

NEUROPROTECTIVE EFFECT OF IFNS AND COPAXONE IN MS - MYTH OR REALITY? - THE ANSWER IS MYTH

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Multiple sclerosis is an immune mediated inflammatory disorder of the central nervous system (CNS) characterized clinically by relapsing-remitting or progressive neurological deficits, and pathologically by inflammation, demyelination, axonal/neuronal loss or damage, and gliosis. The pathological correlate of relapses is inflammation, and radiologically new gadolinium enhancing lesions on magnetic resonance imaging (MRI) scans. Disease progression corresponds to axonal/neuronal damage/loss, associated radiologically with brain and spinal cord atrophy and decreased n-acetyl aspartate on MR spectroscopy. There are heterogeneous patterns of inflammation and neural damage. Clinical studies reveal partial dissociation between inflammation and neurodegeneration. While early relapse frequency predicts disability, and gadolinium enhancement predicts atrophy, axonal damage and brain atrophy can proceed without significant ongoing inflammation.

Neuroprotection is a therapeutic strategy intended to slow or halt the progression of neuronal loss or damage and thereby alter the natural history of disease. (slightly modified from Factor and Weiner, Parkinson's Disease-Diagnosis and Clinical Management, 2002).

In MS, a disease in which inflammation initiates neuronal damage, it can be argued that prevention /suppression of inflammation by interferons (IFN) and copaxone (glatiramer acetate, GA) protects against further neuronal damage. By the same token, anti-platelet therapy for stroke, can prevent further thrombotic events and further neural loss or damage. However, since these strategies do not act on the diseased neuron itself anti-inflammatory treatment is no more neuroprotective (in the strict and direct sense of the term) than aspirin.

To argue in favour of a direct and proper neuroprotective role of IFN and GA one needs evidence that this effect occurs in the absence of inflammation. Do these drugs also prevent ongoing axonal loss independent of their effects on inflammation? No.

IFN: Experimental conditions: In myelin-oligodendrocyte glycoprotein (MOG)-induced EAE in BN rats, IFN- β 1a protects retinal ganglion cells (RGC); this is an indicator of a neuroprotective effect. In a follow-up study, IFN- β 1b was less successful, and only when administered on the day of EAE induction; later treatment did not protect RGC. Moreover, the effect was via preventing inflammation, IFN does not protect RGC in vitro.

MS: In SPMS, several trials have shown a lack of effect on IFN- β in the absence of inflammatory activity as revealed by relapses. Post-hoc subgroup analysis showed the efficacy of IFN- β 1a was only due to relapse reduction in those patients with SPMS with superimposed relapses; there is no, or minimal, effect of IFN- β on disease progression.

PPMS patients treated with IFN- β showed no improvement on the primary and secondary outcome measures, including the rate of disease progression

Other neurodegenerative conditions: Neuroprotective effects can be evaluated in other diseases where neurodegeneration is the primary pathological feature. IFN- β 1a was however, not effective in a randomized controlled trial in ALS.

In an open label, 1-year trial in adrenoleukodystrophy, where TNF and IFN- γ are up-regulated in the CNS, IFN- β , which down-regulates these cytokines, did not stop the progression, and 4 out of 8 patients stopped early due to accelerated progression. This again shows a lack of neuroprotective capacity for IFN- β .

Endogenous type 1 IFN: Some neurodegenerative diseases have genomic and proteomic signatures of endogenous interferon pathway activation although this does not protect from relentless progression. Experimentally, LPS induces neurodegeneration via multiple mechanisms, and a variety of neuroprotective agents are tested for their ability to suppress this LPS effect. LPS is also a most potent inducer of endogenous IFN. Thus, endogenous interferon is not neuroprotective.

A worrisome role for IFN type 1 in the CNS with regard to neuroprotection and neurodegeneration can also be inferred from studies showing significant neurodegeneration and neuroinflammation, despite the ability to clear CNS virus, in transgenic mice overexpressing IFN- α in astrocytes.

GA: Experimental conditions In EAE models where its neuroprotective potential is tested alongside that of IFN- β , it protects RGC better than IFN. It is effective in experimental models of amyotrophic lateral sclerosis (ALS).

Although in the TEMV model of viral induced demyelination, GA-specific antibodies induce remyelination, we failed to show either a neuroprotective or remyelinating effect in mice with MHV-induced demyelination (E. Lavi and CS Constantinescu, unpublished observations).

In the *human system*, there cannot be a direct effect on the threatened neuron, because GA does not cross the BBB and is very short-lived. Its effects are via induction of beneficially altered immune cells. GA induces Th2 and Treg cells, and reduces Th1 cytokines. It induces alternatively activated macrophages and T cell BDNF production. It increases uric acid, an antioxidant and neuroprotector. Immunomodulatory effects are also indirect, through development of beneficially altered immune cells, a process which takes time to develop and in animal models is hastened by using GA not as drug but as immunogen, in adjuvant, to induce GA-reactive immunity. Indeed, in few experimental conditions is GA effective when injected repeatedly without adjuvant, and then only after sufficient time to allow development of protective anti-GA immune responses.

MS: In RRMS, atrophy rate reduction is lower than with IFN- β although relapse reduction is similar. In SPMS it is not recommended because studies show no effect on disease progression. An important argument against GA's neuroprotective potential comes from the PROMISE PPMS trial of nearly 1000 patients receiving GA or placebo for 3 years, showing no benefit on disease progression or brain atrophy.

Other conditions with neurodegeneration: What is the significance of *BDNF induction* by GA in T cells? BDNF is abundantly expressed in the activated microglia of patients dying with HIVE/dementia complex; thus clearly not in itself sufficiently neuroprotective. BDNF is unsuccessful as neuroprotector in ALS trials.

Anecdotal evidence. At the end of the PROMISE trial in Nottingham 4 of 6 starting participants continued on GA. One died due to disease progression, the others have progressed significantly. Moreover, a patient with MS on GA developed ALS and died, showing that GA fails to prevent human ALS.

For the time being, we still need to rely on these DMD for the immunomodulatory function, but we and our patients are better off looking for neuroprotective treatments of MS elsewhere.