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# Doubling the Dose of Glatiramer Acetate Does Not Increase Efficacy

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September 22, 2008 (Montreal, Quebec) — Doubling the dose of glatiramer acetate from 20 to 40 mg/mL did not improve clinical or imaging outcomes after a year of therapy in patients with multiple sclerosis (MS).

Both doses of the drug performed very well, although the higher dose appeared to reduce the number of gadolinium-enhancing and new T2 lesions on magnetic resonance imaging (MRI) sooner, according to research presented here at the World Congress on Treatment and Research in Multiple Sclerosis: 2008 Joint Meeting of the American, European, and Latin America Committees on Treatment and Research in Multiple Sclerosis (ACTRIMS, ECTRIMS, LACTRIMS). Lead author Giancarlo Comi, MD, a professor of neurology and chair of the neurology department at the University Vita Salute, Scientific Institute San Raffaele, in Milan, Italy, presented the results.

For the phase 3 trial multicenter FORTE trial, 1155 patients with definite MS, based on revised McDonald criteria, were randomized to treatment with 20 mg/mL or 40 mg/mL of glatiramer acetate administered once daily by subcutaneous injection for 12 months. All patients had experienced at least 1 documented relapse in the year prior to screening or 2 relapses in the 2 years prior to screening and had an Expanded Disability Status Scale score between 0 and 5.5. They were followed up at months 1, 2, 3, 6, 9, and 12. The primary end point was the rate of confirmed relapse.

Overall, 91% of those on the low dose of the drug and 86% on the high dose completed 12 months of therapy. Based on an intent-to-treat analysis, after 12 months of therapy, the rate of confirmed relapse was 0.33 with the low dose and 0.35 with the high dose ($P = 0.4859$). Similarly, there was little difference between the 2 groups with respect to the proportion of relapse-free patients, the number of T1 gadolinium-enhancing lesions, the number of T2 lesions, and the amount of brain atrophy.

"We expected that doubling the dose would significantly increase the effect, and this is not true. End of story," Dr. Comi told *Medscape Neurology & Neurosurgery*. "But we had 2 positive aspects of the trial, with a tremendous amount of patients — [nearly] 1200 patients — with both doses. If you look at the change from baseline to the end, there was a 70% drop in the MRI activity. So, if we need a confirmation that glatiramer acetate is very active, this is the confirmation. Previous studies had [only] 200 to 300 patients."

In addition, the higher dose of the drug affected the MRI findings more quickly. "With the high dose, there was an anticipation of the effect," said Dr. Comi. "By the end of the third month, it didn't matter which dose you had, you are in the same condition. However, you accumulate more lesions in the first 3 months with the low dose than with the high dose. So, if you want to have a quicker response to the treatment, then the high dose may have some advantages."

Notably, the higher dose was just as safe as the lower dose, with only a small amount of increased treatment discontinuation due to injection-site reactions with the higher dose. Given that both doses are safe, Dr. Comi suggested that it might be useful to give some patients the higher dose for only a month or 2. "Sometimes patients start with very active disease, and you are afraid to wait 2 to 3 months to have a complete effect," he said.

**Enough is Enough?**

Asked for comment on these findings, session moderator Askel Siva, MD, a professor of neurology at Istanbul University Cerrahpasa School of Medicine, in Turkey, told *Medscape Neurology & Neurosurgery* that he disagreed with this last assessment, however. "How much are we really gaining from 1 or 2 months [with a higher dose of glatiramer acetate]? I'm not sure," he said. "Maybe treating these patients with something else at the beginning would do the same thing or even more."

"It seems that there might be a certain dose [for all MS medications at which you attain] satiety in the receptors," Dr. Siva concluded. "Then, enough is enough, and you don't need more. The current dose of glatiramer acetate that we are treating our patients with is enough."

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