

Three Times Weekly Glatiramer Acetate in Relapsing-Remitting Multiple Sclerosis

BACKGROUND:

- Glatiramer is approved as a 20mg daily SQ injection for RRMS. A recent phase 3 study also showed that 40mg once daily resulted in similar safety and efficacy profiles compared with the 20mg dose. This study's objective was to test the safety and efficacy of three times weekly glatiramer acetate 40mg in patients with RRMS who desire schedules with less-frequent injections.

OBJECTIVE

- To evaluate the safety and efficacy of three times weekly glatiramer acetate in the treatment of relapsing-remitting multiple sclerosis

METHODS

- **Design:** randomized, placebo-controlled, double-blinded, parallel-group, multicenter, phase 3 study.
- **Inclusion criteria:** 18-55 years old, a confirmed RRMS diagnosis according to the revised McDonald criteria, an Expanded Disability Status Scale score of ≤ 5.5 , were relapse free for ≥ 30 days, ≥ 1 documented relapse in the 12 months prior to screening, ≥ 2 documented relapses in the 24 months prior to screening, or 1 documented relapse within 12-24 months prior to screening with at least 1 T1 gadolinium enhancing lesion in an MRI performed within 12 months of screening
- **Exclusion criteria:** Patients with progressive forms of MS, previous treatment with GA or any other glatiramoid, treatment with immunomodulators within 2 months of screening, use of immunosuppressive agents, cytotoxic agents, or chronic systemic steroid treatment within 6 months of screening, treatment with any monoclonal antibody within 2 years of screening, known sensitivity to Gd or mannitol, and patients unable to successfully undergo MRI screening
- **Primary outcome measure:** Number of confirmed relapses during the 12 months on the intent-to-treat population
- **Secondary outcome measures:** Cumulative number of new/newly enlarging T2 lesions at month and 12 as well as the cumulative number of Gd-enhancing lesions on a T1WI taken at months 6 and 12
- **Tertiary outcome measure:** Percentage of brain volume change from baseline to month 12
- **Exploratory outcome measures:** time to first confirmed relapse, proportion of relapse-free patients, and the total number of severe confirmed relapses
- 1350 patients (943 glatiramer acetate, 461 placebo) received either
 - Glatiramer Acetate 40mg SQ three times weekly OR matching placebo SQ three times weekly
- 90% power to detect a statistically significant difference in the total number of confirmed relapses between treatment groups calculated for 1350 patients.
- Intent-to-treat data handling

RESULTS

- 84 patients in the GA group and 31 patients in the placebo group discontinued the study. The main reasons for discontinuation across both groups were adverse events, withdraw of consent, pregnancy, loss to follow up, and relapse
- **Primary outcome measure:** Patients receiving GA had a 34% reduction in the risk of confirmed relapse compared to placebo (RR 0.656, 95% CI = 0.539-0.799, $p < .0001$)
- **Secondary outcome measures:** Patients receiving GA experienced 45% reduction in cumulative number of T1 lesions (RR 0.552, 95% CI 0.436-0.699, $p < .0001$) and 35% reduction in new or newly enlarging T2 lesions (RR 0.653; 95% CI = 0.546-0.780, $p < .0001$)
- **Tertiary outcome measure:** Percentage change in normalized brain volume was not statistically different between treatment arms (-0.706 with GA vs -0.645 with placebo, $p = .2058$)
- **Exploratory endpoints:** Time to first relapse significantly longer in GA group compared with placebo (393 vs 377 days, hazard ratio 0.606, 95% CI = 0.439-0.744, $P < .0001$). A greater proportion were

relapse-free in the GA group compared with placebo (77% vs 65.5%). GA was associated with a 35% reduction in annualized rate of severe relapse (RR 0.644, 95% CI = 0.526-0.790, $p < .0001$)

STRENGTHS

- Glatiramer acetate has already been approved for the treatment of relapsing-remitting multiple sclerosis at a similar weekly dose
- Gold standard study design was utilized
- Large study size decreases chance of type II error
- Research methods and outcomes were consistent with endpoints currently used to evaluate multiple sclerosis activity and progression
- Confidence intervals were reported for endpoints, allowing better extrapolation to the population.

LIMITATIONS

- A key limitation to this study was investigator bias. The study was funded by TEVA and many of the authors received funding from TEVA. In the author's discussion, they do not discuss outcomes that were not favorable to the 40mg TIW dose of glatiramer such as EDSS and brain atrophy.
- Another problem with the study is that they clearly compare the 40mg TIW dose with the 20mg daily dose of glatiramer, although they did not do any head-to-head comparisons. If glatiramer 20mg was already approved, it is unclear why the investigators used a placebo in a potentially dangerous disease when the dosage they wanted to compare it to was already approved. Since the 40mg is not currently on the market, it appears as though the company may be making a push for a new product.
- Adherence to therapy was not assessed.
- TO balance groups across multiple centers, a restricted blocked randomization was used. Although this was likely used to help ensure good balance in participant groups, the procedure can still lead to selection bias. Also, proper analysis of data from blocked randomizations require stratification by blocks, which this study did not do.
- 2:1 stratification can lead to a slight loss of statistical power. It is unclear whether the investigators took this into consideration when calculating their initial statistical power.

CONCLUSION

- Based on study results, glatiramer acetate 40mg SQ TIW appears to be an appropriate alternative for patients with relapsing-remitting multiple sclerosis who prefer a less frequent dosing schedule.
- Although this study makes several comparisons to the 20mg SQ daily dosing schedule, it is not possible to make meaningful comparisons without a head to head trial. Further research is needed in this area.
- Long term safety and efficacy of glatiramer 40mg SQ TIW has not been established. Further research is also needed in this area and the open-label phase of this study is ongoing.

Reference:

Khan, O., Rieckmann P., Boyko A., Selmaj K., Zivadinov R. 2013. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. *Annals of Neurology* 2013; 73:705-713

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