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**COMMENT ON THE ORAL STRATEGY TRIAL
Treating Active Rheumatoid Arthritis With Janus Kinase Inhibitors**

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Conflicts Of Interest Statements

David L Scott has received funding from the National Institute for Health Research and Arthritis Research UK for studies of intensive treatment in rheumatoid arthritis. He has advised several pharmaceutical companies including Eli Lilly And Co, Roche Products Ltd, Napp Pharmaceuticals, Baxalta and Novartis on the treatment and assessment of rheumatoid arthritis and related conditions in the last three years (receiving £1000-£3300).

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The Oral Strategy trial [1] studied patients with active rheumatoid arthritis (RA). They had all responded inadequately to methotrexate, the dominant conventional disease modifying drug (DMARD). The key comparison in the trial was the effects of combining different treatments with methotrexate. One treatment was tofacitinib. This is an orally active Janus Kinase (JAK) inhibitor, a relatively new type of drug for RA. The other treatment was adalimumab an established injectable tumour necrosis factor inhibitor biologic therapy for RA. Over 12 months both combined treatments improved disease activity by similar amounts. Their adverse events were comparable.

The non-inferiority head-to-head design used in the Oral Strategy trial is growing in popularity. It avoids using inactive placebos. Several recent RA trials had this design [2-4]. Establishing non-inferiority has complexities. Large sample sizes are usually needed. The trial evaluates whether the confidence interval of the difference between treatments falls within the non-inferiority margin of the primary outcome. The non-inferiority margin is defined before patients enter the trial. In the Oral Strategy trial the primary outcome – ACR50 responses – signifies clinically important improvements. An appropriately narrow non-inferiority margin was used. The proportion of patients achieving ACR50 responses was numerically greatest with tofacitinib-methotrexate. Secondary outcomes were similar. Its conclusion tofacitinib-methotrexate combinations are non-inferior to adalimumab-methotrexate is robust.

The Oral Strategy Trial and other studies [5,6] show tofacitinib is effective in RA without major toxicity concerns. It will have a role in some active RA patients. Another oral JAK inhibitors is currently available for active RA. This is baricitinib, which has comparable efficacy and side effect levels [4]. The merits of one of these JAK inhibitor over the other are uncertain. But patients and clinicians benefit when there are choices between effective oral drugs. Although combining JAK inhibitors with methotrexate is likely to be the way they are generally used in clinical practice, monotherapy gives clinical and functional responses as shown in the Oral Strategy trial; it may be appropriate in some patients. The clinical use of these JAK inhibitors will reflect two things. First their risks and benefits in routine practice settings. Second healthcare funders' views about what is affordable.

Assessing risks and benefits in routine clinical practice is difficult. When biologics were introduced there were substantial uncertainties about their risks. Consequently large prospective registers of treated RA patients were established. Together with trials these

registers showed biologics increased serious infections. However, the balance of risks and benefits were judged acceptable for patients with severe RA. Oral JAK inhibitors also increase serious infections. This risk is shown in the Oral Strategy trial. Caution is therefore needed when JAK inhibitors are used routinely. Reassuringly, a systematic review of serious adverse events in 117 RA trials found no specific concerns with tofacitinib [7].

International recommendations vary on the optimal treatment of active RA after inadequate responses to methotrexate. American experts [8] outline several different strategies: combining traditional DMARDs; adding a biologic; or adding an oral JAK kinase inhibitor. They carefully avoid expressing any preferences. A Cochrane meta-analysis [9] took a different view. The authors suggested preferentially combining conventional DMARDs as triple therapy (methotrexate, sulfasalazine and hydroxychloroquine). Their justification was the balance of efficacies and costs. European experts [10] recommend assessing prognostic factors like autoantibodies. When there are no factors associated with a poor prognosis more conventional DMARDs are suggested. In patients with poor prognoses adding a biologic or oral JAK kinase inhibitor are suggested, with current practice being to give biologics. One key limitation with the intensive use of conventional DMARDs, including triple therapy, is that trials and observational studies show these combinations are often discontinued over 6-12 months [3,11]. To control active RA some patients are bound to need injectable biologics or oral JAK inhibitors.

Costs were not evaluated in the Oral Strategy trial. Yet they will have crucial roles determining JAK inhibitor use. Biologics for severe, active RA fall within, or above, the upper limits of acceptable cost-effectiveness [12]. JAK inhibitors will only be used to any extent if their cost-effectiveness is comparable or better. When treatments have similar efficacy and risks, healthcare funders expect the preferential use of the least expensive option. JAK inhibitors will only be used substantially if their cost is comparable to biosimilars.

The Oral Strategy trial highlighted three benefits from the combination of tofacitinib and methotrexate in active RA. First its efficacy and toxicity are comparable to injectable biologics like adalimumab. Second its onset of action seems equally rapid, Third most patients are able to remain on tofacitinib therapy for 12 months. These findings are extremely encouraging. They show the ongoing benefits of innovation in drug treatment. The trial also underlines the major flaw of all intensive treatment regimens in active RA patients who failed to respond to

methotrexate. Only a minority of patients achieve remission with any treatment strategy. While effective RA treatments have expanded greatly in recent years its overall management still has substantial room for improvement.

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