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Plaferon

Immunomodulator
Antiviral
Antiasthmatic/Antiallergic

Human placental amnionic interferon
Placental interferon with the following composition: interferon alfa 85-90%, interferon beta 8-10%, interferon gamma 3-5%

Plaferon LB (Plaferon preparation developed under thermal process)

EN: 201238

Introduction

Culture of amniotic membranes is one method used to produce interferons and other physiologically active substances. The initial indication for the clinical use of an amniotic preparation (Plaferon) was the prevention and treatment of various viral infections. In *in vitro* and *in vivo* studies, Plaferon demonstrated antihypoxic, antiallergic and antitoxic properties uncommon to other interferons. Plaferon is registered as an antiviral and immunomodulatory drug by the Georgian Ministry of Health Care.

Pharmacological Actions

Antiviral activity in vitro

Plaferon, like other interferons, exhibited antiviral activity in human diploid cells inhibiting the reproduction of herpes, parotitis, rubeola and varicella viruses. The antiviral activity of Plaferon was less potent than that of leukocyte interferon (1-3).

Immunomodulatory activity

Plaferon showed dose-dependent antiproliferative activity in myeloma X-63 cells and in blast transformation reactions using human peripheral blood mononuclear cells (PBMCs) and murine splenocytes. Plaferon inhibited the synthesis of interleukin (IL)-1 and other growth factors but did not alter the production of IL-2 by mitogen-activated lymphocytes from healthy donors. In contrast to leukocyte interferon, which shows antiproliferative activity in PBMCs at all stages of the cell cycle, Plaferon was more active during the early stages of proliferation, when cells pass from the G_0 to the G_1 phase. The antiproliferative activity of Plaferon was inhibited by protein kinase C but not by tyrosine kinase (4).

Antitoxic effects

The antitoxic effects of Plaferon were demonstrated in a study of carbon tetrachloride (CCl_4)-induced impairment of rat liver mitochondria. In this model, respiratory coefficients fell to minimal levels on day 4 of CCl_4 injection, indicating inhibition of mitochondrial adenosine triphosphate (ATP) synthesis. Plaferon treatment, however, prevented CCl_4-induced decreases so that respiratory coefficients remained above 80% of control values, indicating maintenance of ATP synthesis. Liver function was also improved, further demonstrating the hepatoprotective properties of the agent (5).

Antihypoxic activity

The antihypoxic activity of Plaferon was studied in dogs with experimental transmural myocardial infarction; 26 of 27 animals treated with Plaferon survived after the experiment. Further investigations showed that Plaferon treatment prevented cardiogenic shock, fatal arrhythmia and microinfarcts (6).

The action of Plaferon on the heart was also examined in a rabbit model of adrenaline-induced cardiac injury. Plaferon was shown to protect animals from swelling and desquamination of capillary endothelial cells. This effect, in turn, inhibited aggregation of blood cells into the vessel lumen. Moreover, the structure of cardiomyocytes was also preserved by treatment (7).

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Plaferon was also effective in an experimental model of photochemically induced cerebral ischemia in white rats. Intravenous administration of Plaferon 15 min prior to photoexcitation resulted in an 85% reduction in infarct volume, a 20% decrease in thrombic vessel density in the area of infarct and protected the brain tissue against oxygen reduction (8).

The protective effects of Plaferon in obstructive nephropathy and renal ischemia have been evaluated. Drug treatment after urethral obstruction prevented severe tissue damage in the kidney and normal diuresis was restored after removal of the obstruction. Furthermore, Plaferon treatment reversed hypertrophy in uninephrectomized rats (9, 10).

Clinical Studies

The antiviral and immunomodulatory effects of Plaferon have been demonstrated in several clinical studies.

When Plaferon (3000-12000 IU b.i.d. i.m.) was added to standard therapy in patients with acute viral hepatitis B, clinical symptoms of the disease were more rapidly reversed. Treatment with Plaferon also resulted in normalization of biochemical parameters of liver function and a more rapid recovery from symptoms compared to untreated patients, with no toxicity. Follow-up at 12 months showed that none of the Plaferon-treated patients had relapsed. Plaferon also resulted in a 1.7-fold reduction in HBsAg-antigenemia at the time of discharge from the hospital (11).

Results from our investigations showed that 32 patients hospitalized with acute hepatitis B had a decrease in $CD4^+$ and an increase in $CD8^+$ T cells as compared to healthy donors. However, T-cell immunity was restored to normal after 1 month of treatment with Plaferon LB added to standard therapy. In the control group, the number of T suppressor/cytotoxic cells returned to normal, although the reduction in T helper/inductor cells persisted (12).

Results from a study in which 22 HIV-negative intravenous drug users with herpes zoster ganglioneuritis were given either Plaferon injections (10,000 IU b.i.d.) or oral prednisolone (70 mg/day) for 15 days showed that Plaferon-treated patients displayed normal $CD3^+$, $CD4^+$ and $CD8^+$ cell counts and improvements in neurological symptoms as compared to the prednisolone group. None of the Plaferon-treated patients experienced postherapeutic neuralgia in contrast to 4/10 in the control group (13). A similar study in 36 patients with herpes zoster ganglioneuritis showed that Plaferon (10,000 IU b.i.d. for 7 days) significantly normalized the number of T cells carrying HLA-DR antigens as compared to steroid-treated controls; neurological symptoms were also improved with Plaferon treatment (14).

Clinical improvement of diabetic peripheral polyneuropathy was observed with Plaferon LB in a study in which 21 patients were administered the agent after correcting for carbohydrate metabolism. Normalization of electrophysiological data was also observed. Prior to treatment, patients exhibited decreases in the total number of T lymphocytes and in the ratio of T helper/inductor cells. However, patients treated for 1 month with Plaferon LB showed normal levels of $CD3^+$ and $CD4^+$ T-cell phenotypes as compared to controls (12, 15, 16).

Plaferon in combination with prednisolone resulted in earlier and prolonged clinical laboratory remission in children with idiopathic nephropathy syndrome (INS). In the control group, 13/40 patients had experienced acute exacerbation of the disease after 1 year as compared to only 4/50 patients in the Plaferon group. Plaferon treatment also corrected the reduction in $CD3^+$ and $CD8^+$ T lymphocytes observed in patients with INS prior to treatment (12, 17).

The efficacy of Plaferon in 25 patients with juvenile rheumatoid arthritis (aged 18 months to 15 years) was reported in a study in which the agent was given intramuscularly or intravenously in combination with standard therapy for 7-10 days. Treatment was well tolerated with no adverse effects. Improvements in clinical symptoms and laboratory indices, stimulation of leukocyte interferonogenesis and a trend toward normalization of humoral and cellular immunity were observed after 1 month of treatment (18).

Plaferon was shown to be a potential alternative to steroid therapy for chronic, stable, nonatopic, steroid-resistant (*i.e.*, nonresponsive to 24 mg/day or more dexamethasone) asthma in a 24-week, double-blind, placebo-controlled, randomized study in 67 patients. Plaferon LB significantly reduced the average daily dose of oral steroid required for relief and spirometric parameters were moderately improved as compared to placebo. Accompanying *in vitro* studies showed that Plaferon-treated PHA-activated PBMCs displayed an increased sensitivity to dexamethasone (19).

Plaferon LB was effective and well tolerated in 2 studies in pediatric patients with respiratory infections. In the first study, 40 children with recurrent respiratory tract infections (> 6 infections/year) were treated with Plaferon LB or placebo. Immunological indices improved and the frequency of infections was decreased in the Plaferon LB group (20). Similar results were obtained in the second study in which Plaferon LB was administered via aerosol inhalation to 40 infants with acute viral infections of the lower respiratory tract and compared to 30 infants given standard treatment. Clinical recovery associated with normalization of T-cell populations (*i.e.*, increases in $CD3^+$ and $CD4^+$ T cells and decreases in $CD8^+$ T cells) was achieved sooner in the Plaferon LB group (21).

The continuous and extended use of anticonvulsants in people with epilepsy often leads to the development of adverse reactions including acute allergic reactions and acute and chronic drug toxicity. Due to its antihistamine and antitoxic properties, Plaferon was shown to be effective against acute allergic reactions and mild toxicity associated with anticonvulsive therapy. Allergic reactions disappeared in 7/9 patients after Plaferon monotherapy

and in 1 patient treated with a combination of Plaferon and antihistamine. Plaferon treatment increased recovery time from symptoms of mild acute toxicity (nausea, vomiting, headache, dizziness) in 3 patients and Plaferon monotherapy was effective in 15/22 patients with severe acute toxicity. In 4 patients in whom Plaferon was combined with general antitoxic treatment, rapid decreases in toxicity were noted. Plaferon was ineffective against drug toxicity in 3 patients in whom a change in the anticonvulsant regimen was required. The agent was slightly less effective in chronic toxicity where clinical symptoms of intoxication disappeared in 6/11 patients, with significant reductions observed in 2. Plaferon not only reduced clinical signs of drug toxicity in 36.6% of the patients but also suppressed drug toxicity as seen on EEG. The inhibition of toxicity by Plaferon enabled anticonvulsant doses to be increased to levels sufficient for achieving good clinical effects (22).

Preliminary results reported from a study involving 8 patients with early breast cancer demonstrated that Plaferon (90,000 IU i.m.), given preoperatively, may be a potential immunomodulator in this disease. Poor and moderate pathological responses were observed in 3 and 4 patients, respectively; there was 1 case of severe pathology in tumor and lymph nodes. Moreover, the increased levels of the tumor serum marker, CA15.3, were normalized and increases in tumor infiltrating $CD5^+$ T cells and $CD11^+$ macrophages were observed with Plaferon treatment (23).

In a randomized study in 280 patients, treatment with Plaferon LB produced significant changes in cellular immunity as demonstrated by a decrease in $CD3^+$, $CD4^+$, $CD22^+$ and $CD16^+$ T cells and an increase in $CD8^+$ phenotypes. Significant positive changes were also observed in Hbe-antigenemia and seroconversion. Treatment with Plaferon LB also resulted in improvements in clinical symptoms, correction of the biochemical parameters of liver function and immunologic indices and prevented recurrence of the disease (24).

Conclusions

Plaferon therapy resulted in a more rapid improvement of clinical conditions in various disease states in addition to obvious improvements in laboratory indices as compared to controls. Results from experimental and clinical studies indicate that, in addition to antiviral activity, Plaferon possesses immunomodulatory, antihypoxic, antitoxic and antiallergic activities that are not characteristic of other interferons. Further investigations are under way.

Source

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