EFFECTS OF EXPERIMENTAL RECOMBINANT INTERFERONS ON MULTIPLE SCLEROSIS*

KENNETH P. JOHNSON**,† and (*by invitation*) HILLEL S. PANITCH

BALTIMORE

Multiple Sclerosis (MS), first described by Charcot in 1877 (1), is a major crippling disease of young adults. Approximately 300,000 cases exist in the United States and over 60 percent are women. Clinically the disease is remarkably variable, appearing between the ages of 15 and 60 with a peak age of onset at approximately 30 years. Patients may experience any type of the central nervous system (CNS) symptom, however, weakness and sensory change of the extremities indicative of spinal cord disease or optic neuritis are the most common first complaints. Rapidly appearing exacerbations followed by gradual remission characterize the early years of the disease. Usually during the fifth decade, the disease pattern changes to one of chronic, increasing neurologic disability, often producing significant handicaps. As the disease progresses urinary dysfunction is almost universal secondary to spinal cord disease. Another frequent complaint is periodic severe fatigue which is more likely during periods of disease activity or when patients are exposed to increased ambient temperatures.

Pathologic change is restricted to the CNS and appears almost exclusively in the white matter. Discrete foci or plaques of varying size appear more or less randomly with some predilection for periventricular areas. Early on, these plaques have an inflammatory nature but over time they show demyelination, the central hallmark of the disease plus gliosis. Various lymphocytes always reside in the plaque and in perivascular cuffs and increased collections of immunoglobulins in the lesion are universally found as well.

The diagnosis of MS is made by observation of the exacerbating remitting or progressive course and the finding of neurologic impairments on examination which must result from multiple, localized CNS lesions. The magnetic resonance imaging (MRI) scan almost always shows the lesions in cerebral white matter. Various evoked response tests aid in the

* The Department of Neurology, University of Maryland School of Medicine, Baltimore, Maryland

** Research support from the National Institute of Neurological and Communicative Disorders and Stroke and the Research Service of the Veterans Administration is gratefully acknowledged.

† Reprint requests: Kenneth P. Johnson, M.D., Department of Neurology-Room N4W46, University of Maryland Hospital, 22 S. Greene Street, Baltimore, Maryland 21201

detection of clinically silent lesions. Finally, spinal fluid immunoglobulin abnormalities can be detected in over 95% of cases if a search is made for an abnormal IgG index or the presence of oligoclonal IgG bands (2). Once other diseases are ruled out the diagnosis can be made with assurance relatively early in over 90% of cases. The differential diagnosis includes various neurologic infections such as neurosyphilis, Lyme disease and tropical spastic paraparesis produced by HTLV-1 virus infection. Brain tumors and cerebral vasculitis may at times confuse the picture and some cases of a more generalized autoimmune condition which includes CNS lesions, have been described.

Multiple sclerosis occurs primarily in the Caucasian population and occasionally affects several members in one family. Identical twins both show the disease more commonly than fraternal twins or other siblings (3). Certain HLA antigens are over represented in the MS population indicating that there is a genetic predisposition to the disease. Epidemiologic studies have shown that there is a geographic gradient with more cases in temperate areas; migration studies show that one's residence during the first fifteen years of life determine the prevalence of disease. True epidemics of MS have been described indicating that some environmental factor, probably acting during childhood, initiates the process in the genetically susceptible individual (4). The disease process itself is clearly immunologic in nature. The presence of immune active cells and immunoglobulin in plaques and spinal fluid plus the finding that T suppressor lymphocytes are deficient during exacerbations or during the chronic stages of disease all indicate the immunologic nature of the process. Exacerbations occur more frequently after banal infections suggesting that a perturbation of the immune system is likely to reactivate or create a new MS lesion (5). Recent evidence suggests that gamma interferon is a prime pathogenic factor in plaque initiation or activation as noted below. Indirect evidence has suggested that one or more viruses may contribute to the MS process but no convincing studies have settled this point.

Three human interferons (IFN), alpha, beta and gamma, have been identified and all have antiviral activity as well as the ability to stimulate or modify various immunologic functions (6). Alpha and beta IFN are quite similar and in fact use the same cell surface receptor. Gamma interferon is remarkably different in its immunologic functions and is known especially for its ability to stimulate the expression of DR histocompatibility antigen on the cell surface (7). By 1979 (8), it was known that MS patients often produce deficient amounts of various interferons and also show an abnormally low level of natural killer (NK) cells, a population known to be stimulated by interferons. These reasons plus

the fact that MS has been indirectly linked to a past or persistent virus infection all suggested that interferons would be suitable candidates for therapeutic evaluation in MS.

We collaborated in the plans for the first controlled trial of IFN therapy for MS and decided to explore systemic administration of alpha IFN in an effort to reduce new attacks of disease (9). This route was chosen because there are systemically identifiable immunologic changes in MS and because interferons may cross the abnormal blood brain barrier at the site of an evolving plaque even though interferons cross the intact barrier poorly (10). Also there was a concern that repeated intrathecal injections of IFN in a pharmacological vehicle may stimulate late progressive arachnoiditis. This first trial of alpha IFN in MS, conducted in California, investigated natural interferon in a subcutaneous (sc) dose of 5 million units daily for six months. Twenty-four patients participated in a double blind, placebo controlled, crossover format. This small study did show a definite trend toward a reduction of attacks, however, persistent side effects precluded its consideration for long term use in exacerbating-remitting MS (9). At the University of Maryland, we then initiated the second controlled trial of alpha IFN using cloned interferon supplied by the Schering-Plough Corporation. Two million units of interferon were given sc three times a week for one year to fifty MS patients while fifty others received placebo, again in a double blind format. Side effects were almost nonexistent and the number of attacks declined dramatically, however, the attack rate also declined in the placebo population precluding a claim of therapeutic efficacy (11). Of interest, almost any form of therapy which has been evaluated for MS has shown a significant placebo effect (12).

In 1984, we were asked to initiate a study of recombinant gamma interferon again in exacerbating-remitting MS. Because of our concern of adverse immunologic stimulation, a small pilot trial was conducted involving 18 patients who received gamma IFN intravenously in one of three doses, twice per week. During the one month study, seven patients experienced new attacks of MS indicating that gamma IFN was a potent stimulator of new disease activity (13). While this experience was not useful therapeutically, it did indicate the central position that gamma IFN probably plays in activation or initiation of disease activity in MS. As a result of this study, inhibition of gamma IFN and its effects have become major therapeutic objectives in the search for new therapies for MS. Of interest, all of the MS attacks experienced during the gamma IFN trial were mild and all were clinically reversible within a three to four month period.

Currently we are engaged in a large clinical and scientific evaluation

of recombinant Beta interferon in MS (14). A small pilot trial of beta IFN supplied by Triton Biosciences, Alameda, California, has shown that remarkably large doses can be given sc with virtually no side effects. A pilot trial employing 30 patients indicated that 45 million units per dose, administered sc three times per week was well tolerated by young exacerbating-remitting MS patients. No increase in MS disease activity has been noted in this small study; in fact there is a clear trend towards reduction in new disease attacks. Following this two and a half year experience with beta IFN, a large multicenter trial is now being conducted at ten participating centers, six in the U.S. and four in Canada. A total of 330 patients will be enrolled in a blinded, placebo controlled study in which one-third of the patients will receive 45 million units of beta IFN sc every other day, another third will receive 9 million units and the rest will receive placebo. The trial is planned to last for two years and is enhanced by a number of clinical and laboratory evaluators including frequent MRI scans.

Studies in progress at the University of Maryland have shown that peripheral blood leukocytes from patients receiving beta IFN have a decreased ability to synthesize gamma IFN. This inhibitory effect on gamma IFN and its functions seems to persist for prolonged periods of time. The preparation has also been shown to stimulate T suppressor cell activity, another potentially beneficial therapeutic function. Thus there is a clear immunologic and pharmacologic rationale for beta IFN's potential effectiveness in MS.

The sequential studies described in this short report have encompassed over eight years of effort and have required the enrollment of over 250 courageous MS patients who have willingly accepted either therapeutic agents of unknown effects and toxicity or long term dosing with placebo. This series of studies has not as yet produced a clearly effective therapeutic agent for MS. However, the studies and the accompanying scientific investigations have produced a great deal of fundamental information about the immunologic pathogenesis of exacerbating-remitting MS. In addition, the trials now underway rest on a firm foundation of scientific fact which provides great promise that interferons may find an acknowledged therapeutic role in the treatment of this highly variable, long term and, unfortunately, frequently disabling CNS disease of young adults.

REFERENCES

1. Charcot JM. Lectures on the Diseases of the Nervous System. Delivered at La Salpetriere Sigerson G (trans). London: New Sydenham Society. 1877–1889.
2. Johnson KP, Nelson BJ. Multiple Schlerosis: Diagnostic Usefulness of Cerebrospinal Fluid. *Ann Neurol* 1977; 2: 425.
3. Compston, A: Genetic factors in the aetiology of multiple sclerosis. In: McDonald WI,

Silberberg DH eds. *Multiple Schlerosis.* England: Butterworth & Co 1986; 4: 56.
4. Kurtzke JF, Gudmundsson KR, Bergmann S. Multiple sclerosis in Iceland. I. Evidence of a postwar epidemic. *Neurology* 1982; 32: 143.
5. Sibley WA, Bamford CR, Clark K. Clinical viral infections and multiple sclerosis. *Lancet* 1985; 1: 1313.
6. Fleischmann WR Jr, Ramamurthy V, Stanton GJ, et al. Interferon: Mode of Action and Clinical Applications. In: Smith RA, ed. *Interferon Treatment of Neurologic Disorders.* New York: Marcel Dekker Inc: 1988; 1: 1.
7. Merrill JE, Targan SR. The Immunologic Basis for the Use of Interferons. In: Smith RA, ed. *Interferon Treatment of Neurological Disorders.* Marcel Dekker Inc: 1988; 3: 65.
8. Neighbour PA, Bloom BR. Absence of virus-induced lymphocyte suppression and interferon production in multiple sclerosis. *Proc Nat Acad Sci* 1979; 76: 476.
9. Knobler RL, Panitch HS, Braheny SL, et al. Controlled clinical trial of systemic alpha interferon in multiple sclerosis. *Neurology* 1984; 34: 1273.
10. Johnson KP. Systemic interferon therapy for multiple sclerosis: Design of a trial. *Arch Neurol* 1983; 40: 681.
11. Camenga DL, Johnson KP, Alter M, et al. Systemic recombinant alpha-2 interferon therapy in relapsing multiple sclerosis. *Arch Neurol* 1986; 43: 1239.
12. Hirsch RL, Johnson KP. Placebo-induced enhancement of natural killer cell activity in a double-blind trial of recombinant alpha-2 interferon in multiple sclerosis patients. In: Spector NH, ed. *Neuroimmunomodulation. Proceedings of the First International Workshop of Neuroimmunomodulation:* IWGN, Bethesda, Maryland 1985: 219.
13. Panitch HS, Hirsch RL, Schindler J, et al. Treatment of multiple sclerosis with gamma interferon: Exacerbations associated with activation of the immune system. *Neurology* 1987; 37: 1097.
14. Panitch HS, Johnson KP. Treatment of Multiple Sclerosis by Systemic Administration of Interferon. In: Smith RA ed. *Interferon Treatment of Neurologic Disorders.* Marcel Dekker Inc New York 1988; 9: 209.

DISCUSSION

Paterson (Chicago): Ken, that's very nice to get a summary of important and time-consuming clinical trials. Can you tell us whether the recombinant beta enters the central nervous system *per se*?

Johnson: Actually this material disappears after subcutaneous injection and we can't even find it in the blood stream to say nothing about in the central nervous system.

Paterson (Chicago): What about in the spinal fluid?

Johnson: We cannot find it there either. The rationale we have for continuing to use it is that MS is probably a systemic immunologic disease even though it is pathologically a central nervous system disease. Probably it is not terribly important if it crosses the intact blood brain barrier in that in MS there is such a destruction of the blood brain barrier during the disease or new plaque formation that it would get across during that time or in that area anyway.

Greer (Providence): I was interested in your placebo effect and wondered if you had tracked it down. You've looked for reasons why the beta interferon works. What have you done about the placebo effect?

Johnson: Placebo is a marvelous treatment for multiple sclerosis. I think if you use saline and give it a fancy label you can probably have a fairly good effect on MS. The fact is that placebo is not a psychological effect in many diseases. We do have information that looks at NK cell activity in the second trial we did, the second alpha trial. As we expected

NK cell activity increased in peripheral blood in the interferon patients. The number of NK cells increased in the peripheral blood of placebo patients just as much as it did in the interferon-treated patients. Even more surprisingly, at the end of the trial, a year later when patients were anticipating the end of the trial, again the number of NK cells increased in both the placebo and the interferon-treated groups. This indicated to us that there is clearly an immunologic effect of placebo in these patients as well as any psychological one.

Bernier (Pittsburgh): You mentioned looking at the NK cells. Are there any other parameters of the immune system that you have been able to study that you find to be different beyond the production of gamma interferon in those treated with the beta?

Johnson: We have looked at more different parameters of immune function than you can think of almost. The types of lymphocyte populations, antibody production in serum and spinal fluid; none of these have been useful markers for either disease activity or of therapeutic effect except for IA expression.

Tobian (Minneapolis): Has anyone tried cyclosporin for multiple sclerosis?

Johnson: There has been a major trial just completed last January of approximately 500 patients treated at 12 centers with relatively high dose oral cyclosporin 6mg per kilo per day with a placebo-control. We are still analyzing this study, but unfortunately thus far the results are very disappointing in terms of making a difference in the disease. As you heard earlier this morning, the nephrotoxic problems with cyclosporin are considerable especially when you are talking about young people who have normal kidneys to start with that you will probably want to treat for thirty to thirty-five years.