NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Omalizumab for treating previously treated chronic spontaneous urticaria

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Sinisa Savic

Name of your organisation Royal College of Pathologist

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ☐
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Chronic spontaneous urticaria (CSU), or chronic 'hives', is a condition characterised by red, swollen, itchy and painful wheals on the skin, which resemble nettle- rash. There is great variation in its severity and duration, and in how it affects patients. In many cases this a self-limiting condition, which will resolve within 6 months in 50% of patients. However a significant proportion of patients will have a prolonged illness, sometimes lasting decades, and this can have a serious negative impact on their quality of life.

Many CSU sufferers are treated in primary care. However the standard of care offered to patients can vary greatly. The symptoms of CSU are easily confused with allergy, and this mis-daignosis can lead to incorrect treatment. Even when the condition is correctly diagnosed and all appropriate treatment steps have been tried (including a 4 x licensed dose of non-sedating antihistamines) there is considerable variation in access to specialist care with a dermatologist, immunologist or allergist. Even within the specialist setting, there is variation in the treatment of CSU. Despite published guidelines (below), there may be a reluctance to prescribe immunomodulatory drugs such as cyclosporin and methotrexate, for fear of causing potentially serious side-effects whilst treating a condition which is perceived by some to be benign and self-limiting illness. However the effects of CSU can be devastating, including sleep deprivation, depression and social isolation. It has been reported that in comparison to some other dermatological and medical conditions, people with urticaria have a significantly worse quality of life (1). There is therefore a need for safe and effective second line therapy.

Introduction of omalizumab for treatment of CSU has a potential to transform how we manage this condition. Omalizumab has been shown to be very effective and safe but compared to some other immunomodulatory drugs used for CSU, is relatively more expensive. Therefore In order to gain the maximum benefit from this drug we will need to re-examine current

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referral and treatment guidelines, in both primary and secondary care. Omalizumab should be provided by dermatology, immunology or allergy specialist centers with extensive experience in CSU. This is indeed how omalizumab has currently been provided, for a limited number of CSU patients in the UK.

There are currently both national and international guidelines on management of CSU. The international guideline is a result of collaboration between several stakeholders including: European Academy of Allergy and Clinical Immunology (EAACI), Global Allergy and Asthma European Network (GA²LEN), European Dermatology Forum (EDF), World Allergy Organisation (WAO) (2). In the UK, the British association of dermatologists (BAD) and the British society of allergy and clinical immunology (BSACI) have both issued guidelines. These are currently under review, and it is anticipated that in both cases the recommendations will be similar to existing international guidelines (Figure 1).

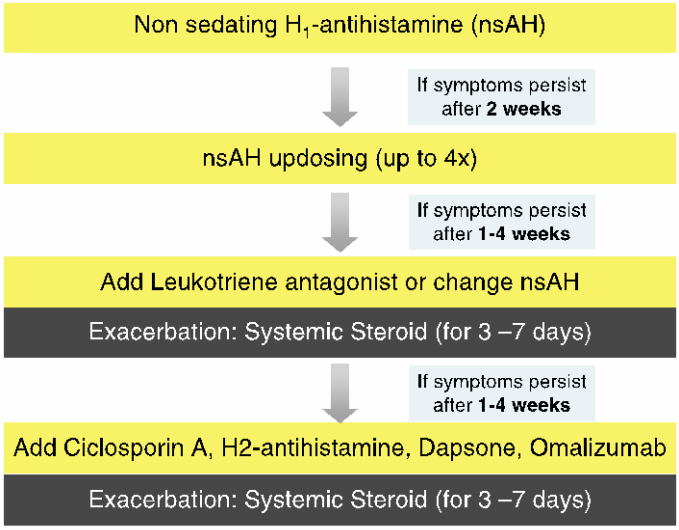

Figure 1 Recommended treatment algorithm for CSU adopted from 2.

The guidelines in Figure1 suggest that immunomodulation be used where patients fail to respond to up-dosing of antihistamines and the addition of a leukotriene antagonist. However, they do not specify whether omalizumab is used, or another immunomodulatory therapy such as cyclosporin or dapsone.

These recommendations were recently revised (3). The number of treatment steps has been reduced and dapsone or H2 blockers such as ranitidine are no longer recommended as there is little data to support their efficacy. Omalizumab is recommended for patients who fail up-dosing of antihistamines for a period of 4 weeks. However, as before, there is no specification of omalizumab over other immunomodulators. To complicate matters further, the addition of a leukotriene antagonist is suggested at this stage as well.

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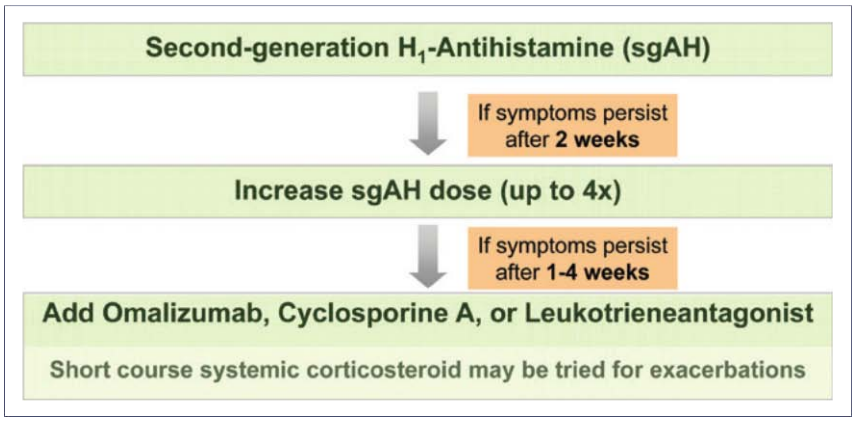

Figure 2 Revised recommendations for treatment of CSU adopted from 3

There are no randomized control trials (RCT) which directly compared omalizumab against other second and third line treatments for CSU. However omalizumab has shown to be effective in many cases where all other treatment modalities, including cyclosporin, have failed (7,8). This reflects my personal experience of treating 28 patients with resistant CSU in St James's University Hospital Leeds. Furthermore, omalizumab has been shown to be safe, with a more favourable side-effect profile than cyclosporin or prednisolone.

1. Weldon DR, Quality of life in patients with urticaria. Allergy Asthma Proceedings: 27(2): 96-00
2. Zuberbier et al, Allergy 2009: 64: 1427-1443
3. Maurer M. JDDG, 2013;1110: 971-978

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of

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life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice

Omalizumab has been show to be effective for CSU in RCTs (4-6) as well as several case series published worldwide (7-10). Altogether omalizumab has been given to more than 900 patients with CSU, and found to be a very effective and safe short-term treatment (11). This body of evidence is significantly larger then for any other treatment option for antihistamine-resistant patients.

In the UK, the use of omalizumab has been limited to patients in whom all other treatment modalities including cyclosporin and other immunomodulatory drugs, were either ineffective, contraindicated or poorly tolerated due to side-effects. This is in contrast to the RTCs, where omalizumab was used primarily in patients who failed antihistamines only (both the licence does and updosing step).

Generally the rate of complete remission and or very good response to omalizumab ranges between 65-90% (4-10). The response to omalizumab is usually rapid, with the majority of responders showing improvement or full resolution of symptoms even after the first dose. However patients who fail to demonstrate any response to treatment after 3 monthly injections are unlikely to respond if treatment is continued.

There is relatively little evidence about the use of this drug beyond the first few months. Data from the RCTs and published case series, as well as my own clinical experience, would suggest that many patients will experience a relapse of symptoms within 12 weeks of stopping the treatment. We do not know what the optimum duration of treatment is, what proportion of patients are likely to achieve long-term remission and be able to stop treatment, and what proportion will need on-going therapy. However there is evidence to suggest that treatment is equally effective when restarted in patients who relapse after initial withdrawal of omalizumab (8). This finding supports my clinical experience.

Omalizumab can transform a patient's quality of life, allowing some to return to work. Such patients dread the prospect of their disease relapsing, and therefore disruption to their treatment can be very stressful (12). This needs consideration when deciding who should be treated, and for how long. A balance will need to be struck, between treating all those who may potentially benefit, and treating long term those with particularly difficult disease.

Omalizumab has been shown to be safe with no serious side-effects reported.

4. Saini SS, Bindslev-Jensen C, Maurer M, Grob JJ, Baskan EB, Bradley MS, Canvin J, Rahmaoui A, Georgiou P, Alpan O, Spector S, Rosén K. Efficacy and Safety of Omalizumab in Patients with Chronic Idiopathic/Spontaneous Urticaria Who Remain Symptomatic on H₁-Antihistamines: A Randomized, Placebo-Controlled Study. J Invest Dermatol. 2014 Jul 21.
5. Kaplan A, Ledford D, Ashby M, Canvin J, Zazzali JL, Conner E, Veith J, Kamath N, Staubach P, Jakob T, Stirling RG, Kuna P, Berger W, Maurer M, Rosén K Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapyJ Allergy Clin Immunol. 2013 Jul;132(1):101-9.
6. Maurer M, Rosén K, Hsieh HJ, Saini S, Grattan C, Gimenéz-Arnau A, Agarwal S, Doyle R, Canvin J, Kaplan A, Casale T. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med. 2013 Mar 7;368(10):924-35
7. Viswanathan RK, Moss MH, Mathur SK Retrospective analysis of the efficacy of omalizumab in chronic refractory urticaria. Allergy Asthma Proc. 2013 Sep-Oct;34(5):446-52.
8. Metz M, Ohanyan T, Church MK, Maurer M. Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. J Dermatol Sci. 2014 Jan;73(1):57-62.

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9. Labrador-Horrillo M, Valero A, Velasco M, Jáuregui I, Sastre J, Bartra J, Silvestre JF, Ortiz de Frutos J, Gimenez-Arnau A, Ferrer M. Efficacy of omalizumab in chronic spontaneous urticaria refractory to conventional therapy: analysis of 110 patients in real-life practice. Expert Opin Biol Ther. 2013;13(9):1225-8.
10. Song CH, Stern S, Giruparajah M, Berlin N, Sussman GL. Long-term efficacy of fixed-dose omalizumab for patients with severe chronic spontaneous urticaria.
Ann Allergy Asthma Immunol. 2013;110(2):113-7.
11. Kaplan AP. Therapy of chronic urticaria: a simple, modern approach.
Ann Allergy Asthma Immunol. 2014;112(5):419-25.
12. Kai AC1, Flohr C, Grattan CE. Improvement in quality of life impairment followed by relapse with 6-monthly periodic administration of omalizumab for severe treatment-refractory chronic urticaria and urticarial vasculitis. Clin Exp Dermatol. 2014 ;39(5):651-2

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Two recent retrospective observational studies were conducted across several secondary/tertiary care centres in the UK. Data on consecutive patients who had started omalizumab between 19/10/2009-14/02/2014, or ciclosporin between 08/08/2008-31/12/2012, were collected from patients' clinical records. Included in th study were forty-six patients [36(78%) female], with mean age 43.3 years, prescribed omalizumab, and 72 patients [61(85%) female], mean age 40.5 years, prescribed cyclosporin.

Most patients in the omalizumab cohort had previously failed second and third-line therapies, including cyclosporin.

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Although it was not possible to directly compare these two cohorts, since the studies were not designed for this purpose, nevertheless some characteristics and outcomes could be compared between groups. Overall, the omalizumab cohort had longer duration of disease (7.2 years) compared to the ciclosporin group (3.2 years). Unfortunately not all patients had their disease activity formally measured using the Uricaria Activity Score (UAS7) and Quality of Life (QoL) (DLQI); however when comparing patients for whom this information was available, the omalizumab group had a higher starting mean DLQI (21.5) compared to the ciclosporin cohort (16.5). This suggests that the omaizumab group had more resistant and severe disease than the ciclosporin group. This could be anticipated, given the clinical criteria used for commencing patients on omalizumab in the UK.

Around 75% of patients treated with omalizumab achieved either full remission, or a significant reduction in their symptoms. This is comparable to most of the published case series. DLQI was measured at baseline and during treatment in 28 (61%) omalizumab-treated and 17 (24%) ciclosporin-treated patients. Omalizumab and cyclosporin were associated respectively with 16.4 and 8.9 point improvements in DLQI. However, ciclosporin had to be stopped in 20/47 patients due to lack of effect and in a further 13/47 due to side effects. Therefore 70% (33/47), of patients (where this information was available) did not continue with ciclosporin either due to lack of efficacy or side-effects (Table 1). In the omalizumab group, the treatment had to be continued beyond the initial 6 moths or restated in a significant number of patients due to relapse of symptoms (Please see Figure 3)

Table 1 Reasons for stopping ciclosporin treatment

Reason documented	Number of patients N=49*
Lack of effect	**20**
• Lack of benefit/no longer benefitting	17
• Failed treatment	1
• Worsening symptoms	2
Successful treatment	**10**
• Condition improved	10
Not tolerated	**13**
• Side effects/unable to tolerate	5
• Hypertension	3
• Hypertension + gum swelling	1
• Hypertension + renal function	1
• ESR rising	1
• Renal function	1
• Dizzy + peripheral oedema	1

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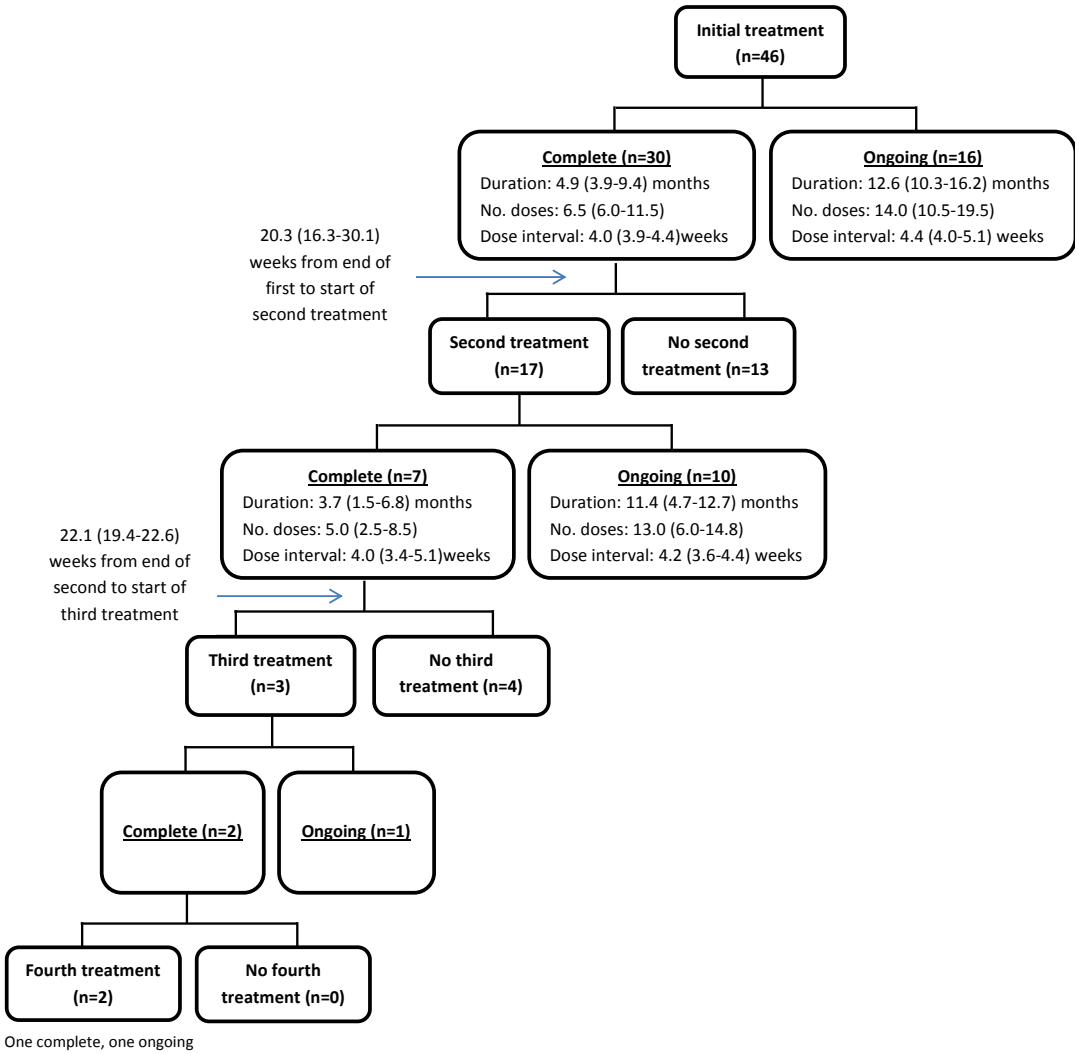
Other	**7**
• Alternative drug	2
• Pregnancy	2
• Patient choice	1
• DNA	1
• Investigations	1

*a total of 50 reasons were given for 49 patients



Duration, number of doses, dose interval and time between treatments presented as median (IQR)

Figure 3 Pattern of omalizumab treatment courses

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Omalizumab was generally well tolerated. Two patients were documented to have had anaphylaxis during the treatment, but it is unclear if this was related to omalizumab itself, or due to disease flare during the course of treatment.

In summary it would appear that omalizumab was more effective and better tolerated then ciclosporin. However there are a number of limitations to these studies, and it is impossible to draw firm conclusions or make specific recommendations based on these findings. These studies were sponsored by Novartis.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

No significant additional resources would be required to make this a standard treatment option, beyond the nursing support required to administer treatment and monitor patients during the therapy. Some of this could be provided by nurses who have previous experience of using omalizumab in patients with asthma