NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Abatacept for the treatment of rheumatoid arthritis only after the failure of conventional disease-modifying anti-rheumatic drugs

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: Professor Peter Charles Taylor

Name of your organisation: Imperial Healthcare NHS Trust and Imperial College London

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.)? ✓ Lead clinician in rheumatology
- other? (please specify)

Peter Taylor

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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.

NICE has previously published guidelines on the management of early rheumatoid arthritis and these broadly reflect current thinking up to the point in treatment at which a patient might benefit from intervention with a biologic agent targeting TNF.[1] NICE have also issued guidance on the use of biologic therapies including anti-TNFs.[2,3,4,5] Recommendations for management of rheumatoid arthritis have also been formulated by the British society for rheumatology and published.[6,7] The most recent BSR recommendations diverge from NICE guidance for initiation of biologic therapies in as much as a threshold disease activity determining recommendation for a trial of biologic anti-TNF is at DAS28 score of greater than 3.2,[8] in line with many other Western European countries whereas the threshold required of NICE guidance restricts access to those with severe disease as determined by a DAS28 above 5.1.[2,4]

In the UK there has been emerging consensus regarding the importance of early intervention in the course of RA with one or more conventional, non-biologic DMARDs of which one will usually be methotrexate unless contra-indicated.[9] Methotrexate dose is titrated up to a level which is tolerated with a view to suppressing inflammation to the point of achieving a low disease activity as assessed by DAS28 of 3.2 or less, or better still, where possible, DAS28 remission criteria with a measure of 2.6 or less. If this treatment goal is not achieved with initial methotrexate as monotherapy or DMARD combination therapy, the next options will depend on the level of DAS28 that is measured. Those patients with severe disease activity represented by DAS28 >5.1 will be considered for anti-TNF treatment. Those with moderately active disease below the threshold recommended by guidance will

usually have adjustments in combination conventional DMARD therapy and very often receive oral or systemic steroid treatment as well.
In the case of patients who either fail to respond to addition of an anti-TNF biologic to their treatment (primary non-response) or those who loose initial response (secondary non-response), the options, depending on the particular anti-TNF used are dose optimisation (within the license for infliximab), class optimisation (anti-TNF switching) or mechanism of action biologic switch. In the latter case, the theoretical options would be B cell depletion with rituximab, IL-6 blockade with tocilizumab, an anti-IL-6R antibody, or co-stimulatory blockade with abatacept. However, the tocilizumab and abatacept options were essentially unavailable to physicians until very recently because reimbursement was widely declined until new NICE guidance issued in 2010.[3,5] This guidance restricts access to tocilizumab and abatacept to third-line (or later) biologic usage.

In May 2010 new European guidelines for management of rheumatoid arthritis were published based on a comprehensive series of systematic literature reviews providing an evidence base and rationale for the recommendations.[10]

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?

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Background comments.

Abatacept is the first, and at present, the only biologic therapy licensed for treatment of RA which targets co-stimulation. Its mechanism of action is entirely distinct from other biologic therapies. It targets the CD28-CD80/86 co-stimulation pathway representing an essential step in activation of T cells required in addition to the trimolecular complex formed by a T cell receptor that uniquely recognises antigen presented in the context of MHC class II expressed by antigen presenting cells. Rheumatoid is known to be a syndrome of heterogeneous expression and pathobiology but the beauty of co-stimulation blockade as a therapeutic approach is that it would be expected to be of benefit in a patient irrespective of the nature of the antigenic drive. There is a compelling clinical trial evidence base demonstrating that abatacept has efficacy in methotrexate naïve,[11] methotrexate-refractory[12] and anti-TNF-refractory subjects.[13] At the present time in the UK, because of various guidance from NICE in recent years, most rheumatologists will have had no experience with abatacept or will have used it as a third or fourth or fifth line biologic therapy. In fact, as is the case with other biologic and conventional DMARD therapies, particularly favourable outcomes are achieved when abatacept is used (in combination with concomitant methotrexate) at early disease stages.[14,15] And because T cell activation is believed to be an initiating event in an immunological cascade observed in rheumatoid arthritis, the theoretical considerations would support the use of abatacept as a first line biologic option. The clinical trial data confirms efficacy.[11]

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?

Abatacept is currently available in the form of an intravenous infusion which is given once monthly. At present, it is envisaged that it will be administered in a secondary care setting although as the best tolerated of currently available intravenous biologics for an RA indication, with the lowest rate of infusion reactions,[16] there are trials underway of administration in a community setting following first three doses in the hospital. Therefore for the short to medium term future it is envisaged that in the UK abatacept will be a secondary care drug administered in dedicated infusion or day case facilities. Infliximab, rituximab and tocilizumab are other biologics delivered intravenously and the same infrastructure support facilities, nursing and medical expertise will be required for each therapeutic option.

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?

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

The use of the technology under clinical trial conditions broadly reflects that observed in clinical practice namely populations of patients with methotrexate refractory disease or anti-TNF refractory disease. There is also trial evidence and theoretical consideration to strongly support use of abatacept in methotrexate naïve patients[11] but this is not within the current abatacept licence in Europe. Standard outcomes were measured in trials including percentage of patients achieving categorical ACR20, 50 and 70% responses at various time points as well as EULAR responses.[12,13] Long term follow up data is available to assess how sustained clinical responses were using either DAS28 as a continuous variable or the ACR categorical measures over time.[12,17,18] Measures of treatment effect on function, assessed by HAQ are also available, and effects on structural damage assessed by standard radiographic scoring methods.[12,13,19] All these measures are of importance from the rheumatologist's perspective; improvement in and duration of response with respect to symptoms and signs, function and joint damage.
Interestingly and importantly, in distinction to clinical trial data with other biologic therapies in RA, for those patients responding to abatacept, incremental responses were observed beyond the first 6 months of treatment.[12,13] This may be related to the unique toleragenic mechanism of action although this has not been proven.

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?

Inflammatory CD4+ T cell dependent processes are highly dependent on co-stimulation whereas anti-viral, CD8 T cell responses are not so dependent.[20] Furthermore, in vitro data shows that LPS induced cytokine production is not inhibited by co-stimulation blockade with abatacept[21] suggesting that such a treatment approach would not abrogate immune responses to bacterial infection. Similarly, in murine models of latent TB, whereas anti-TNF treatment causes TB reactivation and death of all mice, inhibition of co-stimulation with abatacept does not.[22,23] In clinical trials, simple infections are one of the commonest reported adverse events[24] but serious infectious events were observed with lower frequency (2-3 per 100 patient years) than that in most of the clinical studies and registry data concerning other biologic therapies.[25]

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Single Technology Appraisal (STA)

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.

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)?

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

As detailed above, abatacept is given once monthly by intravenous infusion. But because this is already the case for other biologic therapies the NHS infrastructure and staff training required for administration of abatacept is generally already in place around the UK.

[1] NICE. Rheumatoid arthritis. The management of rheumatoid arthritis in adults. NICE clinical guideline 79. Feb 2009. Accessed Online. http://www.nice.org.uk

[2] NICE. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. Technology appraisal guidance 130, Sep 2007. Accessed Online. http://www.nice.org.uk

[3] NICE. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 195, Aug 2010. Accessed Online. http://www.nice.org.uk

[4] NICE. Rheumatoid arthritis – certolizumab pegol: Guidance. NICE technology appraisal 186. Feb 2010. Accessed Online. http://www.nice.org.uk

[5] NICE. Rheumatoid arthritis – tocilizumab. NICE technology appraisal 198. August 2010. Accessed Online. http://www.nice.org.uk

[6] Lugmani R. Hennell s, Estrach C et al. British Society for Rheumatology and British Health Professionals in Rheumatology Guideline for the Management of Rheumatoid Arthritis (The first 2 years). Rheum 2006;45:1167-9

[7] Lugmani R. Hyrich K, Ding T et al. British Society for Rheumatology and British Health Professionals in Rheumatology Guideline for the Management of Rheumatoid Arthritis (After the first 2 years). Rheum 2009;48(3):436-439

[8] Deighton et al. BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. Rheum Mar 2010. 49(6):1197-1199

[9] Management of Early Rheumatoid Arthritis. SIGN Publication No. 48 December 2000, Updated October 2004. Accessed Online. http://www.sign.ac.uk

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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[10] Smolen JS, Landewe R, Breedveld FC et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2009. 69(6):965-975

[11] Westhoven R, Robles M, Ximenes AC et al. Clinical efficacy and safety of abatacept in methotrexate-naïve patients with early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis 2009. 68(12):1870-1877

[12] Kremer JM, Genant HK, Moreland LW et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis. Ann Intern Med. 2006a;144:865-876

[13] Genovese MC, Becker JC, Schiff M et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med 2005;353:1114-23

[14] Bathon J, Genant H, Nayiager S et al. Reduced radiographic progression in patients with early rheumatoid arthritis (RA) treated with abatacept and methotrexate alone: 24 month outcomes. Abs No 639, American College of Rheumatology (ACR)/Association of Rheumatology Health Professionals (ARHP) Annual Scientific Meeting 2009, 17-21 October 2009, Philadelphia, PA, USA.

[15] Westhovens R, Robles M, Nayiager S et al. Disease remission is achieved within two years in over half of methotrexate naïve patients with early erosive rheumatoid arthritis (RA) treated with abatacept plus methotrexate: Results from the AGREE trial. Abs No 638, American College of Rheumatology (ACR)/Association of Rheumatology Health Professionals (ARHP) Annual Scientific Meeting 2009, 17-21 October 2009, Philadelphia, PA, USA.

[16] Yazici Y, Kilfoy SM, Rognan TN et al. Infusible biologic use in an academic and private setting: Different agents are preferred with same low infusion reaction rates with very few discontinuations. Abs No AB0255, Annual European Congress of Rheumatology (EULAR 2009), 10-13 June 2009, Copenhagen, Denmark.

[17] Genovese MC, Schiff M, Luggen M et al. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumor necrosis factor therapy. Ann Rheum Dis 2008;67:547-554.

[18] Kremer JM, Russell A, Emery P et al.: Abatacept demonstrates consistentsafety and sustained improvements in efficacy through 5 years of treatment in biologic-naïve patients with RA; EULAR 2009: FRI0263 Ann Rheum Dis 2009;68 (Suppl 3):444

[19] Genant HK, Peterfy CG, Westhovens R et al.: Abatacept increases the proportion of patients who remain free from structural damage progression through 5 years in methotrexate inadequate responders with RA; Ann Rheum Dis 2009;68 (Suppl 3) 440

[20] Janeway CA Jr, et al. *Immunobiology: The Immune System in Health and Disease,* 6th Ed. New York, United States: Garland Science Publishing 1994

[21] Davis P et al. Abatacept (CTLA4IG) modulates human T-cell proliferation and cytokine production without affecting LPS-induced TNF alpha production. Inflamm Res 2004;(Suppl 3):S226,Abs No A119

[22] Bigbee et al. Abatacept does not exacerbate chronic Mycobacterium Tuberculosis infection in mice. Arthritis Rheum 2007. 56(8):2257-2265.

[23] Haggerty HG, Nadier SG, Simon TA, Corbo M. Utilization of host resistance models (HRMS) in the prediction of human safety of abatacept (ABA): A translational approach. Arthritis Rheum 2007;56(9,Suppl):Abstract 1798 American College of Rheumatology (ACR) and Association of Rheumatology Health Professionals (ARHP) Annual Scientific Meeting, 6-11 November 2007, Boston, USA

[24] Orencia (Abatacept) Summary of Product Characteristics. Accessed Online. July 2010

[25] Hochberg M, Westhovens R & Aranda R et al. *Arthritis Rheum* 2010;62(10 Suppl);S390