Emerging therapy review

FTY720 in multiple sclerosis: the emerging evidence of its therapeutic value

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Abstract

Introduction: Multiple sclerosis is a demyelinating disease of the central nervous system which can cause severe disability and has profound effects on patients' quality of life over several decades. Although there is no cure for the disease, recently developed disease-modifying agents have modest effects on the impact of disease progression. There is therefore a need for a new, effective, and well-tolerated treatment for multiple sclerosis and FTY720 (an orally administered immunomodulatory compound with a novel mechanism of action) is one of a number of agents being evaluated for the treatment of this disease.

Aims: The objective of this article is to assess the therapeutic potential for FTY720, now in phase II clinical trials, for the treatment of multiple sclerosis through a review of the published evidence.

Emerging evidence: There is good evidence that FTY720 achieves immunomodulation as shown by a reversible redistribution of peripheral blood lymphocytes after oral administration. Two meeting abstracts have been published showing results obtained with FTY720 in a 12-month phase II clinical trial in patients with active relapsing multiple sclerosis. There is modest evidence that FTY720 significantly improves both patient-oriented (relapse rate) and disease-oriented outcomes (inflammatory disease activity). There is good evidence that FTY720 is well tolerated.

Profile: Based on these early results from the clinical development program, FTY720 has the potential to be an effective disease-modifying agent for the treatment of multiple sclerosis. Further results from ongoing multinational phase III studies are awaited.

Key words: evidence-based review, FTY720, immunomodulator, multiple sclerosis

Core emerging evidence summary for FTY720 in multiple sclerosis

Outcome measure	Emerging evidence
Patient-oriented evidence	
Disease relapse rates	Reduction in relapse rates and time to first relapse
	Likelihood that patients will at least have longer intervals between relapses
Convenient administration	Daily oral dosing with or without food
	No dose alterations necessary with hepatic impairment
Tolerability	Well tolerated. No serious adverse events noted. Most common adverse event is asymptomatic, mild, and transient reduction in heart rate
	No evidence of increased risk of infections associated with drug-related lymphocyte sequestration
Disease-oriented evidence	
Disease progression determined by magnetic resonance imaging	Reduction of new and existing inflammatory lesions responsible for subclinical disease progression
Immunomodulation	Reversible lymphocyte sequestration, a characteristic of the mode of action of FTY720, is a convenient surrogate marker of immunomodulation

Scope, aims, and objectives

Multiple sclerosis is one of the most common chronic neurologic diseases causing progressive disability in young adults. The life expectancy of patients with multiple sclerosis is at least 25 years following the first onset of symptoms and most patients will die from unrelated causes. In recent years there has been great progress in understanding the pathogenic mechanisms associated with the disease and imaging techniques have been developed to monitor the effects of treatment on neurologic lesions. However, although recently developed disease-modifying agents have improved the management of multiple sclerosis, there is still no treatment that stops the development of disability.

FTY720 is a novel immunomodulatory compound in clinical development for use in the prevention of organ rejection in transplant patients and for multiple sclerosis.

The objective of this review is to evaluate the evidence for the potential of FTY720 as a treatment for multiple sclerosis.

Methods

The English language medical literature was reviewed for relevant articles on FTY720 for the treatment of multiple sclerosis. An initial search of PubMed, BIOSIS, and EMBASE was conducted on June 13, 2005 using the search terms "FTY720 OR FTY720 AND multiple sclerosis" for articles published between January 1993 and June 2005 (inclusive). In addition, relevant abstracts were identified from the annual scientific sessions of the European Neurological Society, the American Society for Neurochemistry, and the International Society of Neuroimmunology, held during 2002 and 2005. The online database, www.clinicaltrials.gov was searched for information on ongoing phase II and phase III studies with FTY720 in multiple sclerosis. A hand search of reference lists in selected publications was carried out to ensure that no relevant articles were omitted.

A total of 16 articles (14 full papers and two abstracts) was identified from the initial search strategy after any animal, *in-vitro*, or other nonrelevant publications were omitted (Table 1). All of the full papers identified initially were excluded from the evidence evaluation. Only one meeting abstract was included for analysis as it reported pertinent clinical outcomes with FTY720. Following the initial search strategy a further six full papers were identified from reference lists in the excluded full publications for inclusion in the review of evidence. The search strategy was also repeated on January 10, 2006 when one further relevant meeting abstract was identified and included. Thus, a total of eight publications (six full papers and two meeting abstracts) were included in the evidence base.

Table 1 | Evidence base included in the review

Category	Number of records	
	Full papers	Abstracts
Initial search	14	2
records excluded	14	1
records included	0	1
Additional studies identified	6	1
Level 1 clinical evidence	0	0
Level 2 clinical evidence	5	2
Level ≥3 clinical evidence	1	0
trials other than RCT	0	0
case reports	0	0
Economic evidence	0	0
Total records included	6	2

For definition of levels of evidence, see Editorial Information on inside back cover.
RCT, randomized controlled trial.

Disease overview

Signs and symptoms

Multiple sclerosis is one of the most common neurologic diseases affecting young adults. It is usually a disease with sporadic of the nervous system in which patchy degenerative inflammatory changes occur within the brain and spinal cord (Compston & Coles 2002). The symptoms of multiple sclerosis are diverse and can include tremor, paralysis, loss of bladder or bowel control, fatigue, pain, loss of cognitive function, disturbances in vision and speech, emotional changes, and nystagmus. These symptoms can have a profound effect on patients' quality of life and can also lead to significant reliance on their family, dependents, and carers.

The severity and prognosis of multiple sclerosis can vary greatly. In about a quarter of all patients the disease does not affect activities of daily living. However, severe disability can affect about 15% of patients within a relatively short period of time (Compston & Coles 2002) and approximately half of all patients will require a cane for walking short distances within about 15 years of first onset of the disease (Weinshenker 1994). Attacks can occur randomly, with an initial incidence of about one per year followed by a steady increase in subsequent years.

Epidemiology

The incidence of multiple sclerosis is estimated to be seven cases per 100 000 per annum, and the prevalence is approximately 120 cases per 100 000. The lifetime risk of the disease is one in 400 (Compston & Coles 2002). There are about 2.5 million individuals with multiple sclerosis in the world, and in the USA alone there are about 350 000 affected patients (Lutton et al. 2004). Multiple sclerosis develops in twice as many women as men and age at onset of the disease is usually 20–30 years. About 5% of all cases occur in patients under the age of 16 years.

Etiologic, genetic, and environmental factors

The relationship between genetic and environmental factors in determining the susceptibility of patients to develop multiple sclerosis is complex and poorly understood. However, it is clear that there is an uneven geographic distribution of the disease in

prevalence in geographically temperate areas (Dyment et al. 1997). Thus it is a disease that predominantly affects northern Europeans.

To date the major histocompatibility complex (MHC) is the only area of the human genome with a clear association with the disease. Results from three genomic searches imply that a number of genes with interacting effects will ultimately be found; however, to date no single genetic region has been identified with a major influence on familial risk (Dyment et al. 1997). In addition, attempts to implicate specific environmental agents as responsible for the disease have been unsuccessful. Possible, but as yet unsubstantiated, candidate agents include *Chlamydia pneumoniae* and human herpes virus 6 (Compston & Coles 2002).

Pathophysiology

Multiple sclerosis is characterized by acute focal inflammatory demyelination and the loss of axons with limited remyelination (Noseworthy et al. 2000). This leads to the presence of characteristic multifocal sclerotic plaques in the white matter of the central nervous system. These lesions are particularly common in the optic nerves, and white matter tracts of the periventricular regions, brain stem, and spinal cord (Hafler 2004). Typically T and B lymphocytes, macrophages, and antibodies can be found at the site of white matter destruction.

A number of fundamental questions remain regarding the pathophysiology of multiple sclerosis. For example, what initiates the inflammation and what is the antigenic target driving the inflammation (Hafler 1999)? Possible triggers for the initial inflammatory insult include an autoimmune response (initiated by autoreactive T lymphocytes) or a structural alteration in the white matter as a result of microbial infection. It has also been hypothesized that multiple sclerosis is a spectrum of diseases and that some are initiated by an autoimmune response and others are induced by viral infections of the central nervous system (Hafler 1999). It is unlikely that the antigenic target driving the disease is due to a single antigen. The inflammatory process initiated by T-cell recognition of one myelin protein epitope subsequently leads to the activation of autoreactive T cells recognizing other epitopes of the same protein. This “epitope spreading” can lead to activation of T cells recognizing other myelin proteins that may get degraded and be presented on the MHC of local antigen-presenting cells (Hafler 1999).

It is known that trauma does not induce multiple sclerosis, nor does trauma activate a latent form of the disease or alter symptoms in a patient with the disease. However, the risk of an exacerbation in a patient with multiple sclerosis has been shown to be associated with stressful life events (Mohr et al. 2004). As yet, specific stressors cannot be linked to exacerbations and patients themselves should not be led to believe that they bear responsibility (through experiencing stress) for them.

Diagnosis

The typical stimulus for patients to seek medical help is the first neurologic examination are crucial for the accurate diagnosis of multiple sclerosis. At present there is no specific immunologic-based test for the disease. Results from imaging investigations should be used to support the clinical diagnosis and to rule out other pathologies. In the absence of clinical evidence, abnormalities detected by imaging are insufficient grounds for a diagnosis (Miller et al. 1998). Annual magnetic resonance imaging (MRI) scans are also recommended for the management of ongoing multiple sclerosis to monitor disease progression and to detect underlying pathology.

MRI has both prognostic and diagnostic applications in multiple sclerosis. It has a pivotal role in the diagnosis of the disease and acts as a surrogate marker of drug efficacy in clinical trials. The use of imaging technology has been important in demonstrating that even during apparently stable periods between attacks the disease is still very active (Miller et al. 1998).

Classification and clinical course

At onset, multiple sclerosis can be categorized clinically as either relapsing remitting multiple sclerosis (RRMS) or primary progressive multiple sclerosis (PPMS). The most common form of the disease is RRMS, which is observed in about 85% of all patients (Fig. 1). RRMS is characterized by clearly defined disease relapses with full recovery or with sequelae and residual deficit upon recovery. On average about 1.5 attacks occur each year and approximately 10 new lesions are detected annually on MRI scan (Hafler 1999). Although RRMS is not classified as a progressive form of multiple sclerosis, residual deficits may occur after each exacerbation. At least half of all patients with RRMS will transition to secondary progressive multiple sclerosis (SPMS). This subform is characterized by disease progression with or without occasional relapses, minor remissions, and periods of stability. In contrast, PPMS is seen in far fewer patients (about 10%; Fig. 1).

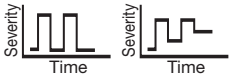
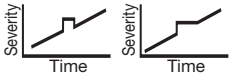
Classification	Type of incidence at presentation	Schematic typical of clinical course
Relapsing remitting multiple sclerosis (RRMS)	~85%	
Secondary progressive multiple sclerosis (SPMS)	~50% of patients with RRMS will progress to this subform	
Primary progressive multiple sclerosis (PPMS)	~10%	
Progressive relapsing multiple sclerosis (PRMS)	~5%	

Fig. 1 | Classification, incidence, and examples of clinical courses of subtypes of multiple sclerosis (adapted with

It is characterized from the outset by the absence of acute attacks but demonstrates a worsening in disease severity.

Progressive relapsing multiple sclerosis (PRMS) is the least common form of the disease, affecting about 5% of patients. From the outset it is progressive, with or without full recovery, and progression is continuous between relapse periods.

Schematic representations of the courses of these four forms of multiple sclerosis are shown in Fig. 1. During a relapse, symptoms can develop over hours to days, persist for several days or weeks, and then gradually dissipate.

Prognosis

Patients with sensory or visual symptoms as the dominant feature, particularly those who experience complete recovery from attacks, generally have the best prognosis. This pattern is common in younger women (Compston & Coles 2002). Prognosis is particularly poor in males when disease onset occurs later in life, and in patients with frequent and prolonged relapses (particularly in the first 2 years) and in those with a short interval between the initial attack and the first relapse (Noseworthy et al. 2000) (Table 2).

Current therapy options

The aim of treatment of multiple sclerosis is to reduce the frequency (and limit the lasting effects) of relapses, relieve symptoms, prevent disability arising from disease progression or incomplete recovery from relapses, and promote tissue repair (Compston & Coles 2002).

The management of multiple sclerosis has greatly benefited from the availability of five disease-modifying agents which have been approved by the US Food and Drug Administration (FDA) since 1993 and are now widely available. However, there is no cure for the disease and available disease-modifying agents are lifelong therapies. Other therapies may be used to alleviate some of the chronic symptoms of the disease (spasticity, neuropathic pain, and fatigue), but by their nature they do not alter the course of the disease and there is a limited evidence base for symptomatic drug treatment for symptom control (Thompson 2001).

Disease-modifying agents

Of the five disease-modifying therapies approved by the FDA for the treatment of multiple sclerosis, four are immunomodulators (three preparations of interferon beta and glatiramer acetate) and one is an immunosuppressant (mitoxantrone). The disease-modifying agents that are indicated for the treatment of RRMS include the immunomodulatory agents interferon beta-1b for subcutaneous administration (Betaseron®), two formulations of interferon beta-1a for either subcutaneous (Rebif®) or intramuscular administration (Avonex®), and glatiramer acetate (Copaxone®). All four immunomodulators can be considered as first-line treatments for RRMS (Goodin et al. 2002; NMSS 2005).

Mitoxantrone (Novantrone®) is an inhibitor of the enzyme DNA topoisomerase II which is responsible for uncoiling and repair of DNA in both dividing and nondividing cells. Because of concerns over cardiotoxicity this agent may only be used up to a cumulative lifetime dose of $\geq$140 mg/m^2 (equivalent to about 11 doses) (Anon. 2005b). It is administered intravenously and due to toxic adverse effects it is generally reserved for the more progressive forms of the disease. Thus it is indicated for the treatment of worsening RRMS, SPMS, and PRMS. Recently, marketing of natalizumab (a humanized alfa-4 integrin antagonist) has been suspended because of reports of two serious adverse events (two cases of progressive multifocal leukoencephalopathy, one proving fatal). This agent had previously received accelerated approval in the USA in November 2004 for reducing the frequency of exacerbations in patients with RRMS after 1 year of treatment (FDA 2005).

The National Multiple Sclerosis Society (NMSS) has revised its consensus guidelines on the use of disease-modifying agents including interferon beta and glatiramer (NMSS 2005). The recommendations specify the use of the following four immunomodulators: interferon beta-1a (intramuscular), interferon beta-1a (subcutaneous), interferon beta-1b, and glatiramer acetate for all relapsing forms of multiple sclerosis and consideration of their use for selected patients with a first attack or who are at high risk of multiple sclerosis. Therefore, therapy is appropriate in all relapsing patients, those with SPMS, PPRS, and many patients experiencing a first attack, providing that no contraindication exists.

All of the agents approved for the treatment of RRMS have been shown to reduce relapse rates in large-scale, randomized, double-blind, placebo-controlled, prospective trials (reviewed in Goodin et al. 2002). Both interferon beta-1a formulations have achieved reductions in sustained disability progression in relapsing multiple sclerosis when used during the early phase of the disease. For example, positive results have been obtained from a number of

Table 2 | Disease course characteristics associated with the prognosis of multiple sclerosis

Poor prognosis	Good prognosis
Motor involvement, in particular disturbed coordination or balance	Sensory or visual symptoms dominate
Onset of disease in older males	Complete recovery from individual attacks
Frequent and prolonged relapses with incomplete recovery within 2 years of disease onset	
Short interval between the initial episode and first relapse	
Onset of progressive phase	

separate 2-year placebo-controlled clinical trials involving patients with RRMS treated with the three interferon beta agents. In summary, interferon-beta treatment significantly reduced the relapse rate by 30 to 37% compared with placebo treatment (interferon beta-treated patient relapse rates ranged from 0.61 to 0.78 and placebo-treated rates from 0.9 to 1.2 relapses per year) (Compston & Coles 2002). This change in relapse rate was also associated with a reduction in the accumulation of disability with the two interferon beta-1a (but not the interferon beta-1b) preparations.

In RRMS glatiramer acetate, mitoxantrone, and azathioprine all reduce relapse frequency and the accumulation of disability. Glatiramer acetate is a random polypeptide composed of four L-amino acids (glutamic acid, lysine, alanine, and tyrosine). Results from a placebo-controlled study involving 251 patients with RRMS showed that treatment with glatiramer acetate significantly reduced the clinical attack rate over a 2-year period by 27% (P=0.007 vs placebo) (reviewed in Goodin et al. 2002). The indications for the use of glatiramer acetate are comparable to those for interferon beta and it is appropriate to consider it for treatment in any patient with RRMS (Goodin et al. 2002). For those patients who fail to adequately respond to the disease-modifying agents, the only therapeutic option is to consider intensive immunosuppression with cytostatic agents or even autologous stem cell transplantation (Kappos et al. 2004).

Disease-modifying agents that can be started and continued on a long-term basis are referred to as “platform therapies.” Key characteristics of an ideal agent used for platform therapy are maximal efficacy, safety, tolerability, convenience, and low rates of neutralizing antibody formation (neutralizing antibodies formed in the body may block or neutralize the biologic effects of the foreign protein or polypeptide, potentially decreasing the therapeutic effects of these agents) (Stuart et al. 2004). During periods of increased disease activity or instability other treatments (e.g. corticosteroids and immunosuppressants) may be used with platform therapy. Although almost all patients who recover from relapses do so spontaneously to some degree, most clinicians recommend treating a relapse if it has a significant effect on function (Polman & Uitdehaag 2000). Corticosteroids have been the first-choice agent for this role for a number of years and although they shorten the duration of relapse and hasten recovery it is unclear whether they affect the overall degree of recovery or alter the course of the disease.

In summary, disease-modifying agents have beneficial effects on relapse rates, relapse-related disability, and MRI outcomes. These effects are more pronounced early in the course of the disease, are long lasting, and have no rebound effects (Kappos et al. 2004). Nevertheless these treatments are only partially effective; they are administered parenterally and although they are generally well tolerated there are some safety issues to be aware of (e.g. potential cardiotoxicity with mitoxantrone).

Unmet needs

One of the most important objectives of successful therapy for term disability. Typically, disability may evolve slowly over many years; however, most clinical trials are conducted for relatively short periods and only short-term outcome measures (e.g. attack rates and MRI measures to establish that treatment at least reduces the biologic activity of multiple sclerosis) are used. Therefore, it is important that any short-term measure is validated based on actual long-term patient outcomes (e.g. reduction in disability). Indeed, there is some uncertainty as to the relationship between the attack rate and long-term disability. It has been suggested that reducing short-term attack rate measures may not be associated with a delay in the accrual of disability in multiple sclerosis (reviewed in Goodin et al. 2002).

Based on results from a number of large, well-designed clinical trials it is generally accepted that interferon beta (1b or 1a) is the treatment of choice for patients with RRMS (Polman & Uitdehaag 2000; Stuart 2004; Stuart et al. 2004). Nevertheless, there are still some unresolved issues relating to its use including optimal timing for the initiation and cessation of treatment; optimal dose, frequency, and route of administration; long-term effects of treatment; occurrence and relevance of neutralizing antibodies; and cost (Polman & Uitdehaag 2000). In addition, up to 60% of patients experience influenza-like symptoms (including fever, chills, myalgia, and headache) with interferon beta (Calabresi 2004). The first-line choice for the treatment of SPMS is interferon beta; mitoxantrone or cyclophosphamide may be considered as second-line treatments for progressive disease. There are no established therapies for either PPMS or PRMS (Kieseier & Hartung 2003).

Multiple sclerosis has a profound effect on patients’ quality of life and it is important to determine the effect of any treatment on this parameter. At present, no study has measured this as a specific outcome of treatment. Instead, because the disease has been shown to be modified by treatment (e.g. reduced relapse rates and improvements in disability) this has led to the inference that quality of life outcomes are likely to be improved by these agents (NMSS 2005). However, this issue may be addressed through the use of a suitably valid and reliable quality of life instrument [e.g. the Multiple Sclerosis Impact Scale (MSIS29)].

Nevertheless, the management of multiple sclerosis has greatly benefited from the development of new disease-modifying agents such as interferon beta and glatiramer acetate as prior to their introduction there were no effective therapies. But, despite their widespread availability, they are still only partially effective (in terms of reductions in relapse rates, relapse-related disability, and imaging outcomes) in the treatment of multiple sclerosis, and all the currently available disease-modifying agents must be administered parenterally either by self-administration or under medical supervision. In addition, there is no agent currently available that is able to stop the disease process. Therefore, characteristics of an ideal agent for the treatment of multiple sclerosis would include oral administration (for convenience), clinically significant effects on disease- and patient-oriented outcomes, limitation of the disease process and reduced

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