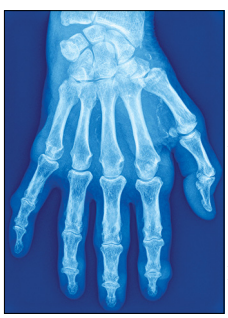
Beyond methotrexate monotherapy for early rheumatoid arthritis



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Findings from the U-Act-Early strategy trial in patients with early rheumatoid arthritis by Johannes Bijlsma and colleagues[1] in *The Lancet* suggest that current standard care initiating monotherapy with the conventional synthetic disease-modifying antirheumatic drug (DMARD) methotrexate is suboptimal. The trial investigators enrolled 317 patients from 21 Dutch rheumatology outpatient departments and randomly assigned them to start tocilizumab (an interleukin-6 receptor-blocking monoclonal antibody) plus methotrexate, or tocilizumab, or methotrexate. With initial methotrexate therapy, 48 (44%) of 108 patients had sustained remission compared with 91 (86%) of 106 patients with initial tocilizumab plus methotrexate therapy and 86 (84%) of 103 with initial tocilizumab therapy (relative risk [RR] 2·00, 95% CI 1·59–2·51 for tocilizumab plus methotrexate *vs* methotrexate, and 1·86, 1·48–2·32 for tocilizumab *vs* methotrexate, p<0·0001 for both). Additionally, 12 (11%) of 108 patients assigned to initial methotrexate therapy had sustained drug-free remission compared with 37 (35%) of 106 patients assigned to initial tocilizumab plus methotrexate and 28 (27%) of 103 patients assigned to initial tocilizumab (p<0·0001 for tocilizumab plus methotrexate *vs* methotrexate, p=0·0037 for tocilizumab *vs* methotrexate). Early intervention and targeting remission were two non-contentious themes in the U-Act-Early trial, whereas intensive initial treatment, which achieved substantially more remissions in the trial, remains challenging because it involves comparing efficacy, toxicity, and costs.

Before 1950, only simple symptomatic care was available for rheumatoid arthritis and only 15% of patients achieved remission.[2] During the next 40 years, first-line treatment was based on non-steroidal anti-inflammatory drugs, with gold and other second-line drugs reserved for non-responders—gold toxicity made this approach reasonable. The advent of effective and safer disease-modifying drugs such as methotrexate created pressures to invert the so-called therapeutic pyramid,[3] and gradually, methotrexate became the initial treatment of choice. With initial methotrexate or other synthetic disease-modifying drugs, 20–30% of patients have remissions.[4]

North American and European guidance recommends methotrexate monotherapy as initial treatment for rheumatoid arthritis,[5,6] but guidance for England differs, recommending initial combinations using methotrexate and other synthetic disease-modifying agents with short-term glucocorticoids.[7] Findings from previous trials assessing the approach from England show more remissions, although these rarely exceed 50%.[8] Biological drugs are highly effective in rheumatoid arthritis but are mainly reserved for patients who do not adequately respond to methotrexate and other synthetic DMARDs. Findings from a systematic review of trials of biological drugs in patients with early rheumatoid arthritis showed that they increased remissions by 74%[9]—therefore, the proportions of patients who achieved remission in Bijlsma and colleagues' trial[1] are among the highest reported.

The benefits of intensive treatments must be balanced against risks and costs. Some combinations of conventional disease-modifying drugs increase toxicity compared with monotherapy,[10] but some have less toxicity—eg, triple therapy with methotrexate, sulfasalazine, and hydroxychloroquine. With biological drugs, infection is the predominant concern, although registry data[11] show that the risks appear acceptable. The findings from the U-Act-Early trial[1] showed no evidence that combinations of drugs increased adverse events.

Another consideration is that biological drugs are expensive and their cost-effectiveness in established rheumatoid arthritis remains debatable, with uncertainties in early disease.[12] However, the cost-effectiveness of biological drugs might cause less concern in the future for several reasons. First, as biosimilars become available, costs should reduce. Second, biological drugs can be tapered or stopped in some responders, especially when used in early disease. Finally, a growing understanding of the long-term benefits of early remission on disability, quality of life, and work disability should provide new health-economic insights that might favour biological

drugs. Short-term remission-induction strategies with biological drugs are also likely to become more affordable and cost-effective.

Many factors influence clinicians' perspectives on optimum intensive treatment strategies. Hazlewood and colleagues[13] present a cogent case for making triple therapy the initial intensive regimen. However, this viewpoint must be assessed against the consistent emphasis placed on seeing and treating early rheumatoid arthritis patients urgently. The paradox of seeing patients quickly to start slow-acting drugs such as methotrexate, which takes months to control symptoms, seems to be illogical—if urgent treatment is genuinely needed, then rapidly acting drugs should be preferable. One evidence-based rapidly acting approach is the combination of short-term, high-dose steroids with conventional disease-modifying drugs. However, although this approach is effective in trials it is often ignored in routine practice because of concerns about its complexity and toxicity. Initial biological drugs therefore seem more attractive, including the tocilizumab plus methotrexate regimen in the trial by Bijlsma and colleagues.[1]

However, moving beyond initiating methotrexate monotherapy for early rheumatoid arthritis will require four changes. First, expert clinical groups must support intensive initial treatments, at least in some patients, and second, specialists must be prepared to use them. Third, rheumatologists should collaborate with health-care funders, pharmaceutical manufacturers, and patient groups to identify how some patients with early arthritis can receive effective and affordable initial biological treatments. Finally, patients who are likely to benefit from initial biological drugs using personalised medicine approaches need to be identified.

During the four decades I have treated patients with rheumatoid arthritis, its management and clinical outcomes have been revolutionised, and the poor long-term outcomes that were common when I started rheumatology are historical. The so-called inversion of the treatment pyramid improved outcomes by moving treatment beyond initial non-steroidal drugs to early methotrexate.[3] The next step is to move beyond methotrexate to initial intensive strategies, which might include biological drugs—and the results from the U-Act-Early trial[1] support such a shift.

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