

dimeric. Salivary IgA is 1 example of secretory IgA. Secretory IgA is the dominant immunoglobulin in luminal secretions and functions by limiting the epithelial adherence and penetration of bacteria throughout the body's mucosal surfaces, such as the gastrointestinal tract, oral cavity, and respiratory system.¹ Secretory IgA protects against infections and toxins via different mechanisms as compared with antibodies in the systemic circulation. That SIgA interferes with the early steps of infection by blocking the adherence of toxins and pathogens to the epithelium via mechanisms such as receptor blockade, steric hindrance, and immune exclusion is commonly accepted. "Immune exclusion" is a series of events that involves agglutination, entrapment in mucus, and clearance through peristalsis that functions as an important component of protective immunity.⁵

Some CF patients have lower levels of intraluminal IgA levels, and this may demonstrate a decreased transmucosal transport of SIgA in these patients.⁶ Secretory IgA is released into the lumen via migration from mucosa-associated lymphoid tissue to exocrine effector sites, such as the gut lamina propria, airways, and salivary glands.⁷ Therefore, diseases such as CF, which impact these effector sites, may lead to decreased migration of SIgA into the body's mucosal surfaces, leading to mucosal immunodeficiency.

Although salivary IgA deficiency is most commonly associated with upper respiratory tract infections, it has frequently been used as a marker for SIgA, given its ease of collection.² In addition, it has been demonstrated in mouse studies that oral replacement of IgA has protective features against gastrointestinal infections and can aid in the homeostasis of the gut microbiome.⁸

This is the first reported case of salivary IgA deficiency in a patient with CF with M470V/V520F mutations. Further research is required to determine when to appropriately test for SIgA deficiency in patients with CF in addition to determining potential appropriate therapeutic options.

Jessica Oh, MD*

David P. McGarry, DO†

Nancy Joseph, DO†

Brian Peppers, DO†

Robert Hostoffer, DO†‡

* Department of Internal Medicine

University Hospitals

Cleveland Medical Center

Cleveland, Ohio

† Department of Pulmonary and Critical Care

Allergy/Immunology Fellowship

University Hospitals

Cleveland Medical Center

Cleveland, Ohio

‡ Allergy/Immunology Associates Inc.

Mayfield Heights, Ohio

Jessica.oh@UHhospitals.org

References

- [1] Yel L. Selective IgA deficiency. *J Clin Immunol*. 2010;30(1):10-16.
- [2] Tsujita S, Morimoto K. Secretory IgA in saliva can be a useful stress marker. *Environ Health Prev Med*. 1999;4(1):1-8.
- [3] Cutting GR. Cystic fibrosis genetics: from molecular understanding to clinical application. *Nat Rev Genet*. 2015;16(1):45.
- [4] Castellani C, Duff AJ, Bell SC, et al. ECFS best practice guidelines: the 2018 revision. *J Cyst Fibros*. 2018;17(2):153-178.
- [5] Mantis NJ, Rol N, Corthésy B. Secretory IgA's complex roles in immunity and mucosal homeostasis in the gut. *Mucosal Immunol*. 2011;4(6):603.
- [6] Hallberg K, Mattsson-Rydberg A, Fändriks L, Strandvik B. Gastric IgA in cystic fibrosis in relation to the migrating motor complex. *Scand J Gastroenterol*. 2001;36(8):843-848.
- [7] Aase A, Sommerfelt H, Petersen LB, et al. Salivary IgA from the sublingual compartment as a novel noninvasive proxy for intestinal immune induction. *Mucosal Immunol*. 2016;9(4):884.
- [8] Corthésy B. Multi-faceted functions of secretory IgA at mucosal surfaces. *Front Immunol*. 2013;4:185.

Omalizumab in chronic spontaneous urticaria

A real-life experience of dose and intervals adjustments in Belgium



Omalizumab was clearly shown to be effective and safe for treating refractory chronic spontaneous urticaria (CSU) not adequately controlled with H1-antihistamines (anti-H1). Supported by data of 5 randomized, placebo-controlled clinical trials,¹ the recommended regimen is 300 mg every 4 weeks, 38.1%/55.1% of patients being completely free or partially free, respectively, of urticaria after 12 weeks with this regimen.

This study aims to assess whether increasing the dose or shortening the interval may provide relief in some nonresponders, or, conversely, whether the dose may possibly be reduced or the dose interval lengthened in patients with good clinical response.

We reviewed the clinical data of all omalizumab-treated patients for CSU at the dermatology department of the Cliniques universitaires Saint-Luc, Brussels, Belgium, between January 2014 and May 2017. The study was approved by the institutional review board of the Université catholique de Louvain, Belgium. The inclusion criteria were severe CSU defined as urticaria unresponsive to anti-H1 treatment at a dose 4 times higher than the licensed one. Fifty-one patients were included. All of the patients were treated with subcutaneous omalizumab (Xolair, Novartis, Camberley, United Kingdom) at the initial

recommended dose of 300 mg every 4 to 5 weeks. Based on the clinical response, dose or interval adjustment was proposed. The clinical response using urticaria activity score over 7 days² (UAS7) was documented at baseline and throughout follow-up. In this letter, the term *regimen* is used to characterize the dose and the between-injection interval. Regimen was considered "adjusted" if the interval was less than 28 days or greater than 35 days at least twice, or if a dose other than 300 mg was administered.

To classify patients according to their treatment response, the following definitions were applied:

- "complete responders": UAS7 of 0
- "partial responders": UAS7 that fell by at least 10 points (but UAS7 ≠ 0)
- "nonresponders": UAS7 unchanged, risen, or fallen by less than 10 points

Mean omalizumab treatment duration was 14.3 months (standard deviation [SD], 10.4; range, 1-39). No significant adverse events occurred except for 1 patient who suffered from headache, dizziness, and vomiting.

Altogether, 26 patients (51%) responded completely to the recommended regimen, 15 patients (29.4%) partially, and 10 patients

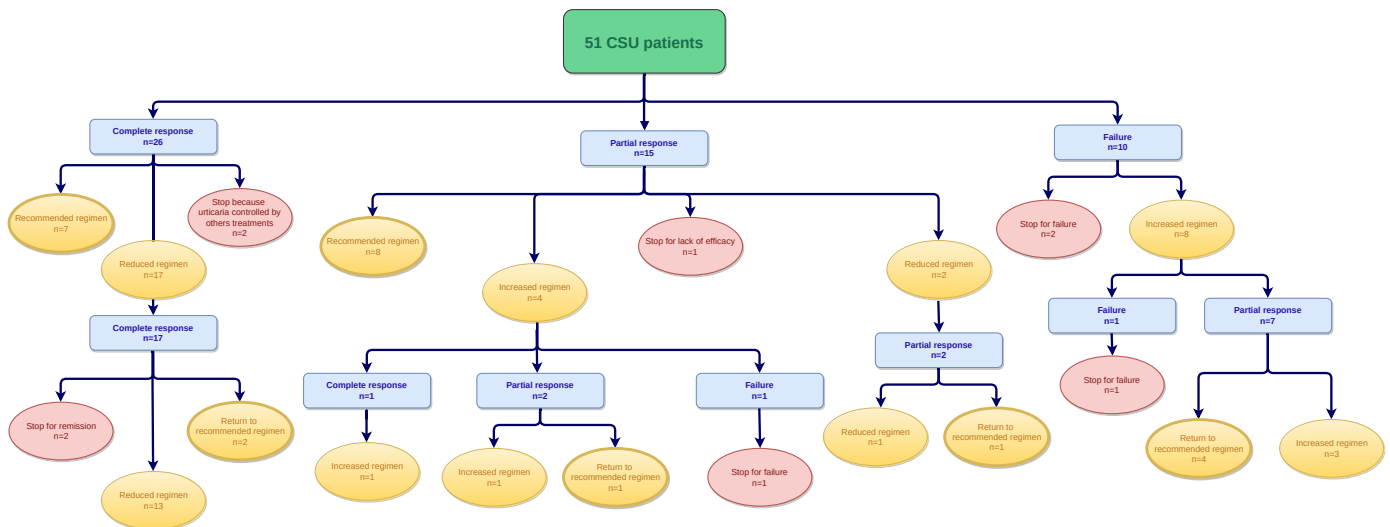


Figure 1. Patients' responses to omalizumab are represented in the blue oblong. Patients' omalizumab regimens are represented in the yellow oval. Patients who interrupted omalizumab are represented in the red oval. Reduced regimen means interval lengthened, dose reduced, or both. Increased regimen means interval shortened, dose increased, or both. Complete response (26 patients, 51%): Seven patients continued omalizumab with the recommended dose, without discontinuation. Two discontinued omalizumab after 2 months because their urticaria was controlled by other treatments (H₁-aH, H₂-aH, LTRA). For 17 patients, the between-injection interval was lengthened (from 36 to 92 days); for 1 of them, the dose was reduced (150 mg). Among the 17 patients, 2 were able to definitely stop omalizumab because of complete remission without relapse (after 6.3 and 9.7 months of omalizumab treatment, respectively, with a remission follow-up of 15.1 and 19.6 months). Thirteen continued with the reduced regimen, and 2 had to return to the recommended one. Partial response (15 patients, 29.4%): Eight patients followed the recommended regimen. One stopped treatment because of lack of efficacy. Four patients had treatment adjustments (increased). For 1 patient, interval was shortened with complete response. For 2 patients, increased dosing and shortened between-injection intervals were associated with partial response, with 1 of them able to return to the recommended regimen after 3 months. One received increased dose but stopped omalizumab because of lack of efficacy. Finally, 1 patient decided to start with reduced dose (150 mg) for 8.1 months before returning to the recommended regimen. Despite only partially responding, another patient decided to have the interval lengthened. Failure (10 patients, 19.6%): Two patients deemed to be nonresponders discontinued omalizumab after 3.9 and 7.4 months, respectively, without any treatment adjustments. Eight patients received higher doses (450 and 600 mg for 6 and 2 patients, respectively) or had their between-injection period shortened, with a good clinical response noted in 7 and failure for 1. Four of them could return to the recommended regimen after a mean of 6.6 months (range, 3.5–10.1), and 3 were still on an increased regimen.

(19.6%) not at all. By using treatment adjustments, complete and partial responses were observed in 52.9% and in 43.1% of patients, respectively. The flowchart represented in Figure 1 summarizes treatment adjustments according to the patients' responses.

The delay of response was different among the 41 patients. Thirty-five patients (85.4%) responded completely or partially within 30 days after the first injection. Four patients (9.8%) responded after 2 or 3 doses, and 2 patients (4.9%) after 4 to 5 doses. For 3 patients, the exact time to response was unknown. Seven patients needed a dose increase to respond. These real-life data are in line with recent studies suggesting 2 categories of omalizumab responders: those who respond early (before 4 weeks) and those who require more than 3 monthly doses to respond.³ Among 51 patients, 20 (39.2%) received the recommended regimen without any treatment adjustments.

Twelve patients (23.5%) required an increased regimen: interval shortened ($n = 1$), dose increased ($n = 1$), or both ($n = 10$). The regimens were modified as follows: 300 mg every 2 to 3 weeks, 450 mg every 3 to 4 weeks, or 600 mg every 2 weeks. The mean shortened interval was 22.1 days (standard deviation [SD], 2.8; range, 10–25). The mean increased regimen duration was 4.9 months (SD, 6.7; range, 1–10.1). Partial or complete response was observed in 10 patients, of whom 5 were able to return to the recommended treatment after a mean duration of 6.3 months (SD, 3; range, 3.5–10), and 5 were still on adjusted treatment at the end of follow-up. The remaining 2 failed to respond despite increased regimen.

Among the responders, for 19 patients (37.3%), intervals were lengthened ($n = 17$), the dose was reduced to 150 mg ($n = 1$), or both ($n = 1$). When patients were free of symptoms, the interval was gradually increased to 5, 6, or 7 weeks or more. The mean lengthened interval was 47.8 days (SD, 7.8; range, 39–92). The mean duration of the reduced regimen was 12.4 months (SD, 8.9; range, 3.3–39). Seventeen patients responded completely and 2 partially without relapse,

despite lengthening intervals or reducing dose, and only 3 of them needed to return to the recommended regimen. Two patients could stop for remission.

This is in agreement with the literature suggesting that an increased regimen significantly enhances response rate,^{4,5} and conversely, a reduced regimen could be suggested to some good responders.^{4,6,7}

In this cohort, shortened interval or increased dose was mostly temporary, and the number of patients for whom interval was lengthened clearly outweighed those with a shortened interval. Two studies^{4,7} also noticed previously that treatment reductions were likewise more common than increased regimens.

From a medical cost-effectiveness perspective, regimen adjustments compared with unchanged doses enhance the rate of responders without causing an over-cost for patients and for society. In this real-life follow-up, with the regimen adapted to the clinical response, approximately 1,466 omalizumab injections (150 mg) were administered, compared with 1,656 injections if the recommended dose had been applied in all the patients. However, a precise evaluation of the cost of an adapted treatment is needed. Moreover, CSU is a very disabling disease. Loss of productivity and number of medical visits/hospitalization of unresponsive patients with the recommended regimen should be taken into consideration. In this cohort, one third of patients already had experienced interruptions of work or school, and one fifth of patients had been hospitalized because of severe urticarial exacerbations.

These real-life data support the emerging evidence for omalizumab dose and interval adjustments in anti-H1-resistant CSU. For a number of nonresponders, a temporary increased dose with or without reduced interval led to remission, with good tolerance. Conversely, a high number of patients maintained a satisfactory clinical response, even with lengthened intervals. However, practical guidelines should be issued to help clinicians in adjusting omalizumab dose and frequency.

Acknowledgments

The authors are most grateful to Dr. Julien De Greef for his meticulous revision of the manuscript and thank Lieven Desmet, Caroline Preud'Homme, Bastien Schnock, and Yves-Alexandre de Montjoye for their active collaboration.

Laurence de Montjoye, MD*

Anne Herman, MD*

Laure Dumoutier, PhD†

Michel Lambert, MD, PhD‡

Isabelle Tromme, MD, PhD*

Marie Baeck, MD, PhD*

* Department of Dermatology

Cliniques universitaires Saint-Luc

Institute of Experimental and Clinical Research

Pneumology

ENT and Dermatology Pole

Université catholique de Louvain

Brussels, Belgium

† De Duve Institute

Université catholique de Louvain

Brussels, Belgium

‡ Department of Internal Medicine

Cliniques universitaires Saint-Luc

Université catholique de Louvain

Brussels, Belgium

laurence.demontjoye@uclouvain.be

References

- [1] Urgert MC, van den Elzen MT, Knulst AC, Fedorowicz Z, van Zuuren EJ. Omalizumab in patients with chronic spontaneous urticaria: a systematic review and GRADE assessment. *Br J Dermatol*. 2015;173:404–415.
- [2] Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. 2014;69:868–887.
- [3] Kaplan A, Ferrer M, Bernstein JA, et al. Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticaria. *J Allergy Clin Immunol*. 2016;137:474–481.
- [4] Sussman G, Hebert J, Barron C, et al. Real-life experiences with omalizumab for the treatment of chronic urticaria. *Ann Allergy Asthma Immunol*. 2014;112:170–174.
- [5] Curto-Barredo L, Spertino J, Figueras-Nart I, et al. Omalizumab uposing allows disease activity control in refractory patients with chronic spontaneous urticaria. *Br J Dermatol*. 2018;179:210–212.
- [6] Vadasz Z, Tal Y, Rotem M, et al. Omalizumab for severe chronic spontaneous urticaria: real-life experiences of 280 patients. *J Allergy Clin Immunol*. 2017;5:1743–1745.
- [7] Barron C, Saperia C, Kobric D, Sussman G. *Chronic Spontaneous Urticaria: Centre of Excellence*. 3rd Ga'len Global Urticaria Forum; 2016; Berlin.

Atopic dermatitis in US adults

Epidemiology, association with marital status, and atopy



Atopic dermatitis (AD) prevalence and risk factors in the US population are not fully elucidated. A study from the 2010 National Health Interview Survey (NHIS) found that 10.2% of US adults reported having “dermatitis, eczema, or any other red, inflamed skin rash”¹ in the past 12 months, likely overestimating AD prevalence by including other rashes. Furthermore, 3.2% reported having rash with asthma or hay fever,¹ likely underestimating AD prevalence by excluding intrinsic AD or those with a remote history of atopic disease. The true 1-year prevalence of AD in US adults likely lies in the middle of that 3.2% to 10.3% range. We sought to provide improved estimates and examine associations of AD prevalence in US adults. Atopic dermatitis is associated with increased psychosocial stressors that negatively impact relationships. We hypothesized that adult AD is associated with higher rates of separation and divorce.

We used the 2012 NHIS, an in-person household survey administered in English and Spanish (n = 34,588 adults). One adult per household was randomly selected for the adult questionnaire. One-year prevalence of AD was determined based on an affirmative response to: “During the past 12 months, have you had eczema or any kind of skin allergy?” Self- and caregiver-report of eczema and skin allergy has been validated and found to have good correlation with clinical examination results.² Using data from the US Bureau of the Census, sampling weights were adjusted for age, sex, race, ethnicity, household size, and educational attainment of the most educated household member. This study was approved by the institutional review board at Northwestern University.

All statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina). Multivariable logistic regression models were constructed with AD as the binary dependent variable (yes/

no) and sociodemographics (Model 1), as well as marital status (Model 2) and each of the atopic diseases (Model 3) as the independent variables. Complete data analysis was performed. *P* values ≤ .05 were considered significant.

The US prevalence of AD in adults was 7.2% (95% confidence interval, 6.9%–7.6%). In multivariable logistic regression models, adult AD was associated with female sex, multiracial/other race, health care interaction in the past year, and current health insurance coverage, but inversely associated with highest-quartile age, currently working, African American/black and Native American race, Hispanic ethnicity, US birthplace, and household income above the FPL (Model 1, Table 1). Atopic dermatitis prevalence was higher among those born in the United States vs all other regions (*P* < .0001).

In multivariable models controlling for all variables in Model 1, AD was associated with being divorced, separated, and never married compared with those married with their spouse in the home (Model 2, Table 1).

In multivariable models controlling for all variables in Model 2, lifetime prevalence of asthma (25.5% [23.1%–27.8%] vs 11.7% [11.2%–12.1%]), point prevalence of asthma (18.7% [16.6%–20.8%] vs 7.2% [6.8%–7.6%]), and 1-year prevalence of asthma attack (11.6% [9.8%–13.4%] vs 3.5% [3.3%–3.8%]) and hay fever or respiratory allergy (34.9.0% [32.5%–37.4%] vs 14.2% [13.7%–14.7%]) were all higher in adults with vs without AD (Model 3, Table 1). The observed prevalences are very similar to previously reported prevalences of these disorders in US children (25.1% [23.1%–27.2%], 19.8% [17.8%–21.7%] and 34.4% [32.1%–36.7%], respectively³).

This study found a 7.2% prevalence of adult AD in the United States, which is approximately in the middle of the range of estimates (3.2%–10.2%) from the 2010 NHIS. The question used to identify AD in this study is more refined than in 2010 NHIS by not including “dermatitis or any other red, inflamed skin rash.” Nevertheless, misclassification of AD may occur when it is defined

Disclosures: T. Hua and J.I. Silverberg have no relevant conflicts of interest to declare.

Funding Sources: This publication was made possible with support from the Dermatology Foundation.