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CASE REPORT

Do neutralising antibodies against exogenous interferon-beta inhibit endogenous signalling pathways?

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Abstract
Introduction: Interferon-beta (IFNβ) is currently the most used disease-modifying treatment for relapsing-remitting multiple sclerosis (RRMS), but it can lead to the production of neutralising antibodies (NABs) against IFNβ.
Clinical case: A lady with a past history of genital herpes was diagnosed with RRMS, started IFNβ treatment with a good initial response. Three years later her treatment was interrupted to become pregnant. After delivery she restarted IFNβ; she had more reactivations of genital herpes and experienced intermittent sensory symptoms often coinciding with herpes reactivation. High NABs titres against IFNβ were found. Since the introduction of famciclovir as prophylactic antiviral therapy and a switch from IFNβ to glatiramer acetate, herpes reactivations ceased and she had no further MS relapses.
Conclusion: Exacerbations of genital herpes coinciding with MS relapses suggest a potential link between the development of NABs and inhibition of anti-viral action of endogenous IFNβ. This case highlights that NABs not only decreases exogenous IFNβ treatment efficacy, but may also interfere with anti-viral properties of endogenous IFNβ. Investigating patients who are treated with biological medication will allow us to better understand the biology and signalling pathways in humans.

Abbreviations: BABs, binding antibodies; IFNβ, interferon-beta; IFNs, interferons; MRI, magnetic resonance image; MS, multiple sclerosis; MxA, myxovirus resistance protein A; NABs, neutralising antibodies; PwMS, patients with MS; RR, relapsing-remitting

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1. Introduction

Interferon-beta (IFNβ) is currently the most used disease-modifying treatment for relapsing-remitting (RR) multiple sclerosis (MS), decreasing the number of relapses by 30% and magnetic resonance image (MRI) activity by 70–90% (Farrell and Giovannoni, 2007). Interferons (IFNs) are endogenous cytokines produced and released by host cells in response to pathogens, that when synthesised in non-mammalian cells or genetically altered, have amino-acid or post-translational changes that may break off pre-existing immune tolerance and induce antibody production (Farrell et al., 2012). Usually they are binding antibodies (BABs) that do not affect the biological activity of the drug. The subset of BABs that bind to the drug are called neutralising antibodies (NABs), they inhibit its biological activity and are associated with decrease in treatment efficacy (Farrell et al., 2012; PRIMS Study Group, 2001).Out of the three IFNβ products available for MS treatment subcutaneous IFNβ1b is the most immunogenic (12.5–24% of patients develop NABs), followed by subcutaneous IFNβ1a, with intra-muscular IFNβ1a being the least immunogenic (PRIMS Study Group, 2001). Some patients with MS (PwMS) with low NAB titres can revert back to being NAB-negative, but those with high titres rarely revert back (Giovannoni et al., 2002).

2. Clinical case

A 31 year-old lady presented to neurology in 2000 with sensory symptoms in all four limbs and Lhermitte's phenomenon. She had no significant past medical history other than glandular fever at 18 years old and a 20 year history of genital herpes that was well controlled at that time, with two or three reactivations per year. Neurological examination showed mild spinothalamic sensory disturbances. Brain MRI was consistent with demyelination indicating a clinically isolated syndrome.

Over the next three years there were further relapses, so she started IFNβ1a 44 mcg in 2003 with clinical control. In 2006 medication was discontinued to become pregnant and she had two uncomplicated pregnancies and births in 2007 and 2009. After the second pregnancy she had a severe relapse and restarted IFNβ. Since then she experienced frequent intermittent sensory symptoms, sometimes with impaired functioning. Coincidentally, reactivations of genital herpes started to occur more than once a month. MS symptoms were worse whenever she had herpes reactivation. A brain MRI, in 2010, showed multiple new white matter lesions typically in a deep and periventricular distribution.

When she was seen for a second opinion in 2011, during a relapse, she had jerky pursuit eye movements and mild weakness in her left arm. She was taking no regular medications, apart from IFNβ, and remained fully functional with limited time off work throughout her MS relapses. Blood analysis showed low serum 25-hydroxyvitamin D3. Full blood count, liver, renal and thyroid function tests were normal. NABs to IFNβ were screened in December 2011 when they proved to be positive (237 NU). Repeated measures in January and May 2012 remained high (185 NU and 317 NU, respectively).

Short courses of aciclovir and valaciclovir proved unsuccessful in effectively controlling the genital herpes reactivations, therefore famciclovir 125 mg twice daily was started in December 2011. In March 2012, IFNβ1a was replaced by glatiramer acetate 20 mg daily and vitamin D3 at 5000 units daily was initiated to treat her MS symptoms.

In September 2013, she described resolution of genital herpes exacerbations and fewer MS symptoms, with only minor sensory symptoms and fatigue two days per month not affecting her daily functioning. She has had no further relapses and annual MRI has shown no new T2/FLAIR or gadolinium-enhancement.

3. Discussion

NABs are clinically relevant in PwMS treated with IFNβ therapy. NAB-positive patients have more relapses, activity on MRIs and disease progression (Farrell and Giovannoni, 2007; PRIMS Study Group, 2001). In months 13–36, once NABs develop, the relapse rate in NAB-positive individuals increase by 50% compared with NAB-negative individuals and is similar to placebo-treated individuals (The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group, 1996). But NABs avidity and IFNβ dosing regimen influence the biological effect (Giovannoni et al., 2002).

It is of note that our patient had history of glandular fever, which has been closely associated with MS and suggested as a potential causative factor.

Other infections have been associated with increased risk of MS relapses; however PwMS are not at higher risk of infections. IFNβ binds to its cell surface receptor activating intracellular signalling mechanism leading to the transcription of numerous genes as myxovirus resistance protein A (MxA), neopterin or β-2 microglobulin genes (Figure 1). Studies showed that development of IFNβ NABs results in a titre dependent reduction in these biomarkers (Giovannoni et al., 2002) and the beneficial shift in immune cell populations also appears to be inhibited, reverting to pre-treatment levels in NAB-positive patients (Giovannoni et al., 2002). These findings support the notion that there are in vivo biological effects of NABs and that they may affect not only the exogenous IFNβ, but also the naturally occurring IFNβ, interfering with physiological pathways. We argue that NABs to IFNβ therapy probably also neutralise endogenous IFNβ and affect the patient's own immune function, which in our patient manifested as frequent reactivations of genital herpes, that could trigger intermittent sensory symptoms and MS relapses. Once the patient was put on famciclovir that stopped genital herpes exacerbations, the MS symptoms improved and she became relapse free. We cannot exclude that the latter could also be due to the initiation of glatiramer acetate.

Glatiramer acetate was the therapeutic choice due to high titre NABs against IFNβ and because NABs are cross-reactive to different IFNβ products (Giovannoni et al., 2002), requiring a switch to a treatment with a different mechanism of action. The patient was not eligible for natalizumab as she did not have disabling relapses or gadolinium enhancement.

The impact of NABs on endogenous IFNβ functions is still uncertain. Endogenous IFNs have a role in cancer prevention