Rheumatoid arthritis: Biologics in second-line therapy show benefit

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The German Institute for Quality and Efficiency in Health Care (IQWiG) examined 9 biotechnologically produced drugs for the treatment of adults with rheumatoid arthritis in whom prior pharmacological treatment had failed. According to the findings, for each drug the data provide proof, an indication, or at least a hint of a benefit in relation to at least one outcome criterion. This is the conclusion of the final report published by IQWiG on 26 August 2013.

In comparison to the preliminary report, additional data and studies confirm the positive effect of biologics. However, there is a lack of long-term data and robust direct comparisons of biologics with each other to be able to assess which of these drugs are better or less suited in second-line therapy.

Alleviation of pain and prevention of damage to joints

Rheumatoid arthritis is an autoimmune disease and the most common form of chronic inflammatory joint disease (0.5 to 1% of the EU population). Patients suffer from pain, fatigue and exhaustion, depressive moods, as well as functional limitations; these symptoms are accompanied by a loss of quality of life, independence and participation in social and occupational activities. The primary aim of treatment is thus to eradicate the symptoms of disease as far as possible and delay or prevent the destruction of joints (remission).

Nine biologics in second-line therapy

Disease-modifying antirheumatic drugs (DMARDs), among others, are used in the pharmacological treatment of rheumatoid arthritis, which, in contrast to anti-inflammatory drugs, intervene with the disease mechanism itself. Biotechnologically produced DMARDs (bDMARDs), called biologics, are harvested from living cell cultures.

The bDMARDs intervene at different points of the inflammation process via different mechanisms. Most of them inhibit the tumour-necrosis factor (TNF)-?, a factor that influences the inflammation process. According to treatment recommendations, the administration of a bDMARD is indicated as second-line therapy for patients in whom prior therapy failed to achieve the desired success or had no effect at all.

Nine such drugs were available in 2010 at the time IQWiG was commissioned to conduct the present benefit assessment: abatacept (trade name: Orencia), adalimumab (Humira), anakinra (Kineret), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), rituximab (MabThera), and tocilizumab (RoActemra).

Treatment in placebo groups discontinued more frequently

A total of 35 studies were relevant for the present benefit assessment; however, some only reported results for subpopulations. In nearly all studies patients received the cytostatic drug methotrexate (MTX), which is used as basic therapy in inflammatory-rheumatoid diseases. One patient group additionally received a biologic; the control group mostly received placebo.

In 28 studies it was possible to adapt therapy if patients responded insufficiently to treatment. This occurred very frequently and was far more common in the placebo groups than in study participants treated with a biologic. Moreover, many participants discontinued the studies due to a lack of efficacy; this mainly applied to patients who had received placebo.

It is therefore possible that the results are biased for some outcome criteria. If possible, the impact of potential bias was tested by IQWIG using sensitivity analyses. According to the findings, despite potential bias, the effects found in the studies in favour of the biologics were often large enough, for example, to infer proof of a benefit instead of an indication of a benefit.

All biologics offer advantages

For 5 drugs (abatacept, adalimumab, certolizumab pegol, golimumab, and tocilizumab), proof of a benefit could be inferred for the outcome criteria "remission", "symptoms" (e.g. pain, swelling of joints, and morning stiffness), "physical functional status" and/or "quality of life". For the other 4 biologics (anakinra, etanercept, infliximab, and rituximab), there was no proof, but indications or at least hints of an advantage in relation to at least one of the outcome criteria.

However, for 3 drugs (adalimumab, certolizumab pegol, and tocilizumab) the data provided at least hints of harm from side effects (e.g. infections or study discontinuations due to adverse events). For the other 6 biologics, on the basis of the available studies the data provided no proof, indications or hints that these drugs caused such harm (or no such harm).

Hardly any direct comparisons available

Informative direct comparisons in which biologics were used according to their approval status are still lacking, as are long-term data on benefit and harm, even though some of the 9 biologics have been on the market for over 10 years. The biologics were solely compared with placebo in nearly all of the studies. However, direct comparisons are needed to draw robust conclusions on the comparison of biologics with each other. Only one direct comparison of 2 bDMARDs used in monotherapy (tocilizumab versus adalimumab) was relevant for the benefit assessment. As other relevant direct comparisons are lacking, it cannot yet be determined which of the 9 drugs are better or less suited in the second-line therapy of adults with rheumatoid arthritis.

Lack of long-term studies

Moreover, the placebo-controlled studies largely covered only a period of at most a year. However, side effects of biologics can also occur after longer periods of time. In addition, structural changes to joints, for which no data were recorded in any of the studies, can only be diagnosed after a longer period of time.

Because of the positive effects of biologics, placebo-controlled long-term studies on the research question investigated by IQWiG would not be ethically acceptable. This underlines the necessity of long-term direct comparisons, particularly for chronic diseases such as rheumatoid arthritis.

Additional data and study results

Changes to the final report in comparison to the preliminary report are predominantly caused by the changed data basis: On the one hand, IQWiG as usual updated the literature search; on the other, the drug manufacturers submitted supplementary information in the commenting

procedure. For several of the drugs investigated, they submitted both new studies and new data on studies already included in the preliminary report.

At least 3 randomized controlled trials (RCTs) were available for 6 drugs: 6 each for abatacept, adalimumab and tocilizumab, 4 each for certolizumab and etanercept, and 3 for golimumab. Only 2 RCTs each were available for the benefit assessment of anakinra and rituximab and only 1 RCT was relevant for infliximab after a further study had to be excluded because the comparator drug (sulfasalazine) had not been administered in compliance with the approval status.

Stefan Lange, the Deputy Head of IQWiG, concludes: "In comparison to the preliminary report we were able to consider 7 further studies and several additional analyses. This again shows that transparency of scientific data and complete publication of all studies are worthwhile – for all parties involved. Unpublished data and insufficiently analysed studies can only cause harm."

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