Healthcare professional group/clinical specialist statement

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

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On behalf of:

British Society for Allergy & Clinical Immunology

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? YES
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.

5.2 million people in the UK have asthma. In the current (2004) British Thoracic Society and Scottish Intercollegiate Guidelines network (BTS/SIGN) guidelines on asthma management, widely used throughout the UK, asthma severity is defined in terms of the amount of treatment needed to control symptoms. According to one study (Hoskins G et al. Thorax 2000;55:19-24), 2.4% of patients receive treatment at step 5 (the highest) according to these guidelines: by definition these patients (a minimum of 125,000) have constant symptoms and frequent exacerbations despite taking all established anti-asthma treatment, including systemic steroids. They have a very poor quality of life (Juniper EF et al. Eur Respir J 2004;23:287-291). Most of the £889 million annual direct costs to the NHS of treating asthma (2001 figures) arise from inadequately controlled, severe disease (Barnes P et al. Eur Respir J 1996;9:636-42; Blainey D et al. Health Trends 1990/91:22:151-153). New approaches to treatment of these severe patients are required urgently.

Omalizumab (OZ) is a new technology which may be helpful for some of these severe patients. Since it has been licensed only recently it is not incorporated into the most recent BTS/SIGN guidelines and is so far merely mentioned in more global guidelines (www.ginasthma.com). Consequently, notwithstanding the manufacturer’s recommendations, there is no clear independent consensus regarding the indications for its use. It is currently available from isolated, generally specialist asthma centres in secondary or tertiary care where funding has been negotiated with the relevant health care providers. If given regularly at sufficient dosage (it is a monoclonal antibody which must be injected subcutaneously at intervals of either 2 or 4 weeks depending on the patient), it removes circulating IgE, both total and allergen-specific. This results in secondary reduction of IgE receptors (both high- and low-affinity) on mast cells, basophils and antigen-presenting cells such as dendritic cells and B cells. A working hypothesis (yet to be clearly demonstrated) is that, by removing allergen-
specific IgE, it reduces symptoms and disease exacerbations in asthmatics caused by clinically significant, IgE-mediated allergic reactions to allergens which would otherwise cause histamine release and bronchoconstriction in the airways. In the same way it is likely to ameliorate associated allergic rhinoconjunctivitis and food allergy. It may also impair IgE-mediated allergen capture by antigen-presenting cells such as dendritic cells and B cells, which may inhibit or realign the Th2-like, T cell-mediated response to allergen which is thought to underlie allergic and asthmatic inflammation. OZ therapy has been shown to reduce bronchial mucosal inflammation in allergic asthmatics (Holgate S et al. J Allergy Clin Immunol 2005;115:459-465; Djukanovic et al. Am J Respir Crit Care Med 2004;170:583-593), although the mechanism (in particular if and how this is related to removal of IgE) remains uncertain.

It seems likely, therefore, that OZ therapy will show most benefit in patients with severe, uncontrolled asthma necessitating frequent hospital admission in whom IgE-mediated allergic reactions play a significant role in creating disease instability. Clinically, it is possible to identify such patients based on the taking of a careful history, a consideration of exposure of individual patients to environmental and occupational allergens and appropriate allergy testing. Allergists are well acquainted with this procedure, whereas non-allergist physicians and even many chest physicians are less well trained to assess the contribution of IgE-mediated allergy to asthma exacerbation. Given these considerations, it is unfortunate that the posology and indications for OZ therapy presented in the manufacturer’s SPC do not clearly identify this target group of patients. Definition of “convincing IgE-mediated asthma” in the SPC is based not on careful consideration of the contribution of allergen sensitivity and exposure to asthma exacerbation backed up by appropriate skin prick or in vitro allergy testing, but on a series of essentially arbitrary clinical characteristics of the patients included in the OZ licensing studies (and most particularly the INNOVATE study (Humbert M et al. Allergy 2005;60:309-316). Specifically, definition of “convincing IgE-mediated asthma” in the SPC is based on a threshold minimum concentration of total serum IgE (76 IU/ml, established empirically by analysis of variability of outcome measures in relation to serum total IgE concentrations in the patients in the trials used to license the product), or otherwise a positive skin prick test or RAST to at least one perennial allergen. As allergists are well aware, however, this definition is utter nonsense since individual patients with clinically significant reactions to allergens which may exacerbate asthma may or may not have elevated total serum IgE concentrations. Conversely, whereas a majority of asthma patients (and indeed the general population as a whole) produces IgE against at least one common aeroallergen (as shown by a positive skin prick test or in vitro test), far fewer have clinically significant reactions to these allergens which may cause asthma exacerbation, some who do are not exposed and many have no reaction at all even if exposed. Consequently, the criteria currently recommended by the manufacturers likely include many asthmatics who do not have significant disease exacerbation caused by allergen exposure. It is the view of the BSACI that these shortcomings form the most compelling explanation for why, in the Cochrane analysis of 14 eligible trials of OZ therapy (3143 patients) performed by one of the authors of this manuscript (Walker S et al. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No. CD003559), some 16% of the actively treated patients showed no useful response to OZ therapy at all.

Dosing of OZ according to total serum IgE concentrations and body weight places further restrictions, often inappropriate, on who can be treated (for example, in the Cochrane analysis it was noted that up to 1 in 3 potentially eligible atopic asthmatics were not suitable for treatment, usually because of serum total IgE concentrations...
outside the threshold limits set down in the SPC). Again these restrictions in no measure reflect clinical responsiveness to allergens.

It is the view of the BSACI that eligibility of individual patients for treatment should be based on experienced assessment of the role of allergy in disease exacerbation, backed up by appropriate allergy testing, and not on the basis of total serum IgE concentrations (although these may limit patient eligibility for practical reasons) or arbitrary skin prick tests. This assessment should be undertaken by allergists experienced in chest medicine or chest physicians experienced in allergy.

For this reason patients are likely to be assessed by allergists or respiratory physicians after referral by colleagues within hospital or from primary care. This might necessitate additional hospital clinic services depending on demand. Alternatively, if inclusion criteria were better defined, patients could be screened according to these criteria and then referred directly to a specialist clinic. It is implicit that patients selected for therapy should have severe, unstable disease (at least 2 or more admissions to hospital within the previous year) despite a full trial of, and documented compliance with all the steps of therapy set out in the BTS/SIGN guidelines.

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

The attraction of the technology is that it is a completely novel approach to the treatment of severe asthma which may help some patients who do not respond to available therapy. Since OZ therapy is time consuming and expensive there must be close scrutiny of its benefits. Arguably the best benefits of the therapy from the point of view of the suffering patients could be listed as:

1. Reduction of exacerbations: Stabilisation of uncontrollable asthma, resulting in fewer A&E and hospital inpatient episodes, is clearly an extremely valuable benefit
for the suffering patient as well as the NHS (according to the 2004 NHS Trust Reference Costs Index www.dh.gov.uk/assetRoot/04/10/55/53/04105553.xls (not currently accessible because of DH web site maintenance) the average hospital admission for asthma in the UK costs £1,118.88, while ICU admission increases this cost to £4,656). Data from 2001 confirm that the NHS spent £49 million on asthma inpatient care in this year, not including drugs. These figures are certainly higher now. Several members of the BSACI who have had “hands on” experience with OZ in clinical practice uniformly agree that, in carefully selected patients with allergic asthma requiring BTS/SIGN step 4/5 therapy, the effects of OZ therapy can be dramatic and potentially life saving. Members have cases on file where patients’ lives have been transformed from chaos (multiple admissions, frequent and extended periods away from work) to relative tranquillity. This effect of OZ is reflected clearly in the results of clinical trials, despite the fact that, as has already been emphasised, these trials likely underestimate it. Overall analysis of 7 controlled trials of OZ (Bousquet J et al. Allergy 2005;302-308) with 4,308 participants aged 12-79 years and of duration 24-52 weeks suggested a reduction in the annualised incidence of hospital admissions by 52% and A&E visits by 61% in the active compared with the placebo treated groups. Although there has been criticism of this analysis on the grounds that some of the included studies were not of “Cochrane quality” and not statistically similar enough to combine, the consistency of the findings in all of the analysed studies is striking, and similar conclusions were reached in the Cochrane analysis.

(2) Reduction of oral corticosteroid therapy: No asthmatic patient wishes to be taking oral corticosteroid therapy for protracted periods of time. As well as being a blow to the morale, the unwanted effects of this therapy are well known and themselves incur costs (for example, screening and treatment of osteoporosis). It is the view of the BSACI that the question whether OZ therapy reduces oral steroid requirements in this particular group of asthmatics has not been adequately addressed by trials currently in the literature. Although one might have expected a majority of patients in these trials to have been receiving oral corticosteroids, in fact this was not the case: on the contrary, there were relatively few of these patients overall. Although some individual trials showed benefit, the Cochrane analysis failed to show statistically significant overall reduction of oral steroid dosages compared with placebo. This may simply have reflected statistical underpowering: certainly it would be fallacious to conclude from the current evidence that OZ therapy does not spare oral steroid therapy in these patients. It could be argued that, for most unstable asthmatics, the bulk of oral steroid exposure occurs in association with disease exacerbations, so that a true assessment of the oral steroid sparing effects of OZ should encompass a protracted period of time, certainly longer than the mean duration of the existing trials in the literature. Further trials could be designed to address this question, but they would be long, large and expensive. Alternatively, this effect could be subject to continuous audit in clinical practice.

(3) Reduction in inhaled corticosteroid therapy: The Cochrane review showed that the odds ratios for reducing (by 50%) or withdrawing inhaled steroids were statistically significant in patients treated with OZ as compared with placebo, although the overall daily reduction in inhaled steroid dose was modest in relation to baseline steroid dose. It is the view of the BSACI that, given the vastly superior safety of inhaled, as compared to systemic steroid therapy for asthma, it is questionable whether reduction in inhaled steroid therapy is a valid, or at least a critical outcome measure of the efficacy of OZ in the particular patients in whom it is likely to be effective. In the same vein, it is the opinion of the BSACI that it would not
be helpful or appropriate to compare OZ with other step 4/5 medications (long-acting beta-agonist, leukotriene receptor antagonist) for its capacity to spare inhaled corticosteroid.

(4) Improvement in lung function: Overall the Cochrane analysis showed no significant improvement in lung function in the patients treated with OZ as compared with placebo. Nevertheless most of the trials included in the analysis were not designed to assess this, and many involved concomitant reduction of oral and inhaled steroids, which makes changes in lung function in the relatively short term difficult to interpret. Again it could be argued that, since patients with very unstable asthma may have normal lung function at one moment and severely impaired lung function at the next, it is questionable whether changes in lung function over a relatively short time period from a valid, or at least critical outcome measure.

Since a proportion of patients treated with OZ, at least according to the manufacturer’s inclusion criteria, show no useful response, it is important to monitor patients after commencing therapy for evidence of clinical improvement. The criteria for this are arbitrary but it has been stated that 16 weeks of observation, which is what the manufacturer recommends, is adequate (albeit that the criteria for response and non-response are poorly defined). At the time of writing the manufacturer has undertaken to refund the cost of all unsuccessful treatments of this duration, although in the view of members of the BSACI who have clinical experience with OZ therapy, an observation period of up to 6 months rather than 4 might be preferable.

If treatment is considered successful then it is potentially life long. It is clear that the effects of anti-IgE are rapidly reversed (typically within 8 weeks) if the treatment is discontinued, although it is not clear whether or not a protracted period of therapy may nevertheless have longer lasting clinical benefits. Continuous therapy requires a great deal of commitment on behalf of the patients not only to cooperate with disease monitoring but also to attend every 2 or 4 weeks for life for continued injections. Hopefully this sort of commitment would be engendered by the patients’ existing terrible lifestyles because of unstable asthma. Treatment involves 1-3 subcutaneous injections of OZ at each visit.

OZ must be reconstituted prior to injection. The excipient contains sucrose. Following injection patients must be observed for one hour (two hours after the initial dose) in case of immediate adverse events. Approximately 40% of patients have bruising, erythema and pain at the injection sites. Anaphylactoid reactions appear to be extremely rare (0.1% in a series of 50,000 injections in the United States).

During treatment, and particularly the first 16 weeks, patients must record daily symptoms, time off school and work, use of systemic steroids, unplanned consultations for asthma and morning and evening peak flow in a diary. Accurate keeping of this diary is essential to assess response, and it is recommended that the patient undertakes to comply with this requirement by signing a “patient charter”.

In a centre where more than a handful of severe asthmatics is commenced on OZ therapy, patients making repeat visits will rapidly accumulate and deplete repeat appointment slots in the average asthma outpatient clinic. For this reason, for any more than a few patients treatment is probably best administered during one or more dedicated sessions in a day care setting, where all of the drug required for a single group of patients can be made up in a single batch, minimising waste. Such day care clinics would be best overseen by a nurse or other care professional with a
knowledge of asthma management, with an experienced asthma physician available for consultation but not necessarily constantly on site. Patients would then also be seen in asthma outpatients less frequently for management decisions.

The treatment is expensive (mean £3,330-13,320 per patient per annum). It is not currently excluded from the Payment by Results tariff, but may be considered for exclusion when this is revised in 2007/2008.

There are no long term outcome or safety data as yet. Apart from local pain at the injection sites, other unwanted effects reported in over 50,000 patients now injected in North America remain trivial and of dubious cause and effect.

It would seem prudent to monitor for increased risk of malignancy and helminthic infections.

Summary

It is the view of the BSACI that OZ therapy shows potentially great promise for the management of carefully selected, unstable atopic asthmatics, and that its potential has likely been underestimated by existing clinical trials. Full realisation of its efficacy and cost effectiveness will require refinement of the definition of patients suitable for treatment, and more long term evidence on key outcome measures (which should, we suggest, include frequency of exacerbations with resultant impact on Quality of Life and exposure to systemic corticosteroid).

It is the view of the BSACI that it would be a very retrograde step to dismiss, with our current state of knowledge, the opportunity of accumulation of further clinical experience with the effects of OZ on carefully selected patients, or to abandon collection of this knowledge to the vagaries of company sponsored pharmaceutical trials. The BSACI would like NICE to endorse the opportunity for further studies with OZ along the lines suggested.

This will require a clear directive to purchasers, not only in terms of the indications for and scope of OZ therapy, and the necessary clinical infrastructure, but also in terms of a broad assessment of the cost/benefit and cost/effectiveness. The latter may not always be apparent when considering individual patients and particularly from the point of view of the single PCT.

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.

Report from the Scottish Medicines Consortium

Implementation issues

Clinical Expert Submission Template
Single Technology Appraisal of omalizumab for severe persistent allergic asthma
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)?

NICE guidance on the cost effectiveness of this therapy, which is extremely difficult to estimate with present knowledge, as well as an outline of the logistics necessary for efficient delivery of the therapy and identification of patients most likely to benefit from treatment would all be valid fields of NICE guidance. Favourable decisions would facilitate delivery of care. There would be implications for extra day care clinics and a minor degree of extra staff training as discussed above.