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A review of interferon use in patients with relapsing remitting multiple sclerosis in the Canterbury region, New Zealand: 2000–2006

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Abstract

We report a retrospective medical chart review of 104 patients resident in Canterbury and surrounding districts with relapsing remitting multiple sclerosis (RRMS), who received funded interferon-beta between 2000 and 2006. The aim of the study was to review relapse rates, Expanded disability status scale (EDSS) scores and intravenous methylprednisolone (IVMP) use in the 2-year period before, and following, the initiation of interferon-beta therapy. Demographic analysis showed that the age at entry, duration of disease and EDSS at entry were each greater than in the landmark clinical trials. Relapse rates and usage of IVMP decreased when compared to the 2 years prior to treatment.

Multiple sclerosis (MS) is the most common debilitating neurological disease of young adults in Western countries including New Zealand. Historical treatments for MS were largely considered to be symptomatic. However, in 1993, based on evidence from several landmark clinical trials which showed benefit in reducing relapse rates, it was suggested that the accumulation of disability might be delayed, Interferon Beta (IFB)[1-3] was licensed by the Food and Drug Administration (FDA) authorities in the United States. Patients included in the pivotal trials[1-3] included those with: a diagnosis of relapsing remitting multiple sclerosis (RRMS); two relapses lasting 24 hours or longer, in the preceding 2 years and an EDSS between 0 (no disability) and 5.5 (able to walk 100 metres without support).

In 1999 the Pharmaceutical Management Agency of New Zealand (PHARMAC) agreed to fund IFB. The Multiple Sclerosis Treatments Assessments Committee (MSTAC) was formed to oversee the allocation of funding. Glatiramer acetate (Copaxone®),[4] a non-interferon, was added to the list in 2006. MSTAC established a unique set of eligibility criteria that required greater disease activity and disability than in the pivotal trials. These included, two relapses, each lasting longer than one week within the preceding 1 year, and an EDSS between 3.0 (moderate disability) and 6.5 (able to walk 20 metres with bilateral assistance).

The criteria were modified in December 2005, to include patients with a lower entry EDSS, (between 2.5 and 5.5 with two relapses in the previous year or between 2.0 and 5.5 with three or more relapses in the previous year). The brand of interferon was chosen by the neurologist in conjunction with the patient. Annual reassessment by a consultant neurologist/physician was required for continuation of funding. Exit criteria were also specified. These included the same or an increased annual relapse rate, a one-point worsening of the EDSS from entry, or worsening of EDSS to 7.0. In 2005, the exit EDSS was decreased from 7.0 to 6.0, or more.

Methods

A retrospective medical chart review of patients within the Canterbury region who received publicly funded interferon therapy was performed. Patients included in the review received funded Interferon between January 2000 and November 2006, 104 patients were identified from the MSTAC database. Complete ascertainment was confirmed by cross-referencing Christchurch Hospital Neurology Department's own database with the national MSTAC database. Local Ethics Committee approval was obtained.

Data was collected from medical records and from annual assessment records submitted by the neurologist to MSTAC. Data collected included: time since onset of first demyelinating symptom, time since diagnosis of MS; birth date; age at diagnosis; age at starting interferon therapy; type of interferon therapy; the number of relapses recorded by a doctor in the 2 years prior to initiating therapy; number of IVMP courses administrated in the 2 years prior to therapy and EDSS at entry. Post IFB relapse rates, IVMP usage and EDSS were analysed. Side effects and adverse reactions were also recorded. Reasons for discontinuation or switching of therapy were also noted.

Demographic data collected included age, gender, and duration of disease. Disease activity was assessed for the 2 years prior to the initiation of therapy by examining recorded relapse rates as well as intravenous methylprednisolone (IVMP) usage. Factors reflecting disease activity following the introduction of IFB including the annualised relapse rate, change in EDSS score and IVMP usage were also recorded. Adverse reactions were noted and details were obtained about patients who discontinued treatment or for whom funded treatment was withdrawn on the basis of reaching exit criteria.

Results

Of the 104 patients identified, 101 charts were available for review. Three of the 101 patients started self-funded interferon therapy prior to the introduction of government funding. The data for these three patients have been included. Seventy-five women and 26 men were started on funded interferon therapy during the period January 2000 to November 2006. Women on funded interferon therapy outnumbered men 2.9:1. Baseline characteristics of patients beginning therapy are given in Table 1. At audit date (November 2006), 72 patients (71%) were still on interferon therapy and 29 (29%) had withdrawn from treatment, 13 of whom were withdrawn because they reached exit criteria.

The average age for starting interferon therapy was 41.3±10.6 years. The average disease duration at initiation of therapy was 8.9±8.4 years. In 2002, two types of interferon were funded by PHARMAC. In 2005, Copaxone®(a non-interferon) was added. In 83 patients (82%) the initial treatment selection was Betaferon®,17 (16%) Avonex® and 1 Copaxone®. Of the 83 who started Betaferon®, 60 (72%) remained on it. Of the 23 no longer on Betaferon®, 5 fulfilled exit criteria, 5 could not tolerate side effects, 10 stopped for reasons discussed below and 3 switched to Avonex® and subsequently reached exit criteria. Of the 17 who started Avonex®, 5 (30%) remained on it, 8 fulfilled exit criteria, 1 planned pregnancy and 3 changed to Betaferon,® of which 1 subsequently fulfilled exit criteria. One patient remains on Copaxone®.

The annualised relapse rates for years 1 and 2 are given in Table 2. Relapse rates are presented by comparing year 1 (year +1) and year 2 (year +2) of therapy with year 1 (year -1) and year 2 (year -2) prior to treatment. Results are presented only for those patients who completed a full year.

Table 1. Baseline characteristics of patients beginning funded interferon therapy between 2000–2006, and comparison to baseline characteristics from pivotal interferon trials

Variables	Patients initiating treatment (M/F)	Type Interferon	EDSS at entry (mean±SD)	Age at entry (mean±SD)	Disease duration (yrs) (Mean±SD)
2000	42 (13/29)	Betaferon® 29 Avonex® 13	4.7±1.2	42.4±9.2	10.0±8.6
2001	4 (1/3)	Betaferon® 2 Avonex® 2	5.1±1.3	50.5±12.9	13.9±8.5
2002	16 (3/13)	Betaferon® 16 Avonex® 0	4.5±1.1	42.5±11.7	8.0±8.6
2003	15 (4/11)	Betaferon® 15 Avonex® 0	4.3±1.2	39.4±12.8	7.0±7.8
2004	10 (2/8)	Betaferon® 10 Avonex® 0	4.8±1.0	39.4±13.2	9.4±11.4
2005	8 (2/6)	Betaferon® 5 Avonex® 2 Copaxone® 1	4.1±1.0	38.6±7.8	9.6±6.8
2006	6 (1/5)	Betaferon® 6 Avonex®	3.6±0.7	37.3±9.2	5.3±4.7
All patients (2000–2006)	101 (26/75)	Betaferon® 83 Avonex® 17 Copaxone® 1	4.5±1.1	41.3±10.6	8.9±8.4
Current patients	72 (19/53)		4.5±1.1	41.5±10.7	8.6±8.7
Fulfilled exit criteria	13 (3/10)		4.8±1.2	43.5±11.7	10.5±7.3
MSCRG 1996 [7]		Avonex®	2.4	36.7	6.6
IFNB MS GROUP 1993 [7]		Betaferon®	2.9	35.2	4.7
PRISMS 1998 [7]		Rebif®	2.5	34.9	5.3

The average relapse rate for all patients in the year preceding therapy was 2.5 relapses±0.7; while the relapse rate for the penultimate year before therapy was 0.8±0.9. The relapse rate following the first year of therapy was 0.5±0.7. Ninety-four patients completed the first full year of therapy. Of the seven not included in the analysis of the first 12 months, 5 started treatment in the 12 months prior to census and two stopped therapy before completing 1 year because of side effects. One discontinued treatment as an alternate diagnosis to MS was made. Seventy-four patients received 2 full years of therapy and the annual relapse rate in the second year of therapy was 0.4±0.6.

Table 2. Annualised relapse rates for years 1 and 2 prior (year -1, -2) to therapy and for years 1 and 2 (year +1,+2) on therapy

Variables	Annual Relapse Rates			
	Year -2	Year -1	Year +1	Year +2
All patients	0.8±0.9 [101]	2.5±0.7 [101]	0.5±0.7 [94]	0.4 ±0.6 [74]
Patients currently on treatment	0.7±0.7 [72]	2.5±0.7 [72]	0.5±0.7 [66]	0.4±0.5 [56]
Patients who fulfilled exit criteria	1.2±1.5 [13]	2.5±0.7 [13]	1.1±1.0 [13]	1±0.8 [8]

Note: The numbers in square brackets represent the actual number of patients in each group.

The average EDSS at entry of all patients was 4.5±1.1. In the 72 patients still on Interferon therapy at audit date the EDSS was 4.5±1.1, while the entry EDSS for the patients withdrawn from therapy because they fulfilled exit criteria was 4.8±1.2 (Table 3). It should be noted that EDSS entry criteria were changed only at the end of 2005. The entry EDSS criterion before this time was greater than or equal to 3.0.

Table 3. Average EDSS scores on treatment

	EDSS Entry (average)	EDSS Year +1	EDSS Year +2	EDSS Current (Nov 2006)
All patients	4.5±1.1 [101]	4.3±1.5 [92]	4.3 ±1.4 [73]	n/a
Patients currently on treatment	4.5±1.1 [72]	4.1±1.4 [67]	4.2±1.4 [59]	4.0±1.5 [67]
Patients who fulfilled exit criteria	4.8±1.2 [13]	5.6 ±1.6 [11]	6.1±0.3 [4]	n/a

Note: The numbers in square brackets represent the actual number of patients in each group.

Annual IVMP treatment of relapse data for the 2 years before, and the 2 years following, treatment are summarised in Table 4.

Table 4. Annual IVMP use for years 1 and 2 prior to therapy and for years 1 and 2 on therapy

Variables	Annualised Use of IVMP			
	Year -2	Year -1	Year +1	Year +2
All patients	0.6±0.8 [101]	1.8±1.2 [101]	0.4±0.6 [94]	0.4±0.6 [74]
Patients currently on treatment	0.5±0.7 [72]	1.8±1.2 [72]	0.2±0.5 [66]	0.3±0.5 [56]
Patients who fulfilled exit criteria	0.8±1.4 [13]	1.9±1.3 [13]	1.1±1.0 [13]	0.9±0.9 [8]

Note: The numbers in square brackets represent the actual number of patients in each group

Nine of the 13 patients who reached funded exit criteria did so on the initially prescribed Interferon-beta (4 Betaferon®, 5 Avonex®), while 4 patients switched interferon brand and subsequently fulfilled exit criteria (1 Betaferon®, 3 Avonex®). Neutralising antibody status was not ascertained in any patient.

Of the 16 other patients who withdrew, the following reasons were recorded: 5 due to side effects (5 Betaferon®- not specified; pustular psoriatic flare; flu like symptoms; drug related hepatitis; mood disturbance; 3 planned pregnancy (2 Betaferon®, 1 Avonex®); 2 considered themselves to be too well to need treatment (2 Betaferon®); 2 moved away (2 Betaferon®); 1 person was non-compliant for reasons unrecorded (1 Betaferon®); 1 stopped for unrecorded reasons (1 Betaferon®); 1 died from deliberate self harm (1 Betaferon®) and 1 person was withdrawn due to an alternative diagnosis being made (1 Betaferon®). Withdrawal rates were similar for both men and women. Thirty-five side effects or adverse reactions from IFB were reported in the medical notes of 30 patients (Table 5).

Table 5. Reported side effects

Symptoms		Patients reporting this side effect
Flu-like symptoms	(1 withdrew)	8
Marked injection site reactions		7
Headache		3
Psoriatic flare	(1 withdrew)	2
Mood change	(1withdrew)	5
Hepatitis	(1 withdrew)	1
Itching		1
Menorrhagia		1
Fatigue		1
Arthralgia		1
Not specified	(1 withdrew)	1
Night sweats		1
Liver function abnormalities		2
Neutropenia		1

Discussion

Currently 520 Correct patients throughout New Zealand are receiving funded disease modifying drugs for RRMS (personal communication MSTAC). This audit of patients residing in Canterbury, details the clinical outcomes of 101 patients who received therapy between January 2000 and November 2006.

The PHARMAC funding eligibility criteria introduced in 2000 presumed that the therapeutic benefits of disease modifying drugs were likely to be greatest in those with a high relapse rate, 2 or more attacks in 12 months and those with more established disability (EDSS 3.0–6.5).

As a result the relapse rate and EDSS at entry is greater in our patient group as compared with the pivotal trials. This is the likely explanation also for the finding that the age at entry and the average duration of disease prior to treatment in this group of 8.9±8.6 years is longer than for patients in the pivotal trials (Table 1). In light of overseas experience suggesting benefit in treating people early in the disease[6], the entry criteria were revised in 2005 to include people with a lesser degree of disability (EDSS 2.0–2.5).

As a result, the trend over the 6 years is towards entering patients with a lower EDSS score and a shorter duration of disease (Table 1). This would seem to be appropriate given that 50% of patients will, within 10 years have converted to secondary progressive multiple sclerosis (SPMS).[5] Similarly the age at which patients first start treatment group has also decreased (Table 1).

Relapse rates decreased in the 2 years following treatment. The high relapse rate over the year prior to treatment (2.5±0.7) is not unexpected as the eligibility criteria required two or more relapses in the year before treatment. The relapse rate for all groups at 2 years prior to entry (year -2) was 0.8±0.9. The relapse rate for all groups at 1 year (year +1) and 2 years (year +2) post therapy was 0.5±0.7 and 0.4±0.6 respectively.

Comparing year -1 with year +1, the relapse rate decreased by 80%. Comparing year -2 with year +2, the relapse rate decreased by 50%. Although there may have been some under-reporting of relapses following the initiation of treatment (as patients whose relapse rate remained unchanged or increased were deemed ineligible for ongoing funding), the reduction in relapse rate recorded in this audit, when compared to trial relapse rates at 2 years, show a better outcome.[1–3] It is also possible that because these patients had MS longer than had participants in pivotal clinical trials they were more likely to show regression to the mean. It seems unlikely however that this would account for all the reduction seen in relapse rate.

Although the correlation between relapse rate and disease progression is still not clearly defined, the impact upon quality of life and the need for hospitalisation from relapses is important. IVMP usage decreased by 33% following treatment (Table 4).

Criteria were modified in December 2005 to include patients with an EDSS of 2.0 or 2.5 (depending on relapse frequency). Despite this the mean disability scores at initiation of therapy over the six year period of the audit remained significantly higher

than for those in the pivotal trials.[7] Of the patients on treatment at the time of audit, 45 patients had been on therapy for three or more years and 51% had had three consecutive years with no relapses and had a decreasing or static EDSS. Patients who fulfilled exit criteria had a slightly higher EDSS and disease duration at entry.

Adherence to therapy was excellent. This most likely reflects the high level of commitment in this particular patient group, together with measures in place that promote compliance. These include training and regular contact by MS nurses, the MS society and company representatives, through support programmes and yearly review by a neurologist or physician.

The rate of withdrawal from therapy was 29%. Of this group, 13 (45%) had funding withdrawn as they fulfilled exit criteria: 9 because of an increase in EDSS and four due to continuing relapses. Of the nine patients who lost funding, all did so because the EDSS score exceeded six. No one was withdrawn because their EDSS increased by 1.0 point, unless it then exceeded 6.0. Current immunodulatory therapies are not curative and it is therefore expected that the mean EDSS will increase over time.

There is currently no consensus among MS neurologists as to what constitutes "treatment failure". It has been shown that the mean change in EDSS over time is greater in those with an EDSS <3. This likely reflects the non-linear nature of the EDSS scale and the greater inter and intra-rater variability at low EDSS scores rather than reflecting greater disease activity. Changes to the entry criteria in 2005 were not adjusted to take this into account, so that this particular patient group may be expected to reach exit criteria earlier than those whose EDSS was greater than 3 at entry.

Limitations of this audit include the retrospective nature of the study in a single-region. However 13% of MSTAC approvals for IFB are from the Auckland region, 14% from Waikato, 26% from Canterbury and 38% from Otago, in part reflecting the latitudinal gradient one sees in the prevalence of MS in NZ. Therefore patients from Canterbury provide a reasonable sample of the overall use of IFB, particularly given that the criteria are centrally administered and universally applied throughout the country.

Another limitation is the possible bias introduced by the fact that data relevant to relapse rate was important for initiation and maintenance of therapy. Whilst this may have lead to some underreporting of relapses the inclusion of treatments with IVMP followed a similar trend. This audit provides only limited data for Copaxone which was not introduced until 2005. It would therefore be interesting to repeat this audit for the period 2006–2010 during which 35% of approvals were for Copaxone, 34% for Betaferon and 31% for Avonex.

This audit demonstrates that the safety profile and the adherence rate amongst patients using disease modifying treatments for MS has been excellent. More than half the patients who had been on therapy for 3 or more years have a stable EDSS and have been relapse free for 3 years or more. These benefits are present, despite entry criteria set to demand a higher level of disease activity and greater level of disability than those in published trials.

At present, less than 30% of all patients with RRMS are receiving funded treatment in New Zealand (Personal communication, MS Prevalence Study 2006,) By comparison

there are approximately 13,500 patients in Australia with relapsing remitting MS (Personal communication, Dr Bruce Taylor 2011of whom about 11,000 (80%) are receiving funded treatment.

It is our belief that similar benefits to those seen in MS patients in the Canterbury region could be achieved in a greater percentage of patients with relapsing remitting MS if the eligibility criteria were broadened.

Competing interests: None.

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