Tumor necrosis factor alpha antagonists in the treatment of rheumatoid arthritis – Economic efficiency


OBJECTIVE
Rheumatoid arthritis (RA) is the most prevalent inflammatory rheumatic disorder. It is a chronic and incurable disease that leads to painful inflammation, often irreversible joint damage, and eventually to functional loss.

Conventional treatment is based on unspecific immunosuppressive agents, e.g. Methotrexate, Azathioprin or Gold. However, the long-term outcomes of these approaches have been poor with frequently ongoing inflammatory disease activity, functional decline, and temporary or permanent work disability. More recently, antagonists of the human cytokine Tumor Necrosis Factor α (TNF-α) have been introduced that are potent suppressors of inflammatory processes. Infliximab is a chimeric antibody against TNF-α. Etanercept is a soluble human TNF-α receptor.

The report assesses the efficacy of TNF-α-antagonists to down-regulate inflammation, improve functional status and prevent joint damage in RA with particular regard to the following indications: Treatment of severe, refractory and ongoing disease activity despite adequate use of conventional antirheumatic agents; and treatment of early RA before conventional treatment failure has been demonstrated.

METHODS
A systematic review of the literature has been performed using established electronic databases. The literature search is supplemented by a hand search of journals and publications relevant to RA, reviews of websites of national and international rheumatologic expert societies, as well as contacts to manufacturers. A priori defined inclusion and exclusion criteria are used for literature selection. Analysis and evaluation of included publications are based on standardised criteria sets and checklists of the German Scientific Working Group for Technology Assessment in Health Care.

RESULTS
Health Technology Assessment reports and metaanalyses cannot be identified. A total of 12 clinical trials are analysed, as well as national and international expert recommendations and practice guidelines. Numerous non-systematic reviews are found and analysed for additional sources of information that is not identified through the systematic search. Case reports and safety assessments are considered as well. A total of 137 publications is included.

The primary outcome measures in clinical trials are suppression of inflammatory disease activity and slowing of structural joint damage. Clinical response is usually measured by standardised response criteria that allow a semi-quantitative classification of improvement from baseline by 20%, 50%, or 70%.

In patients with RA refractory to conventional treatment, TNF-α-antagonists are unequivocally superior to Methotrexate with regard to disease activity, functional status and prevention of structural damage. In patients with early RA, TNF-α-antagonists show a more rapid onset of anti-inflammatory effects than Methotrexate. However, differences in clinical response rates and radiologic progression disappear after a few months of treatment and are no longer statistically significant. Serious adverse events are rare in clinical trials and do not occur significantly more often than in the control groups. However, case reports and surveillance registries show an increased risk for serious infectious complications, particularly tuberculosis. Expert panels recommend the use of TNF-α-antagonists in patients with active refractory RA after failure of conventional treatment. Studies that compare Infliximab and Etanercept are lacking.

There are no pharmacoeconomic studies although decision analytic models of TNF-α-antagonists for the treatment of RA exist. Based on the results of the models, a combination therapy with Hydroxychloroquin (HCQ), Sulfasalazin (SASP) and Methotrexate as well as Etanercept / Methotrexate can be considered a cost-effective treatment for Methotrexate-resistant RA.

CONCLUSIONS
TNF-α-antagonists are clearly effective in RA patients with no or incomplete response to Methotrexate and superior to continuous use of Methotrexate. It refers to both, reduction of inflammatory disease activity including pain relief and improved functional status, and prevention of structural joint damage. Therefore, TNF-α-antagonism is an important new approach in the treatment of RA.
There is still insufficient evidence that early use of TNF-α-antagonists in RA prior to standard agents is beneficial and further studies have to be awaited.

An analytic model suggests that TNF-α-antagonists are, due to their clinical effectiveness in patients with no or incomplete response to Methotrexate, a cost-effective alternative to common therapies chosen in the subpopulations of patients. Nevertheless, it has to be borne in mind that the acquisition costs of TNF-α-antagonists lead to high incremental costs and C/E ratios, which exceed the common frame of assessing the cost-effectiveness of medical methods and technologies. Hence, society’s willingness-to-pay is the critical determinant in the question whether TNF-α-antagonists shall be reimbursed or not, or to define criteria for reimbursement. Changes in the quality of life attributable to the use of TNF-α-antagonists in RA have not yet been assessed which might assist the decision making.

With respect of the questions mentioned above and the potential financial effect of a systematic use of TNF-α-antagonists in the treatment of RA, we come to the conclusion that TNF-α-antagonists should not introduced as a standard benefit reimbursed by the statutory health insurers in Germany.

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