Cleveland Clinic

Mellen Center Approaches: Neutralizing Antibodies to Interferon ß (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 IFNß?

With currently marketed IFNß products, neutralizing antibodies (Nab) develop in 5-35% of patients. The frequency of IFNß Nab is about 5% for IM IFNß-1a (Avonex), about 35% for SC IFNß-1b (Betaseron), and about 25% for SC IFNß-1a (Rebif).

When do patients develop Nab?

IFNß 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 IFNß Nab antibodies on response to therapy?

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

Does the level or titer of IFNß 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 IFNß antibodies be measured?

The Mellen Center approach is to consider the immunogenicity of IFNß products when selecting therapy in the first place, (i.e. selecting low immunogenicity products), and to monitor patients selectively. Because of the kinetics of IFNß Nab, we don't recommend an initial assay before about 6 months of therapy, and if an IFNß Nab assay is negative 18 months or more after initiating IFNß therapy, repeat testing is not required unless the patient switched from Avonex to one of the more immunogenic products. Because the frequency of IFNß 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. IFNß 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 IFNß.

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Is there evidence that patients with IFNß neutralizing antibodies experience deleterious effects from the antibodies?

There is a theoretical concern that patients with antibodies to endogenous proteins (such as IFNß) 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 IFNß Nab develop more aggressive MS as a consequence of the Nab.

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