Current Clinical Applications of Interferon—Multiple sclerosis—

Kazuya TAKAHASHI

Department of Immunology, National Institute of Neuroscience, NCNP

Abstract: Interferon-β-1b (INF-β-1b) has been available in Japan since 2000 as the first therapy to treat relapsing remitting multiple sclerosis (MS). 8 MIU of IFN-β-1b is injected subcutaneously every second day. IFN-β-1b therapy reduces the relapse rate in MS patients. Some biological activities of IFN-β-1b are considered to be inhibitory effects on antigen presentation and proliferation of lymphocytes, and modulation toward anti-inflammation including suppression of interleukin (IL)-12 production from dendritic cells. Adverse reactions associated with IFN-β-1b therapy are as follows: (1) Flu-like symptoms (especially fever, headache, fatigue and myalgia) are experienced by three quarters of patients, but this reaction can usually be managed with NSAIDs and resolved within the first three months after initiation IFN-β-1b treatment. (2) Skin reactions may appear within the first month of treatment. Some of the risk factors in this regard include incorrect injection techniques, use of cold IFN-β-1b solution, and repeated use of the same injection site. (3) A new or exacerbated state of depression may be experienced within the first six months after initiation of IFN-β-1b therapy. (4) Transient increased spasticity usually appears together with flu-like symptoms. (5) One should also note that IFN-β-1b should not be administered to pregnant women, patients with autoimmune hepatitis or with medication containing Sho-saiko-to.

Key words: Multiple sclerosis; Recurrence inhibiting effect; Subcutaneous self-injection; Injection every second day

Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system and is characterized by repeated recurrence and remission. As with many other autoimmune diseases, it is likely to occur in people in their twenties to forties, and the ratio of male to female patients is 1 to 1.5–2.0.

MS was until quite recently treated with steroid pulse therapy during its acute stage and with oral steroids and immunosuppressive agents...
expression of major histocompatibility complex class II (MHC class II) and preventing activated T cells from passing through the blood brain barrier. These effects are also associated with the prevention of the relapse of MS.

**Therapeutic Practice for Multiple Sclerosis**

Usually, IFN-β-1b is subcutaneously administered at 8 MIU every second day in adult patients with MS. The dose is higher than that used for treating hepatitis or malignant melanoma. Another point that characterizes this therapy is auto-injection. Although the patients inject IFN-β by themselves, it is necessary to hospitalize the patients in introducing the therapy because it is not as easy as, say, using pencil syringes in the treatment of diabetes: it requires each patient to dissolve IFN-β-1b in a solvent and inject 1 ml of the solution. Hospitalizing patients is also useful in that any adverse reactions that are likely to develop in the initial stage of the therapy can be immediately treated, and that adequate instructions can be given to the patients and their families to allay their anxieties.
Precautions of IFN Therapy: Adverse Reactions

Most adverse reactions of the IFN-β-1b therapy occur early after it is introduced, and are often controllable. Representative adverse reactions include flu-like symptoms including fever, injection-site reactions, mental changes, and increased spasticity.

(1) Flu-like symptoms

Flu-like symptoms, such as fever, headaches, general malaise, and arthralgia usually develop within 3 to 6 hours after injection and resolve within 24 hours. Fever develops in more than half of patients. These flu-like symptoms often resolve naturally within 6 months; in the meantime, non-steroidal anti-inflammatory drugs (NSAIDs) are used to relieve them. Ibuprofen (400 to 1,200 mg/day) is reported to be more effective than acetaminophen or acetyl salicylic acid.

When an NSAID is not enough, oral prednisolone is added (around 10 mg/day). To prevent the discomfort of the flu-like symptoms, patients are recommended to inject IFN-β-1b before going to bed. This will make the adverse reactions resolve by the next morning, and ensure that the injection will be performed after taking a bath. Sleeping keeps patients calm and helps relieve the adverse reactions.

(2) Injection-site responses

More than half of patients treated with IFN-β-1b suffer from injection-site reactions, such as erythema nodosum, and pain. Although these responses are also resolved within 6 months, they occur after every injection, markedly reducing the injectable area. Thus this adverse reaction is most troublesome in continuing IFN-β-1b therapy. To minimize the symptoms, it is necessary to teach patients to master the procedures for preparing and injecting the drug, and to regularly rotate injection sites. It is useful to warm the injection to body temperature. When stronger responses, such as necrosis, are observed, the injection of IFN-β-1b has to be discontinued. Erythema and pain are treated with steroid ointments and icing, respectively.

(3) Mental change

As with other types of IFN, IFN-β-1b causes symptoms of depression, such as anxiety and despair. The treatment for these symptoms is not described here, and the reader is asked to refer to the appropriate articles.

(4) Increased spasticity

Existing symptoms of MS may transiently worsen. Attention should be paid to the fact that the worsened symptoms are easily mistaken for relapse. The worsening of existing symptoms mostly occurs as increased spasticity, although reduced visual acuity and sensory disturbance have also been reported. These symptoms often occur within 3 months after IFN-β-1b therapy is started. Since most of them are transient and resolve satisfactorily, it is necessary to give a full explanation to the patients to prevent them from discontinuing IFN-β-1b. Since increased spasticity often occurs with the above flu-like symptoms, it is treated with NSAIDs or muscle relaxants, such as baclofen. In the patients who have been treated with a muscle relaxant, increasing the dose of relaxant often relieves increased spasticity.

(5) Others

Other adverse reactions include leukopenia, hepatic dysfunction, abnormal laboratory values, and worsened diabetic control. It should be noted that abnormal glucose tolerance is often overlooked in the blood test for non-diabetic patients. Combination with Sho-saiko-to is contraindicated because it may cause interstitial pneumonia. Attention should be paid to the treatment of patients with autoimmune diseases other than MS. In particular, IFN-β is contraindicated in patients with autoimmune hepatitis. IFN-β is also contraindicated in pregnant or lactating women. Since multiple sclerosis often develops in women with pregnancy potential, it is necessary to inquire about the future childbearing plans of patients before introducing IFN therapy.
Opinions from Patients

A questionnaire survey by the MS CABIN (Japanese Branch of the International Multiple Sclerosis Support Foundation; http://www.msccabin.org/) showed that the patients had the following negative feelings before the introduction of IFN therapy: (1) vague fear of injection (40%); (2) anxiety about continuing the therapy (14%); (3) anxiety about injection technique (7%); and (4) a sense that the explanation from the attending physician was inadequate (5%). It is important to obtain trust from the patients before introducing IFN therapy, and most of these negative feelings can be overcome by giving patients full explanation and guidance. Since the survey also showed that 17% of patients could overcome the negative points through cooperation with their families, it is also necessary to give a full explanation and guidance to their families. It is also necessary to explain that IFN reduces recurrence, severity, and lesion area as determined by MRI, but does not completely inhibit the disease; the patients who expect too much of IFN tend to fail to comply properly with the therapeutic procedures.

Future Development of IFN

IFN-β-1a (Avonex), a type of IFN with the same amino acid sequence as natural-type IFN-β, is now being examined in a clinical study. It is characterized by the finding that neutralizing antibodies for it are unlikely to develop. The drug is intramuscularly injected once weekly, and is expected to be effective for patients with severe injection-site responses to IFN-β-1b preparations.

Conclusions

IFN-β-1b has become available as a drug with proven effectiveness in inhibiting the relapse and progression of MS. Since it can be relatively safely self-injected by patients (so long as full explanations and guidance are provided), clinicians should actively put it into clinical practice as a standard therapy, much as they would recommend insulin therapy for diabetes.

REFERENCES