



Tau Interferon in Multiple Sclerosis

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ABSTRACT

The frequency of flare-ups in women with multiple sclerosis declines during pregnancy. This has been observed for decades and various treatments have assumed that sex hormones, such as progesterone and estriol, must play a role in this protective effect of pregnancy. Ignored in this assessment are numerous other agents that appear with pregnancy and are specific for pregnancy. Tau interferon is one such agent and is an especially promising treatment candidate, given its similarity to beta interferons. What makes it a likely basis for the protective effect of pregnancy is that it is produced by the placenta, the trophoblast, and that it is no longer evident after the pregnancy ends. This would explain the apparent ramp up of protection as the pregnancy progresses into the third trimester and the abrupt return to pre-pregnancy flare-up risk after the infant (and the placenta) is delivered.

BACKGROUND

The immune system does not normally target the developing fetus, despite its aggressive attack on other tissues foreign to the body. The fetus is protected at least in part by the placenta and its products. The trophoblast cells that lead to the development of the placenta produce a variety of proteins and glycoproteins, including a glycoprotein called tau (for trophoblast) interferon in several mammalian species [2,4]. This protein has been identified in several ruminant (cattle, sheep, goats, etc) species and is apparently pivotal in the maintenance of pregnancy in these mammals, at least in part by inducing the persistence of the corpus luteum in the ovary after ovulation [8,14]. It may also play a protective role limiting viral access to the fetus.

Interferons are glycoproteins produced by several tissues which have numerous effects, some of which are immunomodulatory. Humans produce numerous interferons similar to but not identical to tau interferon. Tau interferon is designated as a type I interferon that was identified by cloning the DNA constructed from RNA extracted from bovine embryos and their associated tissues. Tau interferon proved to be a pivotal glycoprotein in maternal recognition of and tolerance of the fetus and the normal progression of the pregnancy in ruminant mammals [8,10].

The frequency and severity of flare-ups in Multiple Sclerosis (MS) decrease during pregnancy [1,3] The protective effect of pregnancy is most obvious in the third trimester, a finding consistent with the protection being at least partly attributable to an increasingly robust placenta or to changes in sex hormones in the mother as the fetus develops. The argument that sex hormones are important players in enhancing this protection is buttressed by higher estriol concentrations correlating with fewer relapses evident in MS patient treated with high doses of this hormone in combination with glatiramer acetate [15].

In multiple sclerosis the immune system inappropriately targets the central nervous system myelin [9]. Manipulation of hormone levels in men and nonpregnant women have been adopted as possible treatments to reduce MS flareups, but the results have been marginal at best [7].

In the late 20th century, glycoproteins were discovered that were produced by cells in culture exposed to a virus that became resistant to infection by a second virus. Because of the interference exerted by these glycoproteins on infection by a second virus, they were called interferons. Subsequent studies indicated that these glycoproteins had a modulatory effect on the immune system, as well as numerous other activities. Recognition of this effect on the immune system led to numerous trials using beta interferon, a material produced by fibroblasts, in clinical trials targeting cancers. These cancer trials and subsequent trials in individuals infected with human immunodeficiency virus (HIV) failed.

Dr. Larry Jacobs at the University of Buffalo hypothesized that beta interferon might have an immunosuppressant effect and conducted a study on individuals with relapsing-remitting multiple sclerosis [6]. He injected beta interferon intrathecally and reported a decrease in flare-up frequency and severity in MS patients receiving the treatment. Subsequent double-blind, placebo-controlled trials administering the interferon subcutaneously confirmed its effectiveness in relapsing-remitting multiple sclerosis. This led to the development of interferon beta-1b (Betaseron) and interferon beta-1a (Rebif, Avonex) for use in multiple sclerosis. Why these beta interferons are helpful in reducing the frequency and severity of flare-ups in multiple sclerosis is still unknown, but that they work is no longer open to debate.

The structure and effects of interferon produced by trophoblast cells (tau interferon) are similar to those of interferon beta-1a and interferon beta-1b [13,12]. Tau interferon has a similar amino acid sequence to that in interferon beta and has the compact 5-helix structure of alpha and beta interferons [12]. Unlike other type 1 interferons tau interferon formation is not induced by viruses [5]. It functions in roles substantially different from other interferons, including the maintenance of pregnancy, at least in ruminant species [13,12]. It is a cytokine that apparently modulates the maternal response to a foreign tissue, that of the fetus [12].

Trials of tau interferon in MS patients have never been conducted despite the high probability that this glycoprotein would exert a more profound protective effect than the currently approved type 1 interferons. Antiviral studies with tau interferon more than 20 years ago demonstrated a more robust antiviral action and less cell toxicity than that found with alpha interferon [11]. Whereas this is a naturally occurring mammalian glycoprotein, it stands to reason that it would be better tolerated than interferon beta-1b, which is a protein (not a glycoprotein) produced by genetically altered bacterial cultures, or interferon beta-1a, which is a glycoprotein produced in chinese hamster ovary cell cultures. Interferon beta-1b is altered from the human amino acid sequence of beta interferon by substitution of homocysteine amino acids by serine to reduce cross-linking of amino acids.

CONCLUSION

That beta interferons have a salutatory effect on MS flare-ups may well be because of their similarity to tau interferon, a glycoprotein pivotal in modulating the immune response in numerous mammalian species. This means that the less effective interferon is currently widely used, rather than the (more likely than not) more effective interferon. The usefulness of tau interferon could be easily established using a double-blind study of beta interferon plus an alternative immunomodulatory agent (such as glatiramer acetate [Copaxone]) as opposed to tau interferon in combination

with the same immunomodulatory agent. The amino acid sequences of tau interferons have been well-elucidated and an appropriate starting point for trials would be to use the tau interferon exhibiting the most similarity to beta interferon. This would minimize the risk of unanticipated adverse events and maximize the likelihood of benefit.

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Multiple sclerosis, an idiopathic inflammatory disease of the central nervous system, is characterized pathologically by demyelination and subsequent axonal degeneration. The disease commonly presents in young adults and affects twice as many women as men. Common presenting symptoms include numbness, weakness, visual impairment, loss of balance, dizziness, urinary bladder urgency, fatigue, and depression. The diagnosis of multiple sclerosis should be made by a physician with experience in identifying the disease.Â

Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. N Engl J Med. - patients with relapsing multiple sclerosis. In clinical trials, this was characterised by two or more acute exacerbations in the previous two years. Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity. Interferon beta-1b 22. Interferon beta-1b is indicated for the treatment of relapsing multiple sclerosis. In clinical trials, this was characterised by two or more acute exacerbations in the previous two years. Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing re

Interferon tau (IFN τ , IFNT) is a Type I interferon made of a single chain of amino acids. IFN- τ , was first discovered in ruminants as the signal for the maternal recognition of pregnancy and originally named ovine trophoblast protein-1 (oTP-1). It has many physiological functions in the mammalian uterus, and also has anti-inflammatory effect that aids in the protection of the semi-allogeneic conceptus trophoctoderm from the maternal immune system. Multiple sclerosis (MS) is a long-term neurodegenerative disorder that affects the central nervous system, causing disturbances in movement, balance and vision. MS is an autoimmune condition and is caused by the body's immune system mistaking the protective covering of nerve fibres for a foreign body and mounting an attack against it. This protective covering is called myelin and diseases that cause damage to the myelin are referred to as demyelinating diseases.