Pre-clinical Studies and Evaluation of Treatment Need of Glatiramer Acetate Depot (Long Acting Injection of GA)

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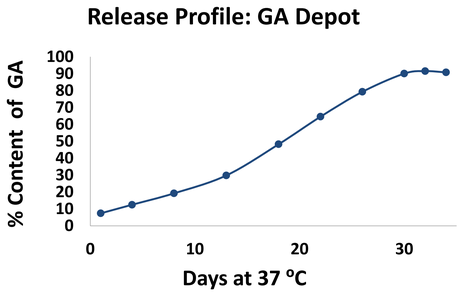
Background: Glatiramer Acetate (GA), the active pharmaceutical ingredient in Copaxone®, is prescribed for treatment of relapsing remitting multiple sclerosis (RRMS). GA Depot is a long-acting formulation of GA intended for slow-release intramuscular (IM) injection once every 28 days. It is expected that GA Depot will significantly increase compliance of GA users and therefore will provide a therapeutic benefit.

Aims: (1) to compare once every 28 days injected GA Depot activity to that of Copaxone®, (2) to assess the willingness to switch to a long acting product among current Copaxone® users.

Methods: GA Depot was evaluated *in vitro* for GA release profile. *In vivo*, GA Depot's effect on clinical manifestations of MOG-EAE was compared to that of Copaxone® and development of GA antibodies was quantified. Additionally a questionnaire study was performed among RRMS patients treated with Copaxone® in order to assess the clinical need for GA.

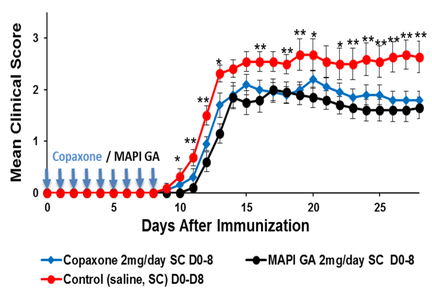
1. GA Depot releases GA for 30 days in a "zero-order" rate, in vitro

Samples of GA Depot were suspended in PBS at 37ºC and mixed continuously for over 30 days. Data demonstrate a steady and linear release of GA from the formulation over 30 days. By day 30, more than 90% of the GA is released from the formulation.



2. Mapi's GA and GA Depot effect on MOG-EAE is similar to Copaxone®

A Mean Clinical Score in Mice



** P<0.05 for MAPI GA compared with untreated control.*
*** P<0.05 for all groups compared with untreated control, single factor ANOVA followed by one-tail two-sample T test assuming unequal variances, n=10 / group, +/- standard error.*

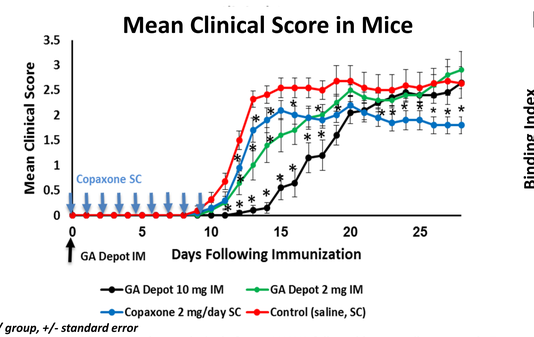
B Computed values, MOG-EAE, day 28

Groups	Maximum Mean Disease Score	Mean Disease Duration	Mean Day of Onset	AUC Clinical Score	Survival Rate at Day 28
GA Depot 10 mg (IM) D0,1	2.85±0.25	12.60±0.74*	16.40±0.74*	25.22±2.22*	90%
Copaxone® (SC) 2 mg/day, D0-D8	2.45±0.17*	17.30±0.49	11.70±0.49	31.35±2.17*	100%
MAPI GA (SC) 2 mg/day, DO-D8	2.05±0.21*	15.90±1.12*	12.50±0.54*	27.17±3.15*	100%
GA Depot 2 mg (IM) D0	3.05±0.33	16.20±0.71*	12.80±0.71*	34.00±2.34*	80%
Control (saline, SC), D0-D8	3.15±0.21	18.09±0.35	10.90±0.35	42.13±3.46	90%

*n=10 / group, +/- standard error. * P<0.05 compared with untreated control, single factor ANOVA followed by one-tail two-sample T test assuming unequal variances*

Development of MOG-induced EAE in C57BL/6 mice was assessed by daily clinical scoring of the mice up to Day 28. The effect of GA Depot, GA and Mapi's GA on EAE symptoms was compared to that of commercial Copaxone®. Mapi GA activity in this model was equivalent to the effect of Copaxone® (figs. 2A & B). GA Depot significantly reduced the mean clinical score AUC (reflecting disease burden over time) in all treatment groups compared with an untreated control (fig. 2C). GA Depot 10 mg showed a notably lower AUC than commercial Copaxone® and GA Depot 2 mg (fig. 2B & C). Immunological response induced by GA Depot in escalating doses and Copaxone® was evaluated using serum samples isolated from mice in MOG-induced EAE study at day 35. Levels of antibodies to GA measured using ELISA assay were similar in all GA Depot treated groups and Copaxone® treated group suggesting similar immunological response to both drug treatments (fig. 2D).

C Mean Clinical Score in Mice



n=10 / group, +/- standard error
**P<0.05 compared with untreated control, single factor ANOVA followed by one-tail two-sample T test assuming unequal variances*

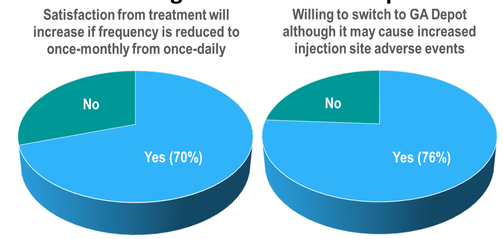
3. Copaxone® users await a long-acting GA product

A Questionnaire study, Summary

Question	Results		
Gender	Male 23.8%	Female 76.2%	
Age (years)	44.7 ± 9.9		
EDSS at study entry	3.1± 2.2		
Quality of life, in past year (1-10)	7.0 ± 2.3		
Had other treatment before Copaxone®	47.6%		
Reasons for change in treatment and switch to Copaxone®	AEs 60%	Discomfort 20%	Other 20%
Full compliance to Copaxone® treatment	90.5%		
Satisfaction from Copaxone® (1-10)	9.2± 1.2		
Satisfaction from dose regimen of Copaxone® (1-10)	6.6± 3.4		

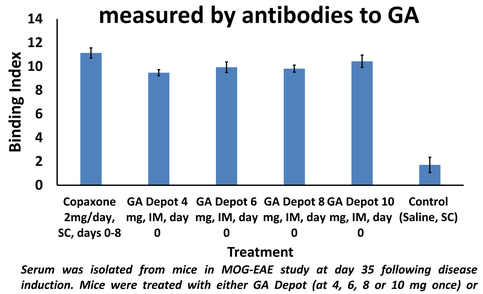
Descriptive statistics, SAS® version 9.1

B Predicted satisfaction from and willing to switch to GA Depot



A questionnaire clinical study among 37 Copaxone® users was conducted in order to assess their willingness to switch to GA Depot. Questionnaires included 37 questions covering general demographics, general quality of life, compliance to Copaxone® treatment and the effect of dosing regimen on quality of life. Data show that while Copaxone® users are highly satisfied from the treatment, they are significantly less satisfied from its dosing regimen (Table 3A). Over 70% of subjects expressed: (1) increased satisfaction if frequency of injections would be reduced from once daily to once monthly, and (2) willingness to switch to a once monthly IM GA Depot despite predicted increased injection site adverse events (fig. 3B) .

D Immunological response in mice measured by antibodies to GA



Serum was isolated from mice in MOG-EAE study at day 35 following disease induction. Mice were treated with either GA Depot (at 4, 6, 8 or 10 mg once) or Copaxone (2mg/day, 9 days). Antibodies (Abs) titer was evaluated using an ELISA assay. Results are expressed as Binding Index (BI).n=5.

Conclusions: *in vitro* and *in vivo* data suggests that GA Depot has a potential beneficial effect in RRMS. Moreover, there is a clear unmet need for such treatment among Copaxone® users. An open-labelled phase IIa clinical study is ongoing in Israel to assess safety, tolerability and efficacy of a once-monthly GA Depot treatment with a 40 mg or 80 mg IM injection of GA Depot.