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Research Paper

Long-Term Follow-Up of Multiple Sclerosis Patients in Saudi-Arabia – The Interferon Beta Therapy Retains its Efficacy Despite Poor Drug Compliance

Medical Science

KEYWORDS :

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ABSTRACT

INTRODUCTION: - In multiple sclerosis (MS), disease modifying therapy (DMT) with interferon beta is used in Saudi Arabia for many years.

OBJECTIVE:- To study Longterm follow up (LTFU) of patients of multiple sclerosis on interferon beta.

METHODS:- A total of 41 patients of MS were identified from the pharmacy records and computer database of a referral centre in Saudi Arabia, and interviewed personally regarding disease activity, relapses and disability.

RESULTS:- The 34 out of 41 patients had received interferon beta subcutaneous therapy for a mean duration of 46.7 months. The annualized relapse rate fell from 0.69 per year to 0.56 per year in these patients after initiation of therapy. Most of the patients not on interferon were ambulatory at the time of the study. In the patients with relapsing remitting MS, on interferon therapy 91% had still not reached a EDSS score of 4.

CONCLUSION:- Subcutaneous interferon beta therapy is efficacious in patients of relapsing remitting MS in terms of relapse reduction and disability, in Saudi patients on longterm follow-up.

INTRODUCTION

Multiple Sclerosis (MS) is a chronic inflammatory demyelinating disease of central nervous system, affecting primarily young individuals, and associated with axonal damage in the long run. The disease prevalence in saudi arabia and middle east region is variable at 4-42.0 per 100,000 inhabitants, derived from hospital based studies[1]. In a recent statement Bolega et al emphasized that the gulf region, though in a low risk zone for MS, is experiencing increasing incidence and prevalence rates, based on studies published in last 20 years[2]. The commonest disease course in this region is relapsing remitting[1] and interferon beta is available as the main disease modifying agent[2]. Although twenty years have passed since the proof of effectiveness of this agent was furnished by placebo controlled, double blind randomized trials in North American patients[3], the longterm effects of this therapy need to be studied in different patient populations to streamline the use of available agents, outside of randomized trial settings. The present study was conducted at Armed Forces Hospital (AFH), Southern region kingdom of Saudi Arabia.

MATERIAL AND METHODS

The study population was ethnically only Saudis, attending one of the main referral centre for the southern region of the country. The data extraction process was carried out in the year 2013, of patients diagnosed earlier with multiple sclerosis, and following the pharmacy, emergency and outpatient services of the hospital. Fortyone (n=41) patients with the diagnosis of multiple sclerosis (MS) were identified, including thirty four (34) from drug dispensing register maintained at the hospital pharmacy which provided refill for the interferon beta and other symptomatic treatment. The historical details of these patients were extracted from the computer database of the hospital records and manual search of the patient files as per the medical registration number of the patient.

In addition to the recorded details, each patient was telephoned and interview fixed as per the convenience of the family. The history was verified and a detailed clinical examination done at the interview, in the hospital, in presence of a family member or spouse. A questionnaire was filled up at the interview regarding the interferon therapy, relapses, pulse therapy, drug compliance, family and pregnancy history and adverse effects experienced by the patient.

The diagnosis of multiple sclerosis was verified at the interview and disability assessed by Kurtzke Expanded Disability Scale. The disability was assessed at outside the relapse setting, with a gap of atleast 2 months. The drug compliance was based on recall of the patient, of regularity in following the dosage of treatment regimen, as well as any longterm (≥1 week) interruptions. The relapse was defined as any new clinical neurological episode lasting > 24 hours, and needing a methylprednisolone pulse or hospitalization.

The diagnosis of multiple sclerosis was verified with the help of review of the MRI scan data from the radiological database in presence of a radiologist, and review of the laboratory data especially cerebrospinal fluid examination for oligoclonal bands. Every patient had undergone lab evaluation for vitamin B12 deficiency, antinuclear antibodies, VDRL test, brucella serology and rheumatologist's consultation for behcets disease. The test results for oligoclonal bands was available for only thirteen (13) patients only, and data for evoked response study and follow-up radiological data were incomplete in some patients records. Compliance with the therapy was assessed in terms of missing or omitting a dose in the schedule prescribed, as well as longterm (≥1 week) interruptions in interferon therapy.

The continuous data is presented as mean and range, while as dichotomous data is presented as percentage. The annualised relapse rate was calculated by dividing the total number of relapses experienced by this cohort with patient-years at risk.

RESULTS

The study cohort consisted of forty one patients, with thirty four patients who were on interferon therapy or had received it at

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some point of time. These included twenty four patients of relapsing remitting MS, one patient of progressive MS with relapse and eleven patients of initially RRMS, who were in secondary progression at the time of evaluation. Of the five patients diagnosed to have a clinically isolated syndrome (CIS) at high risk of multiple sclerosis, three were on INTERFERON BETA. THIS MISTAKE IS AT MANY PLACES. Out of these three patients one had had 3 relapses at the same site, by the time the study began. The demographic characteristics of the cohort, are given in Table 1.

Sensory symptoms of numbness, paresthesias, pain and dysesthesia were the commonest clinical features (34/41), followed by visual impairment (25/41) and motor weakness (21/41) involving the limbs. Unsteadiness of gait and urinary symptoms were also common (15/41 each) (Figure 1-3). The optic neuritis, myelopathy, sensory ataxia and brainstem syndrome, were the main syndromic diagnosis.

The thirty four patients (34/41) of the study cohort, had received interferon beta Ia and Ib for a mean of 46.7 months (average 2-120 months) by the time of inclusion in the study. Out of these, four patients had stopped therapy, two because of secondary progression and two because of residual neurodeficit following cervical myelopathy.

In the patients who received interferon therapy, the annualized relapse rate before the initiation of disease modifying therapy was 0.69/year, and fell to 0.56/year on DMT. Sixty five percent (65%) patients had a true relapse (≥1) while on therapy. Of the 3 patients of CIS on interferon only one had a relapse of the disease on DMT. In the thirty five patients with relapsing remitting disease at diagnosis, 11 patients (31%) had progressed to secondary progression. The incidence of secondary progression was 32% in the group of RRMS put on disease modifying therapy at diagnosis.

The mean EDSS score of the 24 patients including RRMS and those started on treatment at CIS (21+3), at the end of study was 2.2 as compared with mean EDSS of 3.3 for the study cohort overall. Ninety one percent (91%) of this (n=24) group had not reached a EDSS score of 4, while as 9% had reached a score of 6.

Among the patients with relapsing disease including RRMS, CIS and RRMS with secondary progression only 14.6% (5/34) had ≥1 relapse/year while on IFN-β. Sixteen patients (16/34, 47%) had evidence of disease activity on the MRI scan in the form of contrast enhancement and/or new lesions on T2W MRI for variable period of time after the initiation of DMT and majority of these (15/16) had atleast one clinical relapse in their disease course while on DMT. Ten patients who had received interferon therapy had reached secondary progression by the time of inclusion in the study. The annualized relapse rate (ARR) had markedly increased from 0.14/year prior to DMT to 0.52/year after initiation of IFN-β in this group, and they continued the treatment despite that.(Figure 1).

Most of the patients (6/7) in the group not on IFN-β were ambulatory. One had EDSS of 8.0 at the time of inclusion in the study. ARR in this group of patients was lower 0.31/year.

Thirty four patients of this cohort received the disease modifying therapy for a variable period. However , there was a delay in initiation of therapy in two thirds (23/34), ranging from 6 months to 9 years (average 2.6 years). Based on the radiological reviews of the imaging data for dissemination in space and time, in sixteen patients (16/41), the diagnosis was made with average delay of 2.8 years. Thirty percent (5/16) of such patients presented with only sensory symptoms along with other minor signs at the time of presentation. Monoparesis , visual scotoma, myelopathy, isolated unsteadiness of gait and urinary incontinence with backache accounted for rest.

There was a high proportion of cases (44%), missing or omitting one or more doses in the injection schedule prescribed by doctor, while as 56% patients followed the schedule strictly. About two thirds (64%) of the patients had interruptions of a week or more in the disease modifying therapy.

Four patients had stopped the drugs by the time of inclusion in the study. The disease modifying therapy was not initiated in seven patients for the reasons given in box 1. Twentyone patients (61.8%) had developed adverse drug effects on subcutaneous Rebif (IFN beta 1a) and Betaferon (IFN beta 1b). Injection site pain, severe fatigue, flu-like symptoms, injection site abscess and alteration in SGOT and SGPT were the main side effects.

Amongst the patients who received interferon therapy compliance to therapy was good in 56 % and poor in 44 %. Besides, twentytwo patients (64 %) had a drug interruption of one week or longer at sometime in the course of therapy. The reasons for poor compliance and adherence are given in box 2.

DISCUSSION

It has been around two decades since the pivotal trials of the three interferon preparations i.e; subcutaneous interferon beta 1b, subcutaneous interferon beta Ia and intramuscular interferon beta Ia showed benefit of disease modification in multiple sclerosis.[4,5,6] The longterm followup (LTFU) of these patients outside of the randomized double blind trial conditions has become available since. In a chronic disease like multiple sclerosis with a variable clinical course, the study of long term efficacy is difficult. However the three primary endpoints of relapse reduction, disease activity on neuroimaging and progression to disability as measured by EDSS has shown interferon therapy to be efficacious and effective even in longterm. In a patient population of relapsing remitting multiple sclerosis, with a mean disease duration of 5 years, 25% patients were still relapse free at a follow-up of 6 years. The mean ARR was 0.52/year as compared to 1.6/years in the two years preceeding the commencement of treatment and about 58 % of the patients show stability or improvement on EDSS[7] . A sustained reduction in ARR of upto 40 % has been seen over 16 years in patients on interferon beta 1b[8] . Significantly lower mean EDSS scores were seen in patients on interferon beta Ia (intramuscular) at 8 and 15 years as compared to those who were not receiving this therapy at baseline in the Multiple Sclerosis Collaborative Research Group Cohort[9] . In the extension phase of the randomized double blind controlled studies, patients who receive interferon beta therapy in the original part of study, shows a lower likelihood of reaching EDSS of 6.0 and take a longer time to reach the EDSS of 4.0 and 6.0 as compared to those on placebo in the original study[10] . The LTFU of PRISMS study patients 7-8 years later also confirms that time taken to one point, two point progression on EDSS as well as progression to EDSS 6.0 is longer in patients receiving treatment early[11] . Patients receiving longterm IFN βIb treatment reached EDSS 6.0 after a median time of 13 years from the diagnosis as compared with median time of 7 years for patients who received treatment for short term only[8] . The effect of interferon beta Ia[11] and interferon beta Ib[10] on slowing the disease progression in longterm has also been found to be dose dependent.

Twenty percent patients had progressed to secondary progression in LTFU on IFN βIa at 7-8 years of follow-up[11] while as the incidence of secondary progression was reduced depending upon the time of exposure on therapy[10].

The modest reduction of ARR from 0.69/year to 0.56/year in the present study could be related to two factors. The retrospective data collection and incomplete MRI data availability could make

differentiation between true relapse and a pseudorelapse difficult. In addition the high frequency of interruption of therapy (64%) could have reduced the treatment effect. The frequency of relapses has been shown to be higher in drop outs and those with interruption of therapy[12,13]. The proportion of nonresponders or suboptimal responders to disease modifying therapy is variable in multiple sclerosis studies, depending upon the criteria used. In multiple sclerosis, studies have used EDSS progression, any relapse, presence of ≥ 2 relapses, decrease in relapse rate of < 30 % or < 50 % as compared to 2 years preceding the therapy, alone or in combination to define a nonresponse to therapy[14] . A national survey in Portugal found a suboptimal response in 26 % in patients treated for atleast one year and defining suboptimal response as one or more relapses on therapy[15]. The present study found a relapse rate of ≥ 1/year in 14.6 % of patients who received interferon therapy for variable period, in patients of RRMS, Clinically Isolated Syndrome and RRMS with secondary progression. The evidence of continued disease activity on neuroimaging was found in about 47 % patients in MRI brain, following the initiation of disease modifying therapy. The increase in annualized relapse rate (ARR) in patients with secondary progression could probably reflects per se a more aggressive disease in this subset of patients. The variable natural history of multiple sclerosis is further reflected in better ambulatory status in patients who did not receive interferon therapy for various reasons, in our study.

TABLE 1: Demographic and clinical characteristics of patients (n=41)

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VARIABLE		VALUE	
AGE (mean±sd)		36.5±7.88 years (18-48 years)	
GENDER	Male	11 (26.8%)	
	Female	31 (73.2%)	
AGE at onset (mean±sd)		29.7 ± 8.13 years (16.5-47 years)	
Type of MS		RECEIVED DMT	No DMT
	RRMS	21	3
	SPMS	10	1
	PPMS	0	1
	CIS	3	2
Family history of MS		3	
Duration of Disease (mean±sd)		5.6±2.97 years	
Duration of therapy (mean)		46.7 months	
Comorbidities		9	
Depression/Anxiety Neurosis		7	
Pregnancies after diagnosis		16	
Postpartum Relapses		6	
Oligoclonal bands		13 (13/13)	
Side effects of Interferon		21 (21/34)	
Symptomatic Therapy	Neuropathic pain	16	
	Antispasticity	7	
	Neurogenic bladder	8	
	Antidepressants	6	
	Fatigue	2	
	Vitamin D	13	
EDSS (mean) OF THE COHORT		3.3	

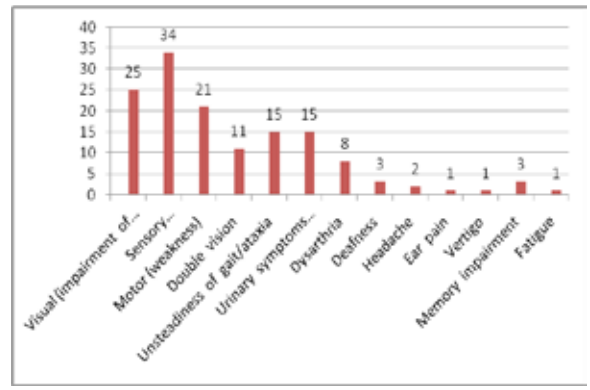

Figure 1: frequency of symptoms experienced by patients (n=41) in the study

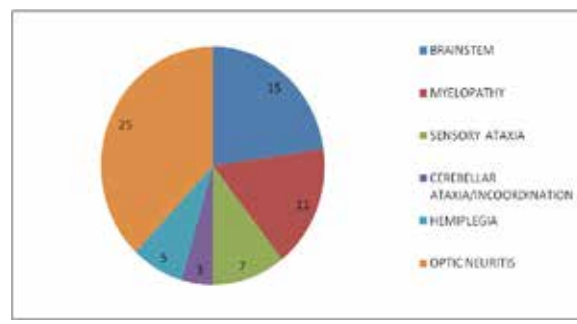

Figure 2: frequency of clinical syndromes (as per localization) in the studied cohort

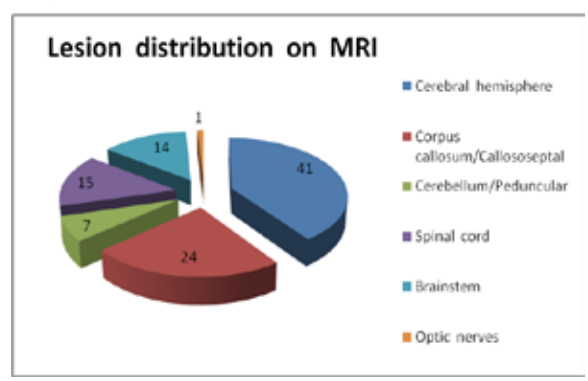

Figure 3: Distrbution of lesion as per MRI in studied cohort

BOX 1 depicting reason for not starting disease modifying therapy.

1.	Pregnancy.
2.	Never told by the physician about such therapy.
3.	Not initiated because of patient fear.
4.	Neuroimaging not sufficient to make the diagnosis.
5.	Resolution of symptoms after steroid pulse.

BOX 2 depicting reason for poor compliance and adherence.

1.	Non-availability of the drug at pharmacy.
2.	Pregnancy.
3.	Loss of motivation.
4.	Lack of effect.
5.	Disease progression.
6.	Poor communication by the treating physician.
7.	Abnormal liver function tests.
8.	Forgetfulness.
9.	Lack of appointment with doctor.

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