The Royal College of Pathologists
Pathology: the science behind the cure

Comments on the Appraisal Consultation Document (ACD) produced for NICE multiple technology appraisal of Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed [ID537]

Thank you for the opportunity to comment on the ACD on behalf of the Royal College of Pathologists (RCPath).

Has all of the relevant evidence been taken into account?

The patients' and clinical experts' perspective that biological therapies have dramatically altered the course of rheumatoid arthritis, RA, contrasts with the analysis presented here that biologics are significantly better than intensive use of conventional agents only in severe disease after failure of conventional DMARDs. We too are convinced the Assessment Group's model has significant advantages over the modelling presented hitherto. However, the sensitivity analyses address technical issues rather than modelling whether plausible clinical effects of biologics are sufficient to reduce ICERs to acceptable levels, which may explain the difference in perspective.

An established body of opinion advocates a paradigm shift in RA towards early intervention with biological therapies when high rates of remission are achievable.[1] The early benefit of clinical remission would be further enhanced by the emerging option of dose reduction or cessation of the biological agent with a significant reduction in drug costs and infection risk .[2, 4] The potential impact of early, durable remission might be further magnified by a delayed effect on reducing the cardiovascular complications of RA which correlate with flares of active disease and the cumulative burden of disease severity.[3, 5] Thus early differences in treatment efficacy might assume increasing importance with time, which is particularly important given the model's lifetime scale. These data inform the likely ranges for key parameters to be tested for their potential impact on the base case assessment that biologics are not cost-effective as initial treatment for severe RA.

Arguably, the potential impact of biologics on cardiovascular disease should also be subject to sensitivity analyses for moderate and severe RA after initial failure of DMARDs (see ID537 Committee papers #1060, #2167).

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes, for the evidence considered but please see above.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

The recommendations are vulnerable to the argument that the model does not adequately address:

i. The potential to reduce or withdraw biologics after inducing remission

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ii. The plausible impact on cardiovascular disease from either

a. Early intervention with biologics in severe RA, OR

b. Following failure of conventional DMARDs in moderate or severe RA

It would be reasonable to ask the Assessment Group to carry out clinically relevant sensitivity analyses with the model to examine the validity of these concerns.

Reference List

1. Emery, P. Why is there persistent disease despite biologic therapy? Importance of early intervention. Arthritis Res Ther. 2014;16:115.

2. Emery P, Hammoudeh M, FitzGerald O, Combe B, Martin-Mola E, Buch MH, *et al*. Sustained Remission with Etanercept Tapering in Early Rheumatoid Arthritis. *N Engl J Med*. 2014;371:1781-92.

3. Myasoedova E, Chandran A, Ilhan B, Major BT, Michet CJ, Matteson EL, *et al.* The role of rheumatoid arthritis (RA) flare and cumulative burden of RA severity in the risk of cardiovascular disease. *Ann Rheum Dis*. 2015; doi: 10.1136/annrheumdis-2014-206411.

4. Singh JA, Cameron C, Noorbaloochi S, Cullis T, Tucker M, Christensen R, *et al*. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. The Lancet 2015;doi: 10.1016/S0140-6736(14)61704-9.

5. Skeoch S, Bruce IN. Atherosclerosis in rheumatoid arthritis: is it all about inflammation? Nat Rev Rheumatol 2015;doi:10.1038/nrrheum.2015.40.

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