

Antihistamine updosing in chronic urticaria – is there enough evidence?

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Linked Article: Guillén-Aguinaga *et al.* *Br J Dermatol* 2016; **175**:1153–1165.

H1-antihistamine updosing is an important element in chronic urticaria management and is backed by the current EAACI/GA²LEN/EDF/WAO guideline treatment algorithm.¹ This algorithm suggests second-generation H1-antihistamines (sgAHs) in licensed dose as first-line therapy, updosing of sgAHs up to fourfold the standard dose as second-line approach, and the addition of omalizumab, ciclosporin or montelukast as third-line options.¹ First-generation antihistamines should be avoided because of their poor safety profile, including fatal events in children and adults.²

The recommendation to updose sgAHs is based on a mix of expert opinion and evidence. The long-standing, favourable experience of urticaria-treating physicians and a global consensus among experts is complemented by a few randomized controlled trials (RCTs) and other clinical studies. The available studies are mostly small and not of high quality. Accordingly, the overall evidence for sgAH updosing in chronic urticaria, an off-label treatment option, is still limited. One straightforward approach to overcome these limitations, at least in part, is to join all available data and to perform a meta-analysis.

In this issue of the *BJD*, Guillén-Aguinaga and coworkers present such a meta-analysis with a focus on chronic spontaneous urticaria (CSU).³ Their first important finding is that less than 40% of patients show controlled disease when treated with sgAHs at licensed doses; less than previously thought.⁴ The second key result is that, comparing standard and increased sgAH dosing, the latter is significantly better, particularly when it comes to itch, a major driver of the patient's disease burden. In contrast, the impact of updosing on wheal numbers seems to be rather small. Nonresponders to standard-dose sgAHs have a 60% chance of achieving control with higher than standard doses. However, because the heterogeneity of the 15 included studies is strong and only a minority are of high quality, the authors decided not to draft a final conclusion.

Importantly, Guillén-Aguinaga *et al.*³ did not consider evidence obtained in chronic inducible urticarias for which the same treatment algorithm is recommended.¹ In this field, several RCTs have been published in recent years that also clearly point towards a superior efficacy of sgAHs when used at higher than licensed doses.^{5–8}

Taken together, there is a clear need for additional large, high-quality RCTs to improve the extent and quality of evidence on sgAH updosing in chronic urticaria. On the other hand, the existing data, despite all of their limitations, can be considered sufficient to support the current guideline recommendations. In this context, sgAH updosing also has to be evaluated with

regard to other aspects: firstly, there are no safety concerns in conjunction with up to fourfold increased doses, and secondly, all current alternatives also have their limitations. Omalizumab is licensed for CSU and very effective⁹ but associated with higher costs than high-dose sgAHs. Ciclosporin is effective^{10,11} but characterized by an unfavourable long-term safety profile.¹ Montelukast is safe but its efficacy is not convincing.¹²

In light of these considerations, a trial of sgAH updosing is justified in all patients with chronic urticaria who do not respond sufficiently to regular doses. Because 40% of patients can be expected not to benefit from this approach, the treatment response should be evaluated shortly after adjustment with appropriate and validated tools, such as the Urticaria Control Test.¹³ In patients who do not respond to higher than standard-dose sgAHs, treating physicians should not hesitate to use third-line treatments to reduce the disease burden in a timely manner.

Meta-analyses on urticaria treatment options, such as the one by Guillén-Aguinaga and coworkers³ as well as others,⁹ are needed and important for the update and revision of guideline recommendations, e.g. during the next EAACI/GA²LEN/EDF/WAO urticaria guideline meeting in Berlin, Germany in December 2016 (<http://www.urticariaguideline.org>). All urticaria-treating physicians are highly welcome to participate and contribute.

Conflicts of interest

K.W. has received honoraria for educational lectures from Dr R. Pflieger, Essex Pharma (now MSD), Uriach, UCB, Novartis and Moxie. In addition, he received honoraria for consulting from Novartis and he is or was involved in the clinical research projects of Dr R. Pflieger, Essex Pharma (now MSD), FAES, Uriach and Novartis. M.M. is or recently was a speaker and/or adviser for and/or has received research funding from Dr R. Pflieger, FAES, Genentech, GSK, Menarini, Moxie, Novartis, Sanofi Aventis, MSD and Uriach.

Department of Dermatology and Allergy,
Charité – Universitätsmedizin Berlin,
Charitéplatz 1, 10117 Berlin, Germany
E-mail: karsten.weller@charite.de

K. WELLER
M. MAURER

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Epidermal growth factor receptor inhibitor-associated rash prevented by oral tetracyclines

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Small molecules and monoclonal antibodies that inhibit the epidermal growth factor receptor (EGFR) are frequently used in the treatment of metastatic non-small-cell lung cancer, colorectal cancer and head and neck cancer. However, EGFR inhibitors, including erlotinib, gefitinib, lapatinib, cetuximab and panitumumab, elicit cutaneous adverse events in more than 70% of patients. Within weeks following start of treatment patients develop an eruption consisting of follicular papules and pustules predominantly affecting skin areas rich in sebaceous glands. In addition, patients may develop xerosis, pruritus, fissures, paronychia and hair growth abnormalities.¹ Although the skin eruption has a tendency to improve

spontaneously in months, the papulopustular rash can be debilitating and a reason for concern and discomfort in patients. In a minority they can be severe and necessitate dose reduction or discontinuation of EGFR inhibitor treatment.

Depending on the severity of cutaneous adverse events, various local and systemic drugs are used, such as skin moisturizers, sunscreens, antibiotic gels, corticosteroid creams, vitamin K cream, oral tetracyclines, isotretinoin and prednisone. Oral doxycycline and minocycline are the treatment of choice for moderate-to-severe papulopustular rash. Initially, treatment was instituted in a symptomatic, reactive manner, i.e. following manifestation of skin symptoms. Increasingly, treatment is given in a prophylactic manner, in order to prevent the onset or reduce the severity of cutaneous toxicity and improve treatment adherence.

In this issue of the *British Journal of Dermatology*, Petrelli and colleagues present the results of a systematic review and meta-analysis of the efficacy of doxycycline, minocycline and tetracycline in the prevention of EGFR inhibitor-induced skin rash.² Of 827 articles on prophylactic treatment with tetracyclines, nine randomized and four retrospective studies met their inclusion criteria. The individual studies included 26–150 patients and mostly pointed to efficacy of prophylactic treatment. This meta-analysis on over 1000 patients clearly showed that the incidence and severity of the EGFR inhibitor-induced papulopustular rash was reduced by prophylactic treatment with doxycycline or minocycline. The likelihood of developing this rash was reduced by 50% by prophylactic treatment; severe rash (grade III–IV) was 70% less likely to develop. Although tetracyclines reduced the severity of the follicular papulopustular eruption and of paronychia, they did not appear to prevent xerosis and skin fissures. Interestingly, treatment effects on all grades of rash were statistically significant only for studies conducted with minocycline, but not for doxycycline. Contrary to the findings in this review, a recent study included in the meta-analysis concluded that prophylactic treatment with doxycycline reduces the severity of skin lesions, but not the incidence.³

The value of tetracyclines in the prevention of severe papulopustular rash, potentially improving compliance with EGFR-targeted therapy, has been convincingly shown by this meta-analysis. A GRADE (Grading of Recommendations Assessment, Development and Evaluation) summary of findings table summarizing the quality of the evidence for each predefined outcome could have strengthened the conclusions. Taking into account that a proportion of patients receiving EGFR inhibitors would never develop cutaneous adverse effects, the option of either prophylactic or symptomatic treatment with tetracyclines should perhaps be part of shared decision-making.

Conflicts of interest

None to declare.

Department of Dermatology, Leiden
University Medical Center, Leiden,
the Netherlands
E-mail: rvandoorn@lumc.nl

R. VAN DOORN
E.J. VAN ZUUREN