Mellen Center Approaches: Neutralizing Antibodies to Interferon β (antibodies to natalizumab are covered in the MC approach to natalizumab)

What are neutralizing antibodies?
Neutralizing antibodies (Nab) refer to antibodies that are induced by treatment with biological therapeutics. They occur in a proportion of patients receiving interferon beta products. Antibodies occurring during the course of treatment can interfere with biological and clinical responses to treatment. Antibodies also occur to glatiramer acetate (GA), but the clinical or biological importance of GA antibodies is not known.

How frequently do antibodies develop during treatment with IFNβ?
With currently marketed IFNβ products, neutralizing antibodies (Nab) develop in 5-35% of patients. The frequency of IFNβ Nab is about 5% for IM IFNβ-1a (Avonex), about 35% for SC IFNβ-1b (Betaseron), and about 25% for SC IFNβ-1a (Rebif).

When do patients develop Nab?
IFNβ Nab develop slowly – they initially appear after 6 months, and almost always occur by 18 months in patients who will become antibody positive.

What is the impact of IFNβ Nab antibodies on response to therapy?
Numerous studies have demonstrated absent or blunted biological responses to IFNβ in patients with high titer IFNβ Nab. Most placebo-controlled studies have shown diminished clinical and MRI therapeutic responses occurring in IFNβ treated patients who develop IFNβ Nab. In the presence of persistently high titer IFNβ Nab, clinical and MRI activity measures are no different from placebo treated patients.

Does the level or titer of IFNβ antibodies matter?
In general mild elevation (e.g. < 1:20) of IFN beta antibody titers may be less important clinically than higher titer elevations. If titres are low, we tend to continue treatment with the interferon agent unless there is evidence of significant disease activity. If moderate (e.g. 1:20 – 1:60), we would repeat a level in 3-6 months. Nab are much less likely to disappear in patients with high titers (e.g. > 1:60).

When should IFNβ antibodies be measured?
The Mellen Center approach is to consider the immunogenicity of IFNβ products when selecting therapy in the first place, (i.e. selecting low immunogenicity products), and to monitor patients selectively. Because of the kinetics of IFNβ Nab, we don't recommend an initial assay before about 6 months of therapy, and if an IFNβ Nab assay is negative 18 months or more after initiating IFNβ therapy, repeat testing is not required unless the patient switched from Avonex to one of the more immunogenic products. Because the frequency of IFNβ Nab in Avonex treated patients is below 10%, and because the assay is expensive, we don't routinely monitor patients who are doing well on treatment, although the European Community requires routine monitoring. IFNβ Nab assays can be most useful in a patient with an intermediate level of disease activity, when the decision is whether to switch to GA or continue IFNβ.
Is there evidence that patients with IFNβ neutralizing antibodies experience deleterious effects from the antibodies?  

There is a theoretical concern that patients with antibodies to endogenous proteins (such as IFNβ) may neutralize the endogenous protein with development of antibodies to the therapeutic agent, and thereby accelerate the underlying disease process. This remains a theoretical concern. There is no current evidence to suggest that development of IFNβ Nab develop more aggressive MS as a consequence of the Nab.

REFERENCES:


Rudick RA, Ransohoff RM. Biomarkers for interferon response in MS: are we there yet? Neurology. 2008; 70:1069-1070

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