ORIGINAL ARTICLE

Dilemmas in Management of Multiple Sclerosis: Type of Study

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ABSTRACT

Objectives*:* To study the availability of oral and injectable treatment options for Multiple Sclerosis and to address the social issues like affordability and availability of medicines.
Design of study: Observational study.
Place and duration of study: The study was done at Fatima Memorial Hospital, Lahore, which is a tertiary care hospital. The majority of the patients in this study were seen at a private Neurology clinic of the consultant. The total number of patients in the study were nine, one of the patients was diagnosed in 1992, others were diagnosed after 2003.
Patients and methods: A total of nine patients who had a diagnosis of Multiple Sclerosis were followed, and were divided into three groups, *group 1* included the patients who were on *Betaseron (interferon beta-1b) "regularly"*, *group 2* included the patients who were on Betaseron "*irregularly", group 3* included the patients who were advised to take
interferon, but *could only afford steroids* (I/V solumedrol for relapses, followed by tapering doses of oral steroids).
Results: Out of nine patients, *six were treated with Interferon beta-1b* (four of them
took Betaseron *regularly* and two took *irregularly*), and the remaining three were on steroids, *the latter group took steroids only due to financial constraints*. The patients in *group I*, who were on *Interferon beta-1b* on *regular basis*, had the lowest number of relapses with minimum functional disability. The patients in *group II and group III*, had greater number of relapses and greater functional disability as compared to group I. *The economic issue was the major issue in use of interferons for long-term immunomodulation.*
Conclusions: The *group I* had fewer number of relapses / exacerbations, than *group II and III.*
Key words: Multiple Sclerosis(MS), Interferon beta-1b, Clinically isolated syndrome, demyelination.

MS is a disabling disease of the brain and spinal cord characterized by focal demyelination[1]. These diseased areas of myelin are called as "plaques"[2]. It is an autoimmune disorder, which affects women two to three times more than men[3]. Peak age of occurrence is 30-35 years, and is rare in children and after 65 years of age. The risk to develop MS is more in the North European descent which is due to the genetic differences[4]. There is a predilection of the MS plaques to develop in the periventricular white matter, corpus callosum, optic nerves, and dorsal spinal cord. The earliest presentation of MS can be a clinically isolated syndrome (CIS). Other forms include relapsing-remitting, primary progressive and secondary progressiveMS[5,6].

Patients and Methods

A total of nine patients were included in the study, out of which seven were ***females,*** and two were ***males***. All patients had MRI done for Brain, spinal cord or both. Five patients had a long-standing illness of four years or more. All patients had RRMS. The acute exacerbation of these patient was managed by intravenous methylprednisolone given for 5 days followed by tapering doses of oral prednisone. ***Four patients*** were able to afford interferon beta 1b on ***regular basis***, ***two patients*** took interferon beta 1b on an ***irregular basis*** due to financial constraints. ***Two patients*** were on i/v solumedrol for relapses, while ***one patient*** could only afford oral steroids for long-term use. Regular follow up of all patients was done, to review the primary disease symptom disability. Patient data is summarized in tables.

Table 1: Summary of the patients (n=9)

Patients taking Betaseron *regularly*	Patients taking Betaseron *irregularly*	Patients on Steroids only
4	2	3

Table 2:

No. of patients with relapsing-remitting type of MS	Diagnosis supported by MRI brain / spinal cord
9	9

Table 3: Functional status of the patient:

Number of patients back to work / usual daily activities	4
Number of patients with limited ability to perform daily function	5

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MS can present with a wide variety of symptoms, which can be visual, motor, sensory or pertaining to co-ordination and balance[7]. The disease course is of the following types[8].

1) **Relapsing-remitting MS (RRMS).** There are symptoms characterized by flares or attacks caused by plaque formation[9]. Almost 80-85% patients follow this disease course These plaques cause symptoms when they occur in brainstem, spinal cord, optic nerves and cerebellum or they can be asymptomatic when in corpus callosum and periventricular white matter, but eventually neurologic impairment can occur at some point in life.
2) **Clinically isolated syndrome.** This is the initial demyelinating event. Some patients develop RRMS while other show no further evidence of MS. The studies show that the second attack occurs even after 14 years in 88% of patients, if lesions were present on the initial MRI.
3) **Secondary progressive Multiple Sclerosis (SPMS**). Almost 85-90% of patients with RRMS eventually develop SPMS. The median time from diagnosis RRMS to SPMS is ten years and the time from disease onset to ambulatory disability requiring use of a cane is 15-25 years.
4) **Primary progressive Multiple Sclerosis(PPMS).** Only 10-15% of patients have this form of MS. Visual loss at onset is rare and it occurs at around 40 years of age

Table 4: FDA-approved disease-modifying therapies for multiple sclerosis.

Drug	Dose, frequency, and route of administration	% Relapse Rate Reduction at 2 years	% Reduction in Disability at 2 years
Once weekly IFN beta-1a (Avonex)	6 MIU, once weekly, IM	18	37
IFN beta-1b (Betaseron)	8MIU, every other day, SC	34	29 (NS)
Thrice weekly IFN beta-1a (Rebif)	12 MIU three times weekly, SC	30	30
Glatimir acetate (Copaxone)	20 mg daily, SC	29	12 (NS)
Mitoxantrone (Novantrone)	12mg/m2, once every 3 month, IV	38	24
Natalizamab (Tysabri)	300mg, every 4 weeks, IV	67	42

Diagnosis of Multiple Sclerosis is made by imaging studies like MRI, CSF analysis and evoked potential studies.[10] The treatment options include disease modifying FDA approved drugs, off label and emerging therapies and symptomatic treatments. These drugs are summarized in table 4.

"Off label therapies" include cyclophosphamide, azathioprine, mycophenolate moftil, methotrexate, cladaribine, natalizumab, alemtuzumab and rituximab.

Table 5: Treatment of acute exacerbation:

Acute relapses in Relapsing-Remitting MS and occasionally Secondary Progressive MS	Methylprednisolone Prednisone Dexamethasone ACTH

The management of MS includes the following.

1) Management of acute attacks.
2) Disease modifying treatments.
3) Symptomatic treatment.
4) Neurorehabilitation.
5) Alternative treatments**.**
6) Therapies under investigations.

1) **Management of acute attacks:** The patients are hospitalized and methyprednisolone is given for acute therapy, administered over 3-5 days.[11] The recommended dose is 1-2 gms / day or dexamethasone in a dose of 2mg/ kg / day over 3-5 days reduces the residual symptoms, after partial recovery that usually occurs after an acute attack. A rebound in disease can occur following discontinuation of glucocorticoid treatment and the endogenous cortisol secretion may be suppressed. Glucocorticoid are not given for purely sensory involvement.
2) **Disease modifying treatments:** The earliest clinical presentation of relapsing-remitting MS (RRMS) is the clinically isolated syndrome in which patient does not fulfill the criteria for diagnosis of MS. Studies have shown the use of interferons during the initial attacks.[12] For relapsing-remitting MS, the more common type of MS, the FDA has approved the following therapies: three interferons; interferon beta -1a (Avonex), interferon beta-1a (Rebif), interferon beta-1b (Betaseron), glatiramer acetate, mitoxantrone (Novantrone), and Natalizumab (Tysabri).
3) **Secondary Progressive MS:** Mitoxantrone is a promising drug for SPMS. Primary progressive MS, the treatment for this form of MS is problematic and many patients who want do not respond to any available therapy. No treatment has been approved for use in this form of disease.

Neurorehabilitation: Multi-disciplinary approaches have been shown to be effective in increasing activity

levels which include input from neuropsychologist, psychiatrist and neurophysicians.

Symptomatic treatment options:

Bladder dysfunction: Alfuzosin for retention, anticholinergics for urgency and incontinence, demopressin for nocturia, and nonpharmacologic measures like pelvic floor exercises, stimulation, biofeedback, intermittent catheterization, bowel problems are dealt with diet change, oral laxatives, enemas and suppositories. Cognitive and emotional issues require antidepressants and donepezil.

Dysphagia and dysarthria require either nasogastric tube placement or PEG tube placement.

Fatigue is common and require amantadine or Pemoline.

Acute pain due to ***trigeminal neuralgia*** is treated with anticonvulsants like. carbamazepine.

Spasticity is treated with physiotherapy, baclofen and dantrolene.

Visual symptoms may require surgery or prisms.

Therapies under investigations*:* Voclizumab, inosine, fingolimod, fumarates (fumaric acid esters—FAE which possesses immunomodulatory properties and is used as a therapy for psoriasis. They also act on myelin-axon unit and exert neuroprotective properties. The MRI analysis of lesions reveals a significant decrease in number and volume of gadolinium enhancing lesions. B-cells are key players in pathophysiology in RRMS, depleting B-cells with anti CD20 agents dramatically reduces disease activity at clinical and radiological level.

DISCUSSION

MS is a debilitating disease of the young, both males and females, early diagnosis and proper management of the disease is necessary to prevent the patient from losing his or her job / livelihood or to make a change in the career, as the disease afflicts people at the prime years of their lives. Unfortunately, in Pakistan, the tests and expertise needed to make the early diagnosis are not readily available to the general population. The treatment with long-term immunomodulating agents is available to a very few lucky ones. The patients mentioned in groups in this article, varied widely as regards to their socioeconomic status and included one patient, who could not even afford intravenous solumedrol for acute exacerbations of symptoms, and thus was put on oral prednisone. Given the financial constraints of this particular patient, after detailed discussion about the lack of scientific evidence of role of oral prednisone in MS, this patient was put on oral prednisone after consent was obtained from the patient's parents. This patient, who was bedridden on initial presentation, is currently, able to walk independently, with minimum side effects of low dose maintenance therapy with oral prednisone.

The patients who were lucky to afford interferons or long-term immunomodulating drugs, on a regular basis, had far less number of exacerbations as well as less number of complications as compared to the ones who were on intravenous steroid or only took oral steroids. It suggests that interferons improve the clinical course of patients over the long-term, however, the patients who were on steroids both intravenous and oral, also showed subjective as well as objective improvement in the course of the disease, although to a lesser extent.

Given the dilemmas of real life circumstances, patients should be treated as early as possible for exacerbations, with intravenous solumedrol and for long-term immunomodulation, interferons are recommended, to decrease morbidity especially as regards to the daily functions of life. In a developing country like Pakistan, the patients with MS should be closely followed for the relapses and complications, so that they can be treated as early as possible with the medicine that the patient can afford, as the number of relapses is directly related to the long-term prognosis of Multiple Sclerosis. This approach can improve the daily functions of life for the patient, as well as decrease the burden for the caregivers.

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