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Subcutaneous Ofatumumab in Patients with Relapsing-remitting Multiple Sclerosis

Relapsing-remitting Multipl Skleroz Hastalarında Subkütan Ofatumumab

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Human clinical studies, initially with chimeric rituximab and then by ocrelizumab, have shown that selectively targeting B cells with selective anti-CD20 monoclonal antibodies is highly effective in limiting disease activity in relapsing forms of multiple sclerosis (RMS) (1,2). Ofatumumab acts by complement-dependent and antibody-dependent cell-mediated cytotoxicity by binding to a small different epitope of CD20, and is currently an approved intravenous drug for use in chronic lymphocytic leukemia (3). In a small phase 2 study in patients with RMS, intravenous ofatumumab was shown to provide an effective reduction in new magnetic resonance imaging (MRI) lesion activity (99%) at B-cell reduction doses (100, 300 and 700 mg) (4). It has been shown that the development of subcutaneous ofatumumab anti-CD20 treatment may facilitate treatment. It is known that subcutaneous ofatumumab treatment is well tolerated in a small group of patients with rheumatoid arthritis (5).

Recently, a study aiming to investigate the possible efficacy of subcutaneous ofatumumab treatment in reducing new brain lesions in patients with RMS and the dose-dependent B-cell reduction was conducted by Bar-Or et al. (6). Patients with active RMS aged between 18 and 55 years with Extended Status Disability Scale (EDSS) scores between 0-5.5 were included in the study. This randomized, double-blind, placebo-controlled, multicenter study was based on 4 phases: screening, 24-week treatment, 24-week follow-up, and individualized follow-up. Patients eligible for the study were randomized to placebo or ofatumumab groups (3-, 30-, 60 mg/12 weeks, or 60 mg/4 weeks). The primary outcome of the study was the cumulative new gadolinium-enhancing brain lesion load at 12 weeks' follow-up. Other MRI outcomes were new gadolinium-enhancing brain lesion at 24 weeks, new and ongoing gadolinium-enhancing lesions, new or enlarging T2-hyperintense lesions, and T1 hypointense lesions (12^{th} and 24^{th} weeks). The clinical outcomes were evaluated using the EDSS, Multiple Sclerosis Functional Composite (MSFC), and Modified Fatigue Impact Scale (MFIS). The clinical outcome, and B-cell decrease and increase were assessed by the number of CD19 B lymphocytes in peripheral blood.

As a result, 232 patients were randomized and 214 patients were treated until 24 weeks. When the primary outcome was analyzed, a statistically significant 65% decrease was observed in cumulative, new gadolinium-enhancing lesion load between 0 and 12 weeks in the entire ofatumumab group. In post-hoc analyses, it was found that this rate increased to more than 90% at doses of 30 mg or more. MRI-based secondary outcomes also supported the primary analysis results. Regarding clinical outcomes, relapses were observed in 26 patients and relapse rates were higher in the placebo group, but there was no statistically significant difference in the relapse frequency in the drug and placebo groups. There was no significant difference between the groups in MSFC and MFIS scores, and EDSS scores remained unchanged at 12 and 24 weeks in most patients (79%), and there was no significant difference between the groups.

On the other hand, B-cell depletion was shown to be dose-dependent and was higher at 60 mg/4-week and 30- and 60

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mg/12-week dosages than 3 mg/12-week dosages. Although the B cell repletion did not change in proportion, it was found to spread over a longer period in the higher dose groups. Overall, adverse effects were 64% in the placebo group and 74% in the patient group in the first 12-week period. It was determined that the adverse effects were usually mild-to-moderate with no deaths. The adverse effect rate was highest (81%) in the 60 mg/4-week ofatumumab group. The majority of the injection-related adverse effects was mild-to-moderate, and improved on the same day or the next day, and was primarily associated with the initial dose of ofatumumab (29-50%). Treatment had to be discontinued in ≤2% of the patients because of the adverse effects to the drug (injection-related reactions in two and decreased immunoglobulin G in two).

In the discussion, it is emphasized that in this study, significant treatment responses (radiologic) were obtained with subcutaneous ofatumumab dose regimens that did not completely suppress B cells. On the other hand, in previous studies on anti-CD20 treatment, it was emphasized that a complete or near-complete reduction in circulating B cells was achieved, but this was not clear for its high efficacy. In the study, post-depletion B-cell repletion was also examined and it was observed that it was more rapid than in previously published anti-CD20 treatments. The authors suggested that repletion kinetics might be a potential marker for patients with near-total depletion. It has also been shown that the tolerability of subcutaneous ofatumumab is good, and that the most common adverse effect is an injection-related reaction, which improves on the following day. Considering that subcutaneous injections are much more practical than intravenous administration, it is emphasized that it may be an important alternative in patients with RMS in the near future. This study is very important because it is the first class 1 study to demonstrate the efficacy of subcutaneous ofatumumab in patients with RMS.

Ethics

Peer-review: Internally peer-reviewed.

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