

## Statement from the Regional HTA Centre of Region Västra Götaland, Sweden

**Treatment of early rheumatoid arthritis with a combination of TNF-alpha inhibitors and methotrexate, versus methotrexate alone**Question at issue:

Is treatment with TNF-alpha inhibitors and methotrexate better regarding effect on disease activity, physical function, bone alterations, quality of life, and ability to work, compared to treatment with methotrexate alone, in patients with early rheumatoid arthritis (RA) with high disease activity and negative prognostic factors?

PICO (Patient, Intervention, Comparison, Outcome)

- P = Patients with early RA (duration  $\leq 3$  yrs.), high disease activity
- I = TNF-alpha inhibitor + methotrexate
- C = Methotrexate alone
- O = Disease activity, measured with validated scale (DAS 28, ACR at least 20%)  
Physical function, measured with HAQ  
Radiographic joint alterations  
Quality of life  
Ability to work

**Summary of the health technology assessment:**Method and patient category:

A systematic literature search was undertaken and followed by a formalized exclusion process. This exclusion process generated a total of 30 articles, of which eight were judged to meet the PICO. With one exception, these articles were based on three different patient populations: ASPIRE (n=1049, St Clair et al 2004), PREMIUM (n=525, Breedveld et al 2006) and COMET (n=542, Emery et al 2008). Three different TNF inhibitors were used (ASPIRE: infliximab; PREMIER: adalimumab; COMET: etanercept), but based on the assumption of a class effect, the studies were pooled. Since there were several large RCTs, we included a limitation to studies of 100 patients or more, and only RCTs. Regarding side effects, these were only reported for the three large randomized 'key' trials. The main reason for this decision was that the adverse events literature was based on other patient populations than the population targeted in this HTA.

Level of evidence:

There is limited scientific evidence (level of evidence 3) for a clinically relevant positive effect of combined treatment for the outcomes: disease activity, physical function, radiographic skeletal alterations, and health-related quality of life. The scientific support was considered to be insufficient (level of evidence 4) for the outcome ability to work. The main reasons for assigning these large RCTs in two cases moderate and in one case low level of evidence, is the lack of report of items related to external validity throughout the articles, and, in one of the trials, an unacceptably high drop-out rate in the methotrexate group.

Adverse effects and risks

In the included studies we consider that there is an acceptable balance between the side effects profile, the therapeutic indication, and the magnitude of the therapeutic response. The main problem is the increased risk of serious infections.

Ethical aspects:

Introduction of anti-TNF-alpha therapy for early RA will entail a substantial cost increase with risk of displacement effects. On the other hand, it is difficult to ethically justify withholding an efficient therapy for prevention of progression of an incapacitating disease in this relatively young patient population.

Economical aspects

Based on an average annual cost of 110,000 SEK per patient, the drug costs are expected to increase by about 10 MSEK/year in Västra Götaland Region. Against this must be weighed the increased need for outpatient resources, the expected reduced need for inpatient beds, as well as the anticipated long-term reduction in sick leave.

Concluding remarks

There is limited scientific support for a clinically relevant positive effect, by addition of a TNF-alpha inhibitor to methotrexate, for treatment of patients with early rheumatoid arthritis and unfavorable prognostic signs. The direct cost of the introduction is expected amount to about 10 MSEK/year in Västra Götaland Region. In addition, it is difficult to estimate restructuring costs in the health care organization. The side effect issue is considered manageable, taking into account the severity of the disease.

On behalf of the Regional HTA Centre of Region Västra Götaland, Sweden.

Göteborg, Sweden, 2009-09-30.

Christina Bergh, Professor, MD.

Head of Regional HTA Centre of Region Västra Götaland, Sweden.