

Urticaria: an evidence-based update. Conference report

A.B. Alexandroff and K.E. Harman

Department of Dermatology, Leicester Royal Infirmary, Leicester LE1 5WW, U.K.

Summary

Correspondence

Anton Alexandroff.

E-mail: anton@alexandroff.org;

anton.alexandroff@gmail.com

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Evidence-based update meetings are held annually by the Centre of Evidence Based Dermatology, University of Nottingham. Topics are chosen by delegates at the previous year's conference and in the past have included blistering disorders, psoriasis, hair disorders and skin cancers. Once the topic is identified, a trials database search is undertaken with the aim of including speakers who are actively involved in trials that address the subject in question. This year, the eighth Evidence Based Update meeting focused on urticaria and took place in Loughborough University on 14 May 2009. The latest data on the diagnosis and management of acute and chronic urticaria, including cold and solar urticaria, and the impact of food intolerance on chronic urticaria, were presented by an international panel of renowned speakers, who sometimes expressed different viewpoints. The highlights of the meeting included an informal atmosphere, an international perspective, and a practical question and answer session. Over 70% of the delegates stated that they would be changing their clinical practice following on from the meeting. The evidence-based update meeting in 2010 will be devoted to eczema.

Urticaria is a common dermatological problem with lifetime prevalence of approximately 20%.¹ Although usually not life threatening, it often impairs quality of life to a degree comparable with triple coronary heart disease.² Its aetiology and pathogenesis are yet to be fully understood and significant efforts have been directed towards elucidation of the underlying mechanisms as well as improvement of optimal management of these patients.^{3–17} Despite recent publication of guidelines from the British Association of Dermatologists as well as the joint guidelines of the European Academy of Allergy and Clinical Immunology, EU-funded network of excellence, Global Allergy and Asthma European Network, European Dermatology Forum, Urticaria Network and World Allergy Organization, there are surprisingly few evidence-based recommendations currently available to medical practitioners and thus this meeting was organized to summarize such evidence and also to draw on the experience of international experts in this area.^{1,18–20}

To set the scene, Dr Stuart Cohen (Nottingham, U.K.) updated the audience on the progress of a systematic Cochrane review of antihistamines use for chronic ordinary (spontaneous) urticaria (CSU). The review aims to assess such important questions as the superiority of one antihistamine over another, the superiority of combination antihistamines over monotherapy, and effectiveness and adverse effects of high-dose

antihistamines. Using standard criteria to identify potentially suitable data, 58 studies have been identified. Unfortunately progress has been hampered by the poor methodology of published trials, the lack of clear outcomes and variable disease scoring tools. In addition, 59% of the identified trials were industry sponsored with approximately 75% of these favouring the sponsor's drug, raising questions of bias. Although the review is still in progress, it is already clear that new well-planned studies are urgently required to compare currently available drugs head to head, including licensed and nonlicensed doses, and with the use of patient-oriented outcomes.

Professor Bettina Wedi (Hannover, Germany) gave an overview of acute spontaneous urticaria (ASU), a common disorder with a 12–15% lifetime prevalence and the commonest form of spontaneous urticaria. But despite this, good evidence guiding management is lacking. While a detailed history and physical examination (including dermographism) remain essential, routine tests are no longer recommended in patients with ASU unless suggested by the history. In the latter case, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), full blood count (FBC), throat swab, skin tests, IgE RAST tests and provocation tests may be considered. The most common cause of acute urticaria in adults and children is infections, particularly upper respiratory tract and viral infections. Food is the second most common cause of acute

urticaria in children, while drugs [nonsteroidal anti-inflammatory drugs (NSAIDs), amoxicillin] may cause acute urticaria relatively often in both children and adults. There is some evidence that short courses of corticosteroids may speed up resolution of urticaria. In a small randomized, double-blind controlled trial of 43 patients addition of prednisolone (40 mg daily for 4 days) to hydroxyzine (25 mg four to six times daily for 4 days) resulted in lower itch scores and greater clinical improvement in rash without apparent adverse effects.²¹ In another unblinded study, 109 patients with acute urticaria were treated with either loratadine (10 mg daily for 3 days) or prednisolone (50 mg daily for 3 days).²² The course of the disease was self-limiting in all cases. Both treatment regimens were effective, but in corticosteroid-treated patients, symptoms ceased earlier, with complete remission occurring within 3 days of treatment in 93%, compared with 65% in patients treated with loratadine.

Dr Randolph Brehler (Münster, Germany) highlighted a possible impact of diet on CSU. In a large prospective study of over 800 patients, 30% of patients with CSU improved on a food additive-free diet, including those both with and without a history of food intolerance, but only a small proportion of these patients had a positive challenge to food additives and none achieved a complete remission.²³ In a smaller open pilot study 50% and 17%, respectively, of patients responded partially or fully to the elimination diet within 5 weeks. The majority of full responders showed recurrence during incremental build up food challenge.²⁴ Although the underlying mechanisms are not clear it has been suggested that the observed phenomenon may be due to altered gastroduodenal permeability.²⁵

Acquired cold urticaria (ACU) is a rare subtype of urticaria. It is difficult to treat and most cases appear to be idiopathic.^{26,27} Fortunately an objective method for measurement of disease activity and the response to therapeutic agents became available recently.²⁸ TempTest® (Emo Systems GmbH, Berlin, Germany) is a cold provocation device which allows the measurement of critical temperature and stimulation thresholds (CTTs and CSTTs). CTTs and CSTTs have been clinically validated and correlated with both the severity and activity of disease.²⁸ Professor Marcus Maurer (Berlin, Germany) presented the results of two placebo-controlled, double-blind trials assessing antihistamine efficacy and dosing in ACU. A three-way cross-over trial ($n = 30$) used CTT and CSTT to demonstrate objectively the superiority of desloratadine 20 mg daily over desloratadine 5 mg daily (standard dose), and desloratadine 5 mg daily over placebo, with a fall in median CTT from 19 °C at baseline to 17 °C with placebo, 15 °C on desloratadine 5 mg and 4 °C on desloratadine 20 mg. In another cross-over trial ($n = 21$), rupatadine 20 mg daily (double standard dose) also increased CSTTs and reduced CTTs compared with placebo.²⁹ Rupatadine is a nonsedating, long-acting dual antagonist of both histamine (blocking H1 receptor) and platelet-activating factor. Both drugs were well tolerated at high dose, and thus these studies provide support for up dosing of antihistamines in patients who do not respond to standard doses.

Solar urticaria (SU) is extremely rare but may have a profound effect on quality of life.^{30,31} The dermatology unit in Dundee has made a significant contribution to this area by collecting and analysing data on almost 90 patients with SU over a 25-year period.³² Professor James Ferguson (Dundee, U.K.) summarized most recent data on pathogenesis, clinical features, investigations and management of SU. SU can affect patients of any age and race, and although rare it may coexist with other photodermatoses including systemic lupus erythematosus and porphyria cutanea tarda. Relevant investigations include monochromator phototesting, plasma porphyrins, lupus serology, exclusion of suspected drugs (tetracyclines, chlorpromazine, fluoroquinolones, NSAIDs, topical dyes and tars) and, in recalcitrant cases, intradermal testing with irradiated autologous plasma. Management includes behavioural modification including clothing cover, sunscreen (e.g. Dundee reflectant sunscreens), window films (Dermagard®/Museum film 200; Bonwyke Ltd, Fareham, U.K.) and antihistamines. It should be remembered that Dermagard® window film may degrade with time,³³ and that in cases of failure of conventional treatment with antihistamines or sunscreens, a combination regimen of antihistamines may be more successful.³⁴ Despite there being a method of objectively measuring the therapeutic response in SU, the minimal urticarial dose, there are scanty trial data. Currently there are only two randomized controlled trials in SU. In one study an H1 antihistamine (chlorpheniramine) but not an H2 antihistamine (cimetidine) was effective.³⁵ No difference was observed between cetirizine and terfenadine in another study.³⁶ The limitation of both studies was a very small sample size. For example, in the latter study two of six patients failed to respond to either therapy, while both drugs were equally effective in raising the threshold of sensitivity in four patients.

Dr Clive Grattan (Norwich, U.K.) dedicated his lecture to the role of diagnostic tests in the management of urticaria. With a pragmatic approach, Dr Grattan does not order blood tests in patients with chronic urticaria who respond to H1 antihistamines. In nonresponders he suggested checking FBC, ESR, thyroid function tests and thyroid autoantibodies, and in patients with angio-oedema without weals, the C4 complement level. In physical urticarias, physical provocation tests can be employed to define relevant triggers and thus aid avoidance: dermatographometer in dermatographism, dermatographometer or weighted rods in delayed pressure urticaria, ice or TempTest® in ACU and exercise or heat in cholinergic urticaria.¹⁹ If required, several tests may be employed in an attempt to diagnose, depending on the clinical situation, the cause of acute urticaria (e.g. skin prick tests or IgE RAST tests to diagnose allergy, viral studies to diagnose infection) or chronic urticaria (bacterial and parasitic studies, autologous serum skin test (ASST) and basophil histamine release assay (BHRA), autologous plasma skin test and D-dimer to diagnose, respectively, infectious, autoimmune or coagulation-related causes.^{22,37-40} Autoimmune urticaria responds poorly to H1 antihistamines and often manifests itself as a severe spontaneous urticaria associated with autoimmune diseases

and positive ASST and/or BHRA tests.^{41,42} Finally, we were reminded that diagnostic tests may be needed for other diseases with an urticarial component such as urticarial vasculitis (skin biopsy) and Schnitzler syndrome (ESR/CRP, IgM levels).

Professor Malcolm Greaves (London, U.K.) shared his experience of urticaria management, focusing on the difficult cases. He reminded us that second-generation nonsedating antihistamines are now recommended as the first-line treatment, with up dosing if there is an inadequate response to standard doses.¹⁸ These are assumed to be safe at even up to four times the licensed dose on the basis of derivative evidence (off-label use). Regular dosage is also advised to avoid pseudotachyphylaxis. Although the European guidelines do not recommend older, sedating antihistamines, Professor Greaves felt that these medications may be useful in selected patients. In cases of resistant urticaria, doxepin, a tricyclic antidepressant with high affinity for the H1 receptor, can be tried at a dose of 25–75 mg at night. Doxepin, however, has significant antimuscarinic activity and it should not be withdrawn abruptly, given to patients with significant heart disease or coadministered with other antidepressants. In the European guidelines, oral steroids are not recommended for maintenance therapy but can be used to treat relapses, while in the U.S.A. systemic corticosteroids are regularly used on a long-term basis (at a dose of 10 mg daily or 20 mg on alternate days). There is little evidence that H2 antihistamines make a clinically relevant impact.^{43,44} There is evidence that antileucotrienes (montelukast 10 mg at night) are effective for NSAID-reactive patients and are worth trying in other forms of chronic urticaria.^{45,46}

While there is no evidence for thyroxine replacement, special diets, rituximab and *Helicobacter pylori* eradication, evidence is accumulating that ciclosporin, methotrexate, intravenous immunoglobulins, plasmapheresis and omalizumab can be useful as second-line treatments. Ciclosporin (3–6 mg kg⁻¹ daily for 2–3 months) in severe urticaria can induce remission in approximately 80% of cases, with one in three patients remaining in remission, one-third experiencing a minor and one-third a significant relapse on cessation of treatment.⁴⁷ While there are no randomized controlled trials of methotrexate in urticaria, it is routinely used in patients with severe urticaria at St John's Institute of Dermatology in London (10–15 mg weekly for 3–6 months).⁴⁸ Omalizumab is a recombinant humanized anti-IgE monoclonal antibody. In a placebo-controlled study seven of 12 patients achieved a complete remission and 11 patients improved.⁴⁹ In a randomized double-blind placebo-controlled trial in 20 unselected patients with treatment-resistant CSU, all patients allocated to omalizumab (given every 2–4 weeks for 16 weeks) showed substantial improvement in symptom score and quality of life.⁵⁰ Finally, Professor Greaves reminded us that if nothing works, consider alternative diagnoses (urticarial vasculitis, Schnitzler syndrome, adult-onset Still disease, autoinflammatory syndrome and urticarial dermatitis).

In conclusion, this was a very practical meeting, the strongest practical message, which was reiterated several times, being the benefit of up dosing nonsedating antihistamines to

three or four times standard doses rather than combining antihistamines. The expert panel felt that loratadine, desloratadine and fexofenadine could be used safely in higher doses without a significant risk of increased sedation. From his personal experience Professor Maurer recommended using four times the licensed dosage of desloratadine. The feedback from the delegates was very positive: 70% said the meeting was very useful and 30% useful. Importantly, over 70% of the delegates stated that they would be changing their clinical practice following on from the meeting.

Further information

Most of the presentations made at the meeting are available on the U.K. Dermatology Clinical Trials Network (UK DCTN) website (<http://www.ukdctn.org>). Details about future Evidence Based Update meetings are available from Dr Carron Layfield, UK DCTN Manager, Centre of Evidence Based Dermatology, The University of Nottingham, Kings Meadow Campus, Nottingham NG7 2NR, U.K.; telephone 0115 846 8625, fax 0115 846 8618.

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