Toxicologic Pathology, 40: 40-54, 2012

ISSN: 0192-6233 print / 1533-1601 online
DOI: 10.1177/0192623311424169

Comparative Long-Term Preclinical Safety Evaluation of Two Glatiramoid Compounds (Glatiramer Acetate, Copaxone®, and TV-5010, Protiramer) in Rats and Monkeys

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Abstract

Glatiramer acetate (GA), the active ingredient in Copaxone®, is a complex mixture of polypeptides used for the treatment of relapsing remitting multiple sclerosis. Glatiramoids are related mixtures that may differ in some characteristics of the prototype molecule. Our aim is to describe the long-term toxicity studies with protiramer (TV-5010), a new glatiramoid, in comparison with similar studies conducted with GA. The toxicity of twice-weekly subcutaneous injections of protiramer to Sprague-Dawley rats (twenty-six weeks) and cynomolgus monkeys (fifty-two weeks) was compared with similar studies done with daily subcutaneous injections of GA. Daily treatment with GA was safe and well tolerated, without systemic effects or death. Protiramer administration was not as well tolerated as GA and led to dose- and time-related mortalities, probably mediated through severe injection-site lesions both in rats and in monkeys. Bridging fibrosis in the liver and severe progressive nephropathy were seen in rats. A dose-related increase in eosinophils was observed in monkeys. The protiramer toxicity studies show that minor variations in the manufacturing of glatiramoids may lead to significant toxic effects. It is therefore essential that the safety of any new glatiramoid be studied in long-term preclinical studies before exposing humans.

Keywords: glatiramoids; toxicity; injection site; glatiramer acetate; protiramer.

Introduction

The glatiramoid class of compounds is a family of synthetic heterogenous polypeptide mixtures that include four natural amino acids, L-glutamic acid, L-alanine, L-lysine, and L-tyrosine, in a distinct molar ratio of 0.14:0.43:0.09:0.34, respectively, with an average molecular weight (MW) in the range of 5,000–9,000 Daltons (Varkony et al. 2009). The first glatiramoid, and the best studied one, is glatiramer acetate (GA), the active ingredient in Copaxone®, which is approved for the treatment of relapsing remitting multiple sclerosis (MS) in over fifty countries. It has been shown that GA has a unique immunomodulatory mechanism, leading to disruption of the pathogenic process in MS by reinforcing immunoregulatory networks (Arnon and Aharoni 2009; Blanchette and Neuhaus 2008; Liblau 2009; Schrempf and Ziemssen 2007; Van Kaer 2011; Weber et al. 2007). The exact mode of action of GA has not been completely elucidated, but it has been suggested that the heterogeneous nature of the mixture plays an important role in securing activity in such a heterogeneous disease (Johnson 2010; Varkony et al. 2009).

Recently, there has been growing interest in glatiramoids in the pharmaceutical industry (Johnson 2010), and many manufacturers are seeking to develop new glatiramoids (Kovalcin, Krieger, Collins et al. 2010; Kovalchin, Krieger, Genova et al. 2010), and others aim to prepare follow-on ("generic") versions of GA itself. An additional new glatiramoid product, protiramer (also denoted as TV-5010), was recently developed by Teva Pharmaceutical Industries, Ltd (Petach Tikva, Israel) as a potential follow-on product to GA with a slightly higher MW distribution. The rationale for developing a high-MW glatiramoid was based on results of fractionation studies of GA that showed that the higher the MW of the fraction, the higher potency and immune reactivity the fraction has in pharmacological models. This new glatiramoid was developed to provide better efficacy or less dosing frequency for MS patients.

Protiramer was made by making minor modifications to the GA synthetic process, mainly a slight change in the temperature in which the precursor molecule is cleaved to yield the final mixture. This minor change results in a product with a different MW distribution and different biological properties than GA (De Stefano et al. 2009; Varkony et al. 2009). Based on encouraging preclinical safety results from short-term toxicity studies, protiramer's safety, tolerability, and efficacy were evaluated in two small phase II clinical trials in MS patients; it demonstrated good general safety and tolerability (De Stefano et al. 2009). Later, long-term preclinical toxicity studies in monkeys and rats revealed marked progression in the severity of injection site reactions, which was also

This work was performed at Teva Pharmaceutical Industries, Ltd, Petach Tikva, Israel. Funds for this project were provided in part by Teva Pharmaceutical Industries, Ltd, Petach Tikva, Israel. Some of the authors are employees of Teva Pharmaceutical Industries, Ltd, Petach Tikva, Israel.

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Abbreviations: CPN, chronic progressive nephropathy; GA, glatiramer acetate; MS, multiple sclerosis; MW, molecular weight.

accompanied by kidney and liver damage, and death of some high-dose animals. The findings in animals led to the termination of the drug development program of protiramer (Varkony et al. 2009) and brought about the understanding that even slight changes in the manufacturing process of glatiramoids may have profound safety implications.

The aim of the present report is to describe the clinical and anatomical pathology findings in the long-term preclinical toxicity studies of protiramer and compare these results with the results of similar preclinical chronic toxicity studies in rats and monkeys that were carried out previously with GA. By comparing these two toxicity studies, we show that minor variations in the manufacturing of glatiramoids may lead to significant toxic effects. In addition, we present and discuss the potential mechanistic association between the severe injection site lesions and systemic toxicities seen in animals.

Materials and Methods

Chemicals

Both GA and protiramer were produced by Teva Pharmaceutical Industries, Ltd, Petach Tikva, Israel, at a fully accredited GMP manufacturing site.

Animals and Housing

The toxicology studies were carried out as fully compliant GLP studies in accredited contract research laboratories. All animals used in this research were treated humanely, with due consideration to alleviation of distress and discomfort. For the protiramer studies, male and female Sprague-Dawley rats (approximately eight weeks old) were obtained from Charles River Laboratories (Saint Germain sur l'Arbresle, France), and male and female cynomolgus monkeys (*Macaca fascicularis*, twenty-six to thirty-nine months old) were obtained from Siconbrec, Simian Conservation Breeding and Research Center, Inc. (Tanay Rizal, Philippines). For the GA studies, male and female Sprague-Dawley rats (approximately four weeks old) were obtained from Charles River (Margate, UK), and male and female cynomolgus monkeys (*Macaca fascicularis*, approximately twenty-four months old) were obtained from Mediprime (Billinghurst, West Sussex, UK). For the rat studies, water and feed were available ad libitum (diet reference A04C-10 for the protiramer study, and SQC rat and mouse maintenance diet No. 1 from Special Diet Services Ltd, Witham, UK for the GA study). For the GA monkey study, animals were offered daily SQC Mazuri Primate Diet (Special Diet Services Ltd, Witham, UK) supplemented by fruit and a Bonio biscuit (Spillers Foods Ltd, New Malden, UK), and for the protiramer study, animals were offered daily expanded complete commercial primate diet (Special Diet Services: OWM (E) short SQC) supplemented by fruit. The room temperature was 18°C–25°C and the humidity was 40–80% throughout all studies. The fluorescent light cycle was twelve hours per day for all studies, and there were at least ten room air changes per hour for the monkey studies, and at least fifteen changes for the rat studies. All animals were randomly assigned to the treatment groups. For the rat studies, animals were housed in groups of three to five (protiramer) or groups of five (GA) in stainless steel mesh cages. For the monkey studies, animals were housed in groups of two or three (protiramer) or individually (GA).

Experimental Design

The route of administration in all studies was subcutaneous injections. Several injection sites were used in each animal and were alternated on each session to minimize local damage. Doses for the chronic toxicity studies were selected based on tolerability observed in shorter range-finding studies (not shown). The GA rat chronic toxicity study included one control and three treatment groups of twenty animals/sex/group that were treated daily at doses of 0, 3, 10, and 30 mg/kg for twenty-six weeks. Vehicle was sterile physiological saline, and a constant dose volume of 2 mL/kg was used. The protiramer rat chronic toxicity study included four treatment groups and one control group; each group consisted of twenty males and twenty females per dose treated twice a week at doses of 0, 2.5, 40, and 300 mg/kg or once every two weeks at 2.5 mg/kg dose (low-dose, low frequency) for twenty-six weeks. Additional animals (five/sex/group) of the control and high-dose groups were assigned to a four-week treatment-free period. The vehicle was mannitol solution in water for injection, and the dose volume was 5 mL/kg. The GA monkey study included three treatment groups and one control group of four animals/sex/group, treated at doses of 0, 3, 10, and 30 mg/kg for fifty-two weeks. The vehicle was sterile physiological saline, and a dose volume of 1.5 mL/kg was used. The protiramer monkey study included four treatment groups and one control group; each group consisted of seven males and seven females. Protiramer treatment of the monkeys was done twice weekly at doses of 0, 2, 10, and 60 mg/kg for either thirteen weeks (interim group of three animals/sex/dose) or fifty-two weeks (main group of four animals/sex/dose). The fifth group was a low-dose, low-frequency group and was administered protiramer once every four weeks at a dose level of 2 mg/kg (the same number of monkeys for this group). The high dose was lowered from 60 to 30 mg/kg on day 280 of the study because of poor tolerability. Additional animals of the control, high-dose, and low-frequency, low-dose groups (two males and two females per group) were assigned to a four-week treatment-free period after fifty-two weeks of dosing. The vehicle was mannitol solution in water for injection, and the dose volume was 1 mL/kg. All animals were observed at least twice daily to detect any mortality or morbidity, and once daily for ill health or reaction to treatment. Individual body weights were recorded weekly. Blood chemistry, coagulation, and hematology parameters were examined at the end of each rat study and at predose and at several predetermined time points during the monkey studies. Urine samples were also collected on several occasions in both the rat and monkey studies. At the scheduled

termination, animals were subjected to a full gross pathology evaluation including weighing of selected organs and histopathological analysis. Moribund animals were also examined for any pathological abnormality.

In the GA studies, the weights of the adrenals, pituitary, brain (including brain stem), prostate, heart, spleen, kidneys, testes with epididymides, liver, ovaries, and thyroids with parathyroids were determined at terminal sacrifice. In the protiramer studies, the weights of the thymus and uterus were also determined. For histological examination, tissues were fixed in 10% neutral buffered formalin, except for the eyes, which were fixed in Davidson's fixative, and the bone marrow smears, which were fixed in methanol (in the GA studies) or air dried (in the protiramer studies). In the protiramer studies, the testes and epididymides were also fixed in Davidson's fixative. Fixed tissues were embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following tissues from all high-dose and control groups animals were sampled: adrenals, brain (including brain stem), esophagus, eyes, femur, Harderian gland, heart and aorta, large intestine (cecum, colon, and rectum), small intestine (duodenum, jejunum, and ileum), injection site, kidney, liver, lung (and main stem bronchi), lymph nodes (mandibular and mesenteric), mammary gland, nose, optic nerves, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, salivary gland, skin, spinal cord and sciatic nerve, spleen, stomach (including forestomach and glandular stomach), testis (with epididymis and seminal vesicle), thigh muscle, thymus, thyroid gland, tongue, trachea, urinary bladder, uterus, vagina, and Zymbal's gland. In the GA rat study, the following tissues were examined microscopically: all tissues from all animals in control and high-dose groups, all tissues from animals that died or were killed in extremis, injection sites, and abnormalities from the low- and intermediate dose groups. In the protiramer group, histopathological examination was performed for all organs from the following animals: for all animals found dead or sacrificed moribund during the study, and all the control group animals, all intermediate dose group males, and all high-dose group females and all high-dose group males sacrificed after twenty weeks of treatment. Histopathological examination was also performed for kidneys, liver, and injection sites from all other dose groups as well as for the animals that were assigned to the treatment-free ''recovery'' groups. The severity of microscopic lesions observed was graded based on the following numerical scale: 0 (no lesion), 1 (minimal), 2 (mild), 3 (moderate), and 4 (severe), based on the criteria explained by Shackelford et al. (2002).

Statistical Analysis

In all studies, statistical analysis was performed separately for males and females.

For the analysis of the clinical chemistry and hematology parameters, the Levene test for homogeneity of variances and the Shapiro-Wilk test to assess for normality were performed in protiramer studies, and the Levene test was performed in GA studies. Parametric methods were performed in protiramer studies in the case of homogeneous variances and normal distribution in all groups and in GA studies in the case of homogeneous variances between groups. Such analysis consisted of the one-way analysis of variance (ANOVA) followed, if the ANOVA test was significant, by the Dunnett test for pairwise comparisons. Nonparametric methods were performed in protiramer studies in the case of evidence of heterogeneous variances or a non-normal distribution in at least one group and in GA studies in the case that there was a significant group effect or a significant sex–group interaction in the Levene test. Such analysis consisted of the Kruskal-Wallis ANOVA followed, if the Kruskal-Wallis test was significant, by the Wilcoxon rank sum test for pairwise comparisons. The Jonckheere-Tersptra trend test was used to test for an increasing or decreasing trend in response (excluding the low-dose, low-frequency group). In the GA studies, in the case of homogeneous variances between groups, a regression test for post-dose variables was used instead. The ANOVA results are not reported.

For histopathology data, nonparametric methods were used. Such analysis consisted of the Kruskal-Wallis test followed, if the Kruskal-Wallis test was significant, by the Wilcoxon rank sum test for pairwise comparisons. The Jonckheere-Tersptra trend test was used to test for an increasing or decreasing trend in response (excluding the low-dose, low-frequency group). The Kruskal-Wallis results are not reported. Statistically significant results for pairwise comparisons are indicated on the tables next to the appropriate mean value, using the following abbreviations: * $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$. Statistically significant results for trend test are indicated on the tables next to the appropriate mean value, using the following abbreviations: [a] $p \leq .05$; [b] $p \leq .01$; [c] $p \leq .001$.

RESULTS

Survival, Clinical Observations, Body Weight Gain, and Food Consumption

Glatiramer Acetate Studies

In the rat chronic toxicity study, treatment was well tolerated at the tested dose levels. Six animals died during the six months of the study, but none of these was considered to be related to treatment, as the deaths were evenly distributed among the dose groups including control animals, and since the pathological examination did not reveal any association to treatment. Two of these animals died accidentally as result of the bleeding procedure. There were no effects on body weight gain or food consumption at any dose level, except for a slight, probably incidental, increase in weight for high-dose females during the interval of weeks 1–4. Clinical observations were restricted to occasional rough hair coat, stained fur, and appearance of sores at the injection sites that were noted occasionally in rats in the 10 and 30 mg/kg/day GA groups. Few dosing sites were abandoned or left to recover because of the above mentioned findings.

In the monkey GA study, one female of the intermediate dose group was removed from the study because of poor food consumption and loss of body weight. Histopathology revealed lymphoid and bone marrow atrophy and adrenal cortical hypertrophy, signs that are consistent with stress. Because of the isolated nature of the mid-dose finding, the condition of this animal was not considered to be treatment related. Clinical signs in the remaining animals were restricted to the sites of injection. Thickening of the skin was noted in all treated groups, with high-dose animals experiencing greater frequency and earlier occurrence, starting generally by week 11. Signs in the low-dose group of 3 mg/kg were milder and noted from week 20. Sores were occasionally accompanied by swelling and abscess. By week 52, thickening was consistently noted in all high-dose animals.

Protiramer Studies

In the rat chronic study, nine out of seventy-two high-dose and one out of fifty-two mid-dose animals died during the study, and these deaths were attributed to treatment with protiramer. Seven other deaths were considered unrelated. Clinical signs consisting of pallor, subdued behavior, thin appearance, stained fur, lacrimation, hair loss, scabs, and piloerection were noted in all treated groups. Local reactions to treatment were dose dependent and included induration associated with erythema and/or hematoma in both the high- and mid-dose groups. There was no obvious local reaction to treatment in animals given the low dose of 2.5 mg/kg (twice weekly or once every four weeks). Most of the local reactions to treatment had disappeared by the end of the four-week treatment-free period. There was a dose-related reduction in mean body weight and mean body weight gain in males given protiramer, with significant differences and even weight loss in males at the dose levels of 40 and 300 mg/kg, but not at 2.5 mg/kg or in the females of any group. The poor tolerance of animals in the high-dose group (300 mg/kg) necessitated the early termination of this group in week 20 of the study.

In the monkey chronic study of protiramer, four unscheduled deaths were noted, two of which were clearly treatment related. The two treatment-related cases were animals in the high-dose group that were diagnosed at necropsy with multiple subcutaneous areas of hemorrhage and vascular necrosis, and lymphoid and eosinophilic infiltrates, which were considered to be factors contributing to death. It should be noted that the first treatment-related death occurred only after more than six months of treatment. The two other deaths that were not treatment related were low-dose animals, one animal that died probably from an accident and one animal that was removed from the study after being diagnosed as a carrier of hepatitis B. Body and organ weights were unaffected by treatment. Occasional animals in the high-dose group were salivating or subdued, or had loss of balance, were retching or circling, had stiff limbs, or were motionless. In the severe cases, there was also a decrease in blood pressure, decrease in body temperature, and increase in respiratory rate. These signs started appearing after seven weeks and were more pronounced and frequent after thirteen weeks. Accordingly, a decision was taken in week 40 to reduce the high-dose level from 60 to 30 mg/kg.

Injection site reactions were observed in all treated monkeys in a dose-dependent manner. In the control animals, the lesions were infrequent and consisted mostly of scabs, and slight erythema and induration at a very low incidence (usually single animals on a very small number of occasions). Skin lesions at the injection site in animals treated at 2 mg/kg once every four weeks were similar to those in controls. In animals treated at 2 mg/kg twice weekly, there was a slight increase in the incidence and severity of the lesions of the type seen in control animals, and in addition, tumefaction was noted. Injection site lesions in animals treated at 10 mg/kg were more frequent and pronounced. The frequency and severity of the injection site lesions were greatest in the animals treated with 60/30 mg/kg. Because of the severity of these lesions, the original injection sites could not be used starting from week 40, and new injection sites were introduced. Lesions at the new sites of injection were similar to those seen in this dose group at the beginning of the study, indicating that these reactions do not involve immunological sensitization.

Clinical Chemistry and Hematology

Glatiramer Acetate Studies

In the rat study, there was no effect of the GA treatment on hematology or clinical chemistry results. In the monkey study, there were occasional minor changes in AST and ALT values at the high dose level (Table 1). However, these changes were sporadic, minimal, and without a clear dose- or time-dependent relationship. There were no corroborating histological findings.

Protiramer Studies

In the rat study, hematology analyses revealed a minor decrease in activated partial thromboplastin time (APTT) and prothrombin time (PT) and a small increase in platelet counts in the males and females given 40 and 300 mg/kg (Table 2). A small decrease in red blood cell count and hemoglobin concentration was evident in females given 40 and 300 mg/kg. This effect was accompanied by a slightly higher percentage of reticulocytes in these groups of females. Red blood cell parameters were also slightly affected in males at both dose levels, but to a lesser extent than in the females, with a slightly increased reticulocyte percentage at 300 mg/kg. The absolute and relative polymorphonuclear neutrophil counts were increased in females given 40 mg/kg and in males and females given 300 mg/kg, associated with reduced relative lymphocyte counts. There was also an increase in the absolute and relative monocyte counts at the end of the treatment-free period in females given 300 mg/kg (Table 2). The above treatment-related changes in hematology and coagulation parameters were no longer evident at the end of the four-week treatment-free period, except for the decreased PT time and increased monocyte and platelet counts in females given 300 mg/kg.

TABLE 1.—Mean clinical chemistry in male and female glatiramer acetate–treated monkeys at week 52.

	Males				Females			
Dose level (mg/kg/d)	0	3	10	30	0	3	10	30
AST (IU/L)	52	52	50	83***	50	58	52	63*
ALT (IU/L)	48	46	49	75*	41	42	49	53
Alk Phos (IU/L)	1492	1820	1378	1372	1068	1038	936	1112
GGT (IU/L)	154	175	148	118	95	93	93	71*
Na (mmol/L)	147	146	147	143	146	146	146	146
K (mmol/L)	4.3	4.2	4.2	4.4	3.8	4.2	4.3	4.3
Cl (mmol/L)	109	110	111	113	111	108	110	111
Ca (mmol/L)	2.34	2.34	2.3	2.35	2.3	2.33	2.27	2.3
P (mmol/L)	1.8	1.8	1.7	1.7	1.5	1.8	1.7	1.8
Glucose (mmol/L)	3.3	3.3	4.1	3.8[a]	2.5	3.7	3.5	3.3
Urea (mmol/L)	7.2	6.4	6.5	6.8	6.5	6.7	5.8	6.4
Total bilirubin (micromole/L)	1.2	2.7	2.1	2.7	2.5	3	1.5	1.9
Creatinine (micromole/L)	85	82	80	88	74	83	79	80
Total protein (G/L)	83	81	83	87	79	82	86**	84*
Albumin (G/L)	46	44	49	46	40	43	43	45

[a] Significant at $p < .05$ using the dose-response test.
* $p < .05$
** $p < .01$
*** $p < .001$

TABLE 2.—Mean hematology parameters in male and female protiramer-treated rats at week 20 for group 4 males and week 26 for other groups.

	Males					Females				
Dose level (mg/kg)	0	2.5	40	300	2.5 (low)	0	2.5	40	300	2.5 (low)
Red blood cell count (T/L)	8.99	9.11	8.31	8.11	9.16	8.12	8.01	7.76	7.21[b]	7.73
Hemoglobin (g/L)	155	161	145	143	158	153	151	146	133*[b]	151
Reticulocytes (%)	1.7	1.3	1.9	1.9	1.4	1.4	1.5	1.7	2.7[b]	2.2
Packed cell volume (%)	47.1	48.3	43.6*	41.8	47.2	45.1	44.7	42.9*	39.7*[b]	44.1
Platelet count (G/L)	1331	1314	1688**	1623[a]	1235	1170	1228	1328	1951**[c]	1201
Activated partial thromboplastin time (s)	29.4	32.3	21.6*	21.2[a]	29.9	17.4	16.7	16.1	13.8[a]	15.7
Prothrombin time (s)	21.7	25.1	15.6*	16[a]	21.2	14.1	14.2	14.2	13[a]	14.5
Polymorphonuclear neutrophils (G/L)	2.04	1.48	2.79	2.79	2.33	0.88	1.08	0.99	1.44**[b]	0.89
Polymorphonuclear neutrophils (%)	18.8	17.1	26.6	23.3	22.2	12.2	16.8**	14.6	17.8*	12
Lymphocytes (%)	76.7	77.6	67.1	70.8	71.5	82.8	77.4**	79.7	76.1*[b]	82.6
Monocytes (G/L)	0.23	0.22	0.33[a]	0.32	0.36	0.15	0.17	0.16	0.29**[b]	0.19
Monocytes (%)	2.1	2.5	3.2**[a]	2.5	3.4**	2.1	2.6	2.4	3.4[a]	2.5

[a] Significant at $p < .05$ using the Jonckheere-Terpstra trend test.
[b]Significant at $p < .01$ using the Jonckheere-Terpstra trend test.
[c]Significant at $p < .001$ using the Jonckheere-Terpstra trend test.
* $p < .05$
** $p < .01$

There were several treatment-related changes in serum clinical chemistry parameters in males and females given 40 and 300 mg/kg (Table 3). These parameters included decreased total protein and albumin concentrations, increased globulin concentrations, increased total cholesterol levels, and slightly decreased serum sodium. Most of the above treatment-related changes in serum clinical chemistry were still evident after the treatment-free period (Table 4).

In the monkey study, hematology evaluation revealed a marked dose-related increase in absolute and relative eosinophil counts in the groups treated twice weekly at 2, 10, and 60 mg/kg throughout the treatment period (Table 5). Animals treated with 2 mg/kg once every four weeks were unaffected. Throughout the treatment period, animals treated at 60 mg/kg tended to have lower mean phosphorus, cholesterol, and albumin concentrations, and from week 13, lower globulin concentrations (and lower A/G ratios). After four weeks without treatment, these differences had essentially returned to normal, although a slight difference in serum cholesterol concentrations remained.

Pathology

Glatiramer Acetate Studies

Gross pathology examination at the end of dosing of both rats and monkeys did not reveal treatment-related changes in

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