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BY EMAIL

10th July 2015

RE: Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and RoActemra for the treatment of rheumatoid arthritis [ID537]

Dear Meindert,

Thank you for giving us the opportunity to comment on the Appraisal Consultation Document (ACD) for the Rheumatoid Arthritis (RA) Appraisal. We are pleased that the Committee has recognised the important place that biologics have in the treatment of RA.

We remain unconvinced that the Assessment Group (AG) have adequately modelled the patient population which is being assessed within the scope of the Appraisal. In our response to the DSU report in April 2015, we highlighted that there were significant differences between the patient population being assessed and those used to evaluate the long term HAQ progression rate. We strongly believe that the Committee is making a recommendation on evidence which is not reflective of the RA population considered in this Appraisal.

We are gravely concerned that those patients who are unable to tolerate MTX will have their access to proven and effective treatments withdrawn. The Committee's draft decision would result in the removal of access for a well-defined group of patients with high unmet need, on the basis of factors that are outside of the scope of this appraisal (i.e. second-line treatment options), despite RoActemra® (tocilizumab) having demonstrated comparable efficacy with or without MTX at the same cost.

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A number of errors and oversights have also been identified, which we believe have not allowed the Committee to generate recommendations based on a complete view of the relevant information.

The following appendix provides further detail on our concerns with the evidence supporting the ACD and suggested approaches to allow the Committee to make a more considered recommendation.

Yours sincerely,

[redacted]

[redacted]

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Significant unmet need in UK patients unable to tolerate MTX

We would like to highlight to the Committee the significant unmet need which exists for a clinically distinct group of RA patients, those who are unable to tolerate or are contra-indicated MTX. The Committee's decision as it stands will remove all biologic treatments for this group of patients, increasing the risk of severe disability and disease progression.

Not all RA patients have the option to use MTX with their biologic due to a number of contra-indications, including (but not limited to) liver or lung disease [Methotrexate Summary of Product Characteristics July 2014[i]]. Furthermore, of those that begin treatment with MTX, a significant proportion (17%) will stop treatment within the first 6 months [Lie et al, 2010**Error! Bookmark not defined.**]. A large body of evidence suggests that between 6-21% of patients will become intolerant to MTX [Calasan et al, 2013[ii]; Fitzpatrick et al, 2012[iii], Hoekstra et al, 2003[iv]; Vertappen et al, 2010[v]; Jacobs et al, 2012[vi]; Schabel et al, 1996[vii]; Kremer et al, 1992[viii]; Lie et al, 2010[**Error! Bookmark not defined.**]].

MTX intolerance can stem from a number of different adverse events, but most commonly cited are those related to gastrointestinal effects. However, just as debilitating, but less well known, are the behavioural symptoms which includes restlessness, irritability and refusal of MTX which develop in response to MTX-induced gastrointestinal symptoms and anticipation thereof [Calasan et al; 2013[ii]].

The current draft recommendation – which will remove patient access to a biologic when administered as monotherapy – will have a significant clinical impact on this group of patients, and will create a significant unmet need.

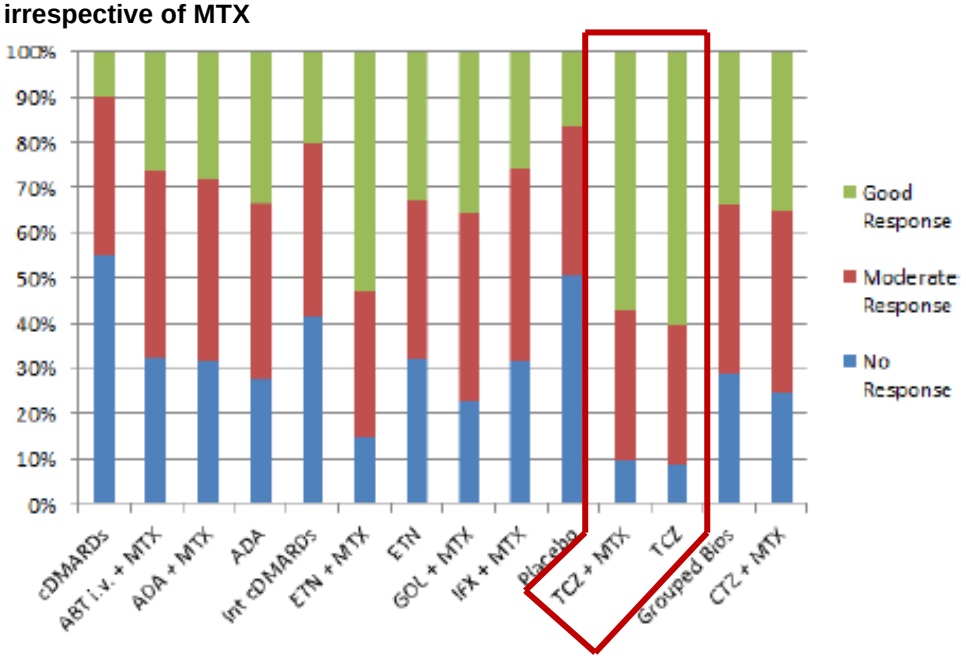
MabThera® as a second-line treatment

The AG report states that RoActemra® (tocilizumab) is less cost-effective in monotherapy than if received as part of combination therapy. This lacks face validity, as RoActemra has comparable outcomes with or without the use of MTX [ACT-RAY Study, Dougados et al, 2012[ix]]. The ACT-RAY study demonstrated that after 24 weeks of treatment in patients who had previous exposure to MTX, there was no statistically significant difference in clinical or radiographic outcomes, between patients treated with RoActemra monotherapy and patients treated with RoActemra + MTX

combination therapy. The data demonstrate that RoActemra efficacy is not compromised for patients who require biologic monotherapy and who are intolerant to/cannot continue to take MTX.

The AG correctly identified the main driver for the difference in the ICERs to be a result of the cost of later line therapies, and not the efficacy of the interventions under assessment in this Appraisal (as highlighted in Figure 1).

Figure 1: Assessment Group Network Meta-Analysis: no difference in RoActemra (TCZ) outcomes, irrespective of MTX



The analyses conducted by the AG did not consider the use of MabThera® (rituximab) as a monotherapy agent following a patient's progression on one of the interventions considered in the scope. Although not licensed, MabThera is routinely used in the UK as monotherapy treatment, as supported by numerous local treatment protocols [Pan Mersey; Guys and St Thomas'; Lancashire; Manchester[x]].].

We have provided a recent real world study, which evaluated the outcomes of patients treated with MabThera in Germany [Wendler et al, 2014[xi]]. The efficacy of MabThera as a monotherapy treatment is comparable to that when used as part of combination therapy. Therefore, when MabThera is included in both treatment lines as a second line therapy, the ICER for RoActemra will be similar in monotherapy and combination treatment. We would be disappointed if the Committee made the decision to not recommend biologics in those RA patients who cannot receive MTX,

based on an analysis which does not reflect UK treatment practice and falls outside the scope of this Appraisal.

While MabThera does not have a licence for use as a monotherapy treatment in RA, it is common practice in the UK for it to be used in this setting, as supported by numerous local protocols [Pan Mersey; Guys and St Thomas'; Lancashire; Manchester**Error! Bookmark not defined.**]. If the AG were to reflect routine UK clinical practice for the treatment of RA patients intolerant or contra-indicated to MTX, the clinical data for RoActemra and MabThera would support a similar cost-effectiveness result in the AG analyses, irrespective of the use of MTX.

Factual error and oversight in the AG modelling

i. Applicability of 'fast progressing' patients in the monotherapy

The Committee considered at the last Appraisal Meeting a subgroup of patients who are deemed to have 'faster progressing' RA. The AG completed the analysis for patients with 'faster progressing' RA when biologics are prescribed in combination with MTX. We believe the Committee has overlooked the relevance of this subgroup in those patients who cannot tolerate MTX. We consulted an expert clinical specialist, who explained that the baseline progression rate would be the same whether a patient can or cannot tolerate MTX. Therefore, it would be appropriate for the AG to perform a similar 'fast progressing' analysis for monotherapy patients. The AG did not present this analysis to the Committee, and we believe this is critically important in order for a fair and equitable decision to be made.

ii. Monotherapy analysis in the economic model

In replicating the results of the AG, we believe the treatment costs of MTX have been erroneously included in the modelling of the monotherapy treatment arm. Based on the terms of the confidentiality agreement under which the economic model was distributed, we have not rerun the model, but believe the impact of replacing the cost of MTX with sulfasalazine would slightly improve the ICER for all treatments.

References

[i] Methotrexate 10 mg Tablets, Summary Product Characteristics.
http://www.medicines.org.uk/emc/medicine/12034/SPC/Methotrexate+10+mg+Tablets+(Hospira+UK+Ltd)

[ii] Ćalasan MB, van den Bosch OF, Creemers MC, Custers M, Heurkens AH, van Woerkom JM, et al. Prevalence of methotrexate intolerance in rheumatoid arthritis and psoriatic arthritis. Arthritis Res Ther. 2013;15(6):R217.

[iii] Fitzpatrick JD, *et al.* EULAR 2012; Poster THU0135

[iv] Hoekstra M, van Ede AE, Haagsma CJ, van de Laar MA, Huizinga TW, Kruijsen MW, Laan RF. Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. Ann Rheum Dis. 2003 May;62(5):423-6.

[v] Verstappen SM, Bakker MF, Heurkens AH, van der Veen MJ, Kruize AA, Geurts MA, Bijlsma JW, Jacobs JW. Adverse events and factors associated with toxicity in patients with early rheumatoid arthritis treated with methotrexate tight control therapy: the CAMERA study. Ann Rheum Dis. 2010 Jun;69(6):1044-8. doi: 10.1136/ard.2008.106617. Epub 2009 Jul 5.

[vi] Bakker MF1, Jacobs JW, Welsing PM, Verstappen SM, Tekstra J, Ton E, Geurts MA et al. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. Ann Intern Med. 2012 Mar 6;156(5):329-39. doi: 10.7326/0003-4819-156-5-201203060-00004.

[vii] Schnabel A1, Herlyn K, Burchardi C, Reinhold-Keller E, Gross WL. Long-term tolerability of methotrexate at doses exceeding 15 mg per week in rheumatoid arthritis. Rheumatol Int. 1996;15(5):195-200.

[viii] Kremer JM, Phelps CT. Long-term prospective study of the use of methotrexate in the treatment of rheumatoid arthritis. Update after a mean of 90 months. Arthritis Rheum. 1992 Feb;35(2):138-45.

[ix] Dougados M, Kissel K, Sheeran T, Tak P, Conaghan P, Mola E, et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). Ann Rheum Dis doi:10.1136/annrheumdis-2011-201282.

[x] UK Local RA procotols.
http://www.panmerseyapc.nhs.uk/results.html?cx=008571615822552885495%3AWMX-310891607&ie=UTF-8&q=rheumatpid+arthritis+biologic+pathway&sa=Search
http://www.lambethccg.nhs.uk/news-and-publications/meeting-papers/south-east-london-area-prescribing-committee/Documents/Clinical%20guidelines%20and%20pathways/Rheumatoid%20Arthritis%20Biologic%20Drug%20Treatment%20Pathway%20March%202015.pdf
http://www.lancsmmg.nhs.uk/wp-content/uploads/sites/3/2013/04/LMMG-Recommended-Rheumatoid-Arthritis-Biologic-Pathway-September-2014.pdf
http://gmmmg.nhs.uk/docs/guidance/GMMMG%20RA%20Pathway%2022%20april_2015.pdf

[xi] Wendler J, Burmester G, Sorensen H, Krause A, Richter C, Tony H, et al. Rituximab in patients with rheumatoid arthritis in routine practice (GERINIS): six-year results from a prospective, multicentre, non-interventional study in 2,484 patients. Arthritis Research & Therapy 2014, 16:R80.