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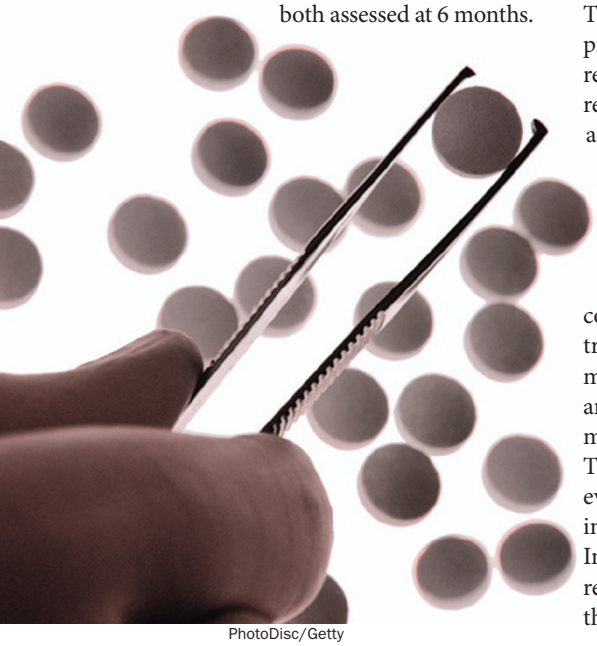
RHEUMATOID ARTHRITIS

Can tofacitinib be used as first-line monotherapy for RA?

The Janus kinase inhibitor tofacitinib was originally approved by the FDA for use in patients with rheumatoid arthritis (RA) who did not achieve a sufficient response to (or who did not tolerate) methotrexate, the most widely used antirheumatic drug. However, the 24-month results of the ORAL Start trial, reported in the *New England Journal of Medicine*, suggest that tofacitinib might be superior to methotrexate as first-line monotherapy for RA.

Individuals were invited to participate in this phase III randomized, controlled trial if they had been diagnosed with active RA and had radiographic evidence of joint erosion but had not yet been treated with methotrexate or therapeutic doses of methotrexate. If they consented, they were randomly assigned to receive either methotrexate (mean dose 18.5 mg per week; $n = 186$), tofacitinib 5 mg twice daily ($n = 373$) or tofacitinib 10 mg twice daily ($n = 397$). The co-primary efficacy endpoints were the mean change from baseline in modified total Sharp score and the proportion of patients who achieved an ACR70 response (≥70% improvement from baseline in ACR core set measures), both assessed at 6 months.



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"The efficacy of tofacitinib was superior to that of methotrexate in the two most important domains: in terms of symptoms and signs, and in terms of radiographic progression," says study investigator Ronald van Vollenhoven. "This is really a new finding, in that no other treatment has ever been shown to achieve both of these results compared with methotrexate."

At 6 months, differences from baseline in modified Sharp score were modest in all three treatment groups but were smaller in the tofacitinib groups (0.2 and <0.1 points for the 5 mg and 10 mg groups, respectively) than in the methotrexate group (0.8 points; $P < 0.001$ for both comparisons). These between-group differences persisted at months 12 and 24. Tofacitinib-treated patients also had lower erosion and joint-space narrowing scores than those in the methotrexate group at 6, 12 and 24 months.

With regard to clinical outcomes, 25.5% and 37.7% of those in the tofacitinib 5 mg and 10 mg groups, respectively, had an ACR70 response at 6 months, as compared with 12.0% of the methotrexate group ($P < 0.001$ for both comparisons). The tofacitinib groups had a greater proportion of patients with an ACR70 response through 24 months. Rates of remission and low disease activity, defined according to 28-joint disease activity score based on erythrocyte sedimentation rate, were also higher in the tofacitinib groups than the methotrexate group at 6, 12 and 24 months.

"This impressive efficacy must of course be weighed against the risks of the treatment with tofacitinib, some of which may be greater than with methotrexate, and the much higher financial cost of this medication," advises van Vollenhoven. The most commonly reported adverse events in the ORAL Start trial were infections and gastrointestinal disorders. In particular, herpes zoster infection was reported by 3.5% and 4.5% of patients in the tofacitinib 5 mg and 10 mg groups, respectively, and in 1.1% of those who received methotrexate.

As patients with RA are known to be at increased risk for herpes zoster, the incidence of this infection in trials in the tofacitinib RA development program was the subject of a separate study by Winthrop *et al.*, now reported in *Arthritis & Rheumatology*. Retrospective evaluation of 4,879 tofacitinib-treated patients across phase II, phase III and long-term extension studies identified 239 cases of herpes zoster reported by trial investigators. Sixteen (7%) cases in this analysis were considered serious, and 24 (14%) patients with herpes zoster infection permanently discontinued tofacitinib therapy. The overall crude incidence rate was calculated at 4.4 per 100 patient-years; rates were similar in those who received tofacitinib 5 mg or 10 mg twice daily but, interestingly, rates varied by region and were markedly higher within some regions of Asia. By contrast, in patients in phase III trials who received placebo, herpes zoster incidence was 1.5 per 100 patient-years.

Further studies are needed to determine whether vaccination might mitigate the risk of this infection. Additionally, therapeutic decisions will take into account potential benefits as well as adverse events. The ORAL Start trial results suggest tofacitinib could reduce disease activity and joint damage better than methotrexate over 2 years. It remains to be seen whether tofacitinib will be approved by regulatory bodies such as the FDA and European Medicines Agency as a first-line therapy for RA, or indeed whether the drug's manufacturer (and sponsor of the studies discussed herein), Pfizer, will seek such approval.

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Original articles Lee, E. B. *et al.* Tofacitinib versus methotrexate in rheumatoid arthritis. *N. Engl. J. Med.* **370**, 2377–2386 (2014) | Winthrop, K. L. *et al.* Herpes zoster and tofacitinib therapy in patients with rheumatoid arthritis. *Arthritis Rheum.* doi:10.1002/art.38745