Biologics for early rheumatoid arthritis

This is an excerpt from the full technical report, which is written in Norwegian.

The excerpt provides the report's main messages in English.

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Systematic review

kunnskapssenteret

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Norwegian Knowledge Centre for the Health Services summarizes and disseminates evidence concerning the effect of treatments, methods, and interventions in health services, in addition to monitoring health service quality. Our goal is to support good decision making in order to provide patients in Norway with the best possible care. The Centre is organized under The Norwegian Directorate for Health, but is scientifically and professionally independent. The Centre has no authority to develop health policy or responsibility to implement policies.

We would like to thank all contributers for their expertise in this project. Norwegian Knowledge Centre for the Health Services assumes final responsibility for the content of this report.

Norwegian Knowledge Centre for the Health Services
Oslo, April 2010

Key Messages (in English)

Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes inflammation of the joints. The disease affects 0.5% to 1% of the adult population, and causes severe pain and disability. Direct costs related to treatment, and indirect costs associated with occupational disability, is significant. RA is treated with an interdisciplinary approach, in which disease modifying anti-rheumatic drugs (DMARDs) are an important component. The recommended first choice is one or more DMARDs. In the absence of treatment effect, a biologic drug may be added.

The purpose of this systematic review was to investigate the efficacy and safety of biologics, compared with DMARDs in patients with early (≤ 3 years) RA. The commisioner is the Norwegian Rheumatism Association, whose members are concerned with good treatment at the early stages of RA.

We included a total of 12 randomised controlled trials that examined the effect of biologics infliximab, adalimumab, etanercept and abatacept. The results suggest that, compared with DMARDs alone, biologicals in combination with DMARDs give:

- more patients in remission
- neither more or less serious adverse events
- more patients who achieved a 50% improvement
- improved physical function
- less joint destruction

Due to methodological weaknesses in the included studies most results contain some degree of uncertainty.

Biologics for early rheumatoid arthritis

What kind of report is this?

Systematic review
-A systematic review of knowledge is the result of collecting, critically review and summarize relevant research results using pre-defined and explicit methods.

This report includes:

- We included a total of 12 randomised controlled trials that examined the effect of biologics infliximab, adalimumab, etanercept and abatacept.

Not included:

- Studies that did not fulfill the inclusion criteria.

Who produced it?

- The Norwegian Knowledge Centre for the Health Services on behalf of the Norwegian Rheumatism Association

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When was it written?

Latest search for studies: September 2009.

Executive summary (in English)

Biologics for early rheumatoid arhritis

BACKGROUND

Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes inflammation of the joints. The disease affects 0.5% to 1% of the adult population. More women than men are affected, and the incidence increases with age. RA causes tender, swollen and stiff joints. Other organs may also be affected. Most RA patients experience reduced physical function and occupational disability.

RA is treated with an interdisciplinary approach that includes pharmacotherapy, physical therapy, occupational therapy and patient education. Disease modifying anti-rheumatic drugs (DMARDs) are an important component of the pharmacotherapeutic approach. Early introduction of DMARDs provides greater health benefits than delayed treatment. Biologic medicines are a relatively new treatment option with documented effect on established RA. The biologic agents, however, entail a risk of resistance development, and are very costly. Both Norwegian and international rheumatologists and health authorities recommend DMARDs as the first line pharmacotherapy. If the desired effect is not achieved, they recommend the addition of a biologic agent.

In February 2009, the Norwegian Rheumatism Association commissioned the Norwegian Center for Health Services to summarise the available research on the effects and safety of early interventions in rheumatoid diseases, and to prepare an economic evaluation of such interventions. In understanding with the commissioner, we have chosen to limit the current report to a systematic review of the efficacy and safety of biologics compared with DMARDs in people with RA for less than three years.

METHOD

We searched systematically for literature in EMBASE, Medline (Ovid) and Cochrane Library. In addition, we went through the reference lists of relevant publications, searched for relevant websites and contacted experts, affected companies and the

Norwegian Rheumatism Association.

Two researchers independently reviewed abstracts and full text publications for inclusion. We included randomised controlled trials (RCTs) that studied the efficacy and safety of biologics (etanercept, infliximab, adalimumab, rituximab, tocilizumab, anakinra or abatacept), alone or in combination with DMARDs, in people with RA of the maximum three years' duration. Relevant RCTs should have one or more DMARDs as comparison, and outcomes should include disease progression, quality of life, employability, functioning and safety. We included publications in all languages, provided that the abstract was in English or one of the Scandinavian languages.

The included studies were critically appraised before we extracted relevant data. Where possible and appropriate, we combined results in meta-analyses. We also assessed the overall quality of the documentation for each outcome. The final report has been subject to internal and external peer reviews.

RESULTS

The search strategy resulted in 1560 unique references, of which abstracts we reviewed. Of 144 possibly relevant full-text publications, we included 15. The included publications covered 12 RCTs that examined the efficacy and safety of infliximab, adalimumab, etanercept or abatcept among RA patients with less than 3 years disease duration. All studies except one combined a biologic agent with the DMARD methotrexate (MTX), and MTX was the control condition in all studies. We assessed the risk of bias as low for all outcomes in four of the studies, as unclear in five trials, as unclear for some outcomes, and high for some outcomes in two studies, and as high for all outcomes in one study.

We found evidence of low quality that biologics in combination with MTX for more patients in remission after one year than MTX alone (RR 1.78 [1.55 to 2.03]). Documentation of very low quality showed no difference between groups in the incidence of serious adverse events (RR 1.08 [0.84 to 1.39]). More patients receiving the combination biologics/MTX achieved a 50% improvement (RR 1.44 [1.30 to 1.60], medium quality), and this patient group had greater improvement in physical function (MD -0.28 [-- 0.35 to -0.21], medium quality) and less radiographic progression (MD -4.13 [-5.22 to -3.04], high quality).

Most results for individual biologics had weak evidence, except the following: less increase in disease activity with infliximab/MTX, less increase in radiographic progression with infliximab/MTX and with etanercept/MTX, and equal incidence of adverse events with infliximab/MTX and with etanercept/MTX.

DISCUSSION

Methodological weaknesses in the included studies implie that most results contain some degree of uncertainty. Still, some of the evidence was high quality. Moreover, the results were consistent with results from meta-analyses of effects and safety of biologics in patients with established illness. This strengthens our confidence in the effect estimates.

Our main outcome, remission, was only reported in five of the included studies. The evidence was unclear, but clinically significant.

We found that the risk of side effects and severe adverse events were similar in groups randomised to biologics and DMARDs. Our findings confirm some of the existing evidence, but there are also studies showing the contrary. It seems that the issue of safety of biological drug use is still unresolved.

We have probably used a fairly broad definition of early RA, and may thus have included patients with established disease. ACR and EULAR have developed new classification criteria for RA, which will be published in the near future. With the new criteria it is likely that RA could be identified at an earlier stage.

Our systematic review has not compared biologics to each other. We are therefore unable to contribute to decisions on the choice of drug.

Further, we have not been able to answer the important question about which patients would be most likely to achieve remission after early intervention with biologics.

CONCLUSION

This systematic review has shown that biologics combined with DMARDs may increase remission by 78% compared to treatment with DMARDs alone. In absolute figures, 45% and 25% achieved remission with the use of biologics combined with DMARDs and DMARDs alone, respectively. It remains unclear whether biologics use is associated with an increased risk of adverse effects. Compared with DMARDs, the use of biologics can be expected to limit radiographic progression during the first year of therapy, but the clinical significance of this finding implies that the difference in the effect persists over the years. All other outcomes were in favour of biologics, but methodological weaknesses imply a degree of uncertainty.

Future research should focus on very early RA, and perhaps only include people who are recently diagnosed with the new ACR-/EULAR-criteria. Moreover, an important future research task is to identify subgroups of early RA patients who would obtain

remission with biologics as first line treatment. Head-to-head studies that examine the relative effects of the various biological agents are also an imminent research need.

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