma, a member of the World Allergy Organization Communications Council, and Secretary General of the Global Allergy and Asthma European Network. J. Bousquet has received honoraria from Stallergenes, Acadian, Almirall, AstraZeneca, Chiesi, GlaxoSmithKline, Merck, MSD, Novartis, OM Pharma, Sanofi-Aventis, Schering-Plough, Teva, and Uriach. The rest of the authors have declared that they have no conflict of interest.

REFERENCES

1. Bousquet J, Bachert C, Canonica GW, Casale TB, Cruz AA, Lockey RJ, et al. Unmet needs in severe chronic upper airway disease (SCUAD). J Allergy Clin Immunol 2009;124:428-33.
2. Bousquet J, Bodez T, Gehano P, Klossek JM, Liard F, Neukirch F, et al. Implementation of guidelines for allergic rhinitis in specialist practices: a randomized pragmatic controlled trial. Int Arch Allergy Immunol 2009;150:75-82.
3. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001;108(suppl 5):S147-334.
4. Juniper EF, Thompson AK, Ferrie PJ, Roberts JN. Validation of the standardized version of the Rhinoconjunctivitis Quality of Life Questionnaire. J Allergy Clin Immunol 1999;104(2 pt 1):364-9.
5. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4:353-65.