Measurement of anti-glatiramer (GA) acetate antibodies in the serum of RRMS subjects treated with GA Depot for 24 months

S. Flechter[1], A. Miller[2,3], L. Popper[4], N. Bleich Kimelman[4], S. Rubnov[4], U. Danon[4], E. Marom[4], R. Milo[5,6], J. Chapman[7,8], A. Shifrin[9], R. Gilad[10], C. Hoffmann[11], D. Karussis[12], T. Brenner[13], T. Ben-Hur[14], A. Karni[8,15]

[1] Multiple Sclerosis Clinical Research and Therapy Service, Department of Neurology, Assaf Harofeh Medical Center, Zerifin, [2]Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, [3] Multiple Sclerosis & Brain Research Center, Carmel Medical Center, Haifa, [4] Mapi Pharma LTD., Ness Ziona, [5] Department of Neurology, Barzilai University Medical Center, Ashkelon, [6] Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, [7] Diagnostic and Interventional Imaging, Sheba Medical Center, Ramat Gan, [8] Department of Neurology, Sheba Medical Center, Ramat Gan,[9] Department of Neurology, Rambam Medical Center, Haifa, [10] Department of Neurology, Kaplan Medical Center, Rehovot, [11] Diagnostic and Interventional Imaging, Sheba Medical Center, Ramat Gan, Israel, [12]Unit of Neuroimmunology-MS Center, Hadassah Medical Center, Ein Kerem, Jerusalem, [13] Laboratory of Neuroimmunology, Department of Neurology, The Agnes Ginges Center for Human Neurogenetics, Hadassah-Hebrew University Medical Center, Jerusalem, Israel, [14] Department of Neurology, Hadassah – Hebrew University Medical Center, Jerusalem, Israel, [15] Neuroimmunology Clinic, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

BACKGROUND

GA Depot is a long-acting formulation of GA given IM once-monthly. In pre-clinical studies, we showed that GA Depot is as efficient as Copaxone® in ameliorating MOG-induced EAE in mice and that GA Depot exerts similar immunologic response to that of Copaxone® as expressed by the total antibodies (Abs) level to GA. GA Depot safety and efficacy is being evaluated in a Phase IIa study in RRMS patients switching from Copaxone® treatment. Main eligibility criteria included: age 18-70 years, diagnosis of RRMS and treatment with Copaxone® for ≥12 months prior to study enrollment. Patients received GA Depot intramuscularly every 28 days, at doses of 80mg or 40mg in the core study (52 weeks) and 40mg in the study extension (additional 48 weeks, figure 1). A 24-months' analysis of a 13-subject cohort that completed the 1st year core study and continued to the study extension, showed no disease progression. This was manifested by stable mean EDSS scores (figure 2), no MRI activity and only two relapses occurring in the same subject, with 2 years NEDA score of 81.8%.

OBJECTIVE

To analyze the immunological response to GA Depot in subjects participating in the phase II study, expressed as a total level of antibodies (Abs) to GA during 24 months' time period.

DESIGN/METHODS

Serum samples were retrieved from subjects treated with once every 28 days injections of GA Depot 40mg in the core study (52 weeks) and in the study extension. Samples were collected at base line, after one month and every 3 months during the one-year core study and every 6 months in the first extension year. Total anti-GA Abs level was determined using ELISA. The results are expressed as Binding Index (BI= mean optical density of tested serum / mean optical density of normal human serum).

Figure 1: study design

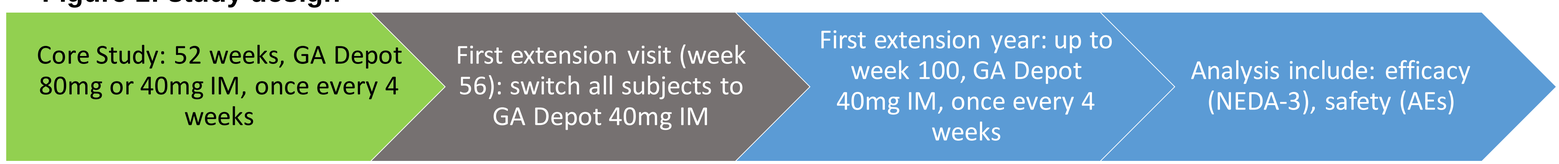
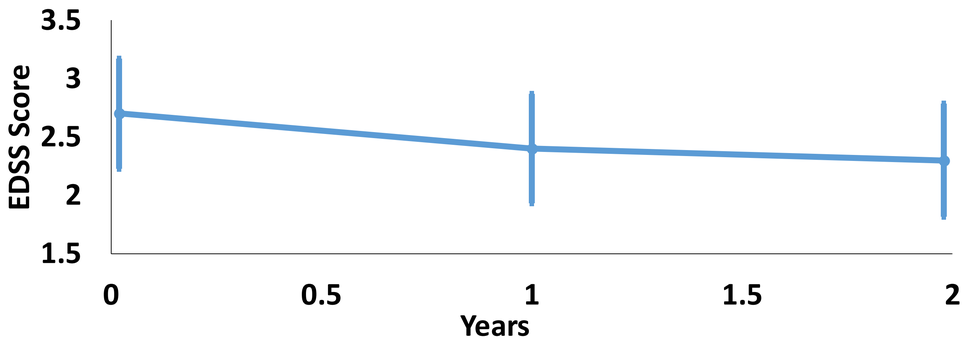


Figure 2: Mean EDSS score from baseline until two years (mITT*)



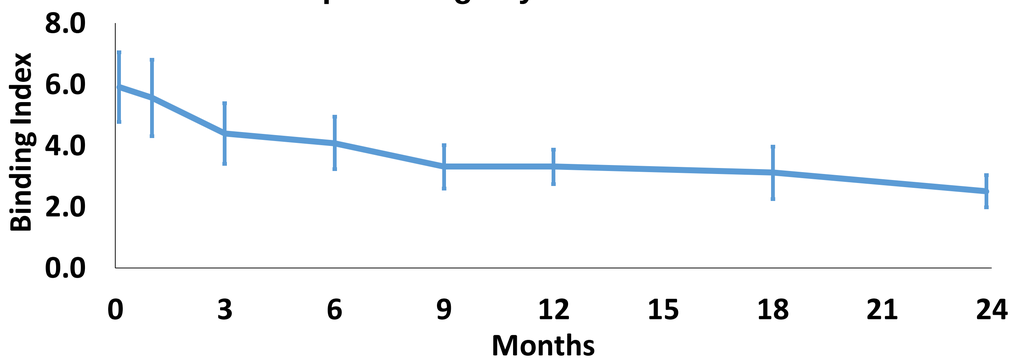
Data presented as mean ± SE. n=13 for screening and 12 months, 11 for 24 months. Two patients had early termination. EDSS of these patients was 3.5 at screening and at early termination (no change).

* EDSS performed up to 4 weeks following planned time point was included in the analysis. mITT: modified Intent To Treat population.

RESULTS

All subjects but one had anti-GA Abs measured at baseline. Overall, a clear trend of reduction of the BI over time up to two-years is noted (figure 3). Only one subject showed an elevation of the anti-GA Abs level after switching treatment from Copaxone® to GA Depot.

Figure 3: Mean GA antibodies in serum from RRMS subjects treated with GA Depot 40 mg: 2 years data



Abs to GA were measured using ELISA. The figure presents the average Abs titter at each time point ± standard error (n=6 for screening, 7 for 1-month time point, 8 for 3-18-months time points and 7 for 24-months time point). ANOVA analysis showed no statistically significant difference between mean Abs titer in the different time points.

CONCLUSIONS

Previous studies have found that Copaxone® treated subjects develop anti-GA Abs with gradual reduction in its level over time, and that these Abs do not inhibit Copaxone® therapeutic activity. Our findings suggest that switching from Copaxone® to GA Depot injected IM does not induce a renewed immunologic response towards GA and its trend is unchanged. This suggests similar humoral immune reactivity of Copaxone® and GA Depot.

DISCLOSURES

Prof. Ariel Miller participated as the core-study Coordinating Principal Investigator and as a site Principal investigator (PI) in the study funded by Mapi Pharma. Dr. Shlomo Flechter participated as the extension-study Coordinating Principal Investigator and as a site Principal investigator (PI) in the study funded by Mapi Pharma .Dr. Ron Milo, Prof. Joab Chapman, Dr. Alla Shifrin, Prof. Ronit Gilad, Prof. Dimitrios Karussis and Dr. Arnon Karni participated as PIs in the study funded by Mapi Pharma.Dr. Chen Hoffmann participated as the central reading MRI facility in the study funded by Mapi Pharma.Laura Popper, Prof. Talma Brenner performed the antibodies analysis as a contracted laboratory. Prof. Tamir Ben Hur served as a consultant for Mapi –Pharma. Nadav Bleich Kimelman, Shai Rubnov (co-inventor of GA Depot) and Uri Danon are employed by Mapi Pharma. Ehud Marom is a co-inventor of GA Depot, and founder and CEO of Mapi Pharma. Study supported by Mapi Pharma Ltd.