New Developments in the Treatment and Management of Multiple Sclerosis

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Summary

Therapy for multiple sclerosis (MS) continues to evolve. Available disease-modifying therapies target the inflammatory process of this disease and are only effective for relapsing-remitting MS. Clinicians have a wide range of oral and injectable medications to select from, each of which has advantages and disadvantages.

Key Points

- There are effective medications to reduce relapses in relapsing-remitting MS.
- These agents reduce the annualized relapse rate at least 30 percent.
- Comparative effectiveness is difficult to determine because of lack of sufficient comparative trials among all the agents.

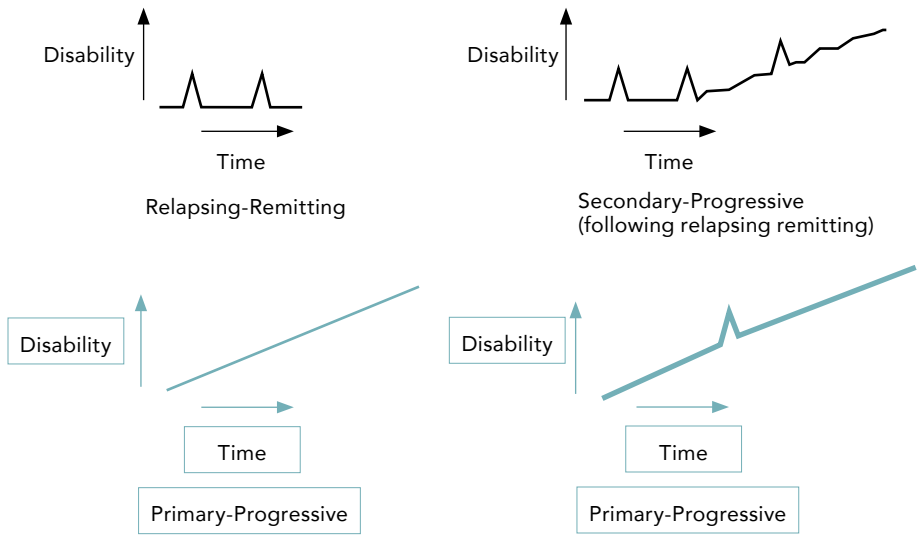
MULTIPLE SCLEROSIS (MS) IS A CHRONIC inflammatory condition of the central nervous system (CNS) induced by an environmental trigger in a genetically susceptible person with CNS lesions disseminated in time and space without an alternative explanation. It is the most common, nontraumatic cause of disability in young adults. There are an estimated 400,000 MS patients in the United States. It is more common in women at a two to one ratio. Onset is typically between ages 20 to 40.

The etiology of MS is unknown but is thought to be a combination of an environmental trigger in a susceptible person. Genetics definitely plays a role; a much higher rate of MS is seen in identical twins compared to non-identical twins or siblings (20 to 30% vs 2 to 5%). Given that there is not a 100 percent rate in identical twins, genetics is not the only reason someone develops MS. Only 20 percent of people with MS have a family member with the disease, thus 80 percent of the cases are considered sporadic. Environmental exposures play a role. Infectious agent exposure, smoking, geographical distance from the equator, and sunlight exposure (vitamin D) have all been implicated in the development of this disease.

MS has three components – inflammation, demyelination, and neuron loss. The diagnosis requires a multifocal CNS process (dissemination in space) and relapses or progression by history or new lesions on MRI (dissemination in time).[1,2] There are people who have one episode of symptoms such as optic neuritis and never develop MS. Thus, patients have to have symptoms of multiple CNS lesions which recur or worsen over time.

The disease can be classified into several categories: Radiologically Isolated Syndrome (RIS), Clinically Isolated Syndrome, Relapsing-Remitting MS, Secondary-Progressive MS, Primary-Progressive MS, and Primary-Progressive with Relapses. RIS is the newest identified type, with classic MS findings on an MRI without any CNS manifestations. Many people get MRI scans for some reason other than

Exhibit 1: MS Disease Classification[3]



MS symptoms and findings classic for MS are identified. Someone with RIS is followed over time to see if they develop overt MS. CIS is an isolated symptomatic event without enhancing lesions on MRI and is also a precursor to overt MS. Once someone has lesions on MRI and symptoms, they are considered to have MS. Exhibit 1 illustrates the four presentations of MS.[3]

The disease is expressed clinically and subclinically. Clinically, people have symptomatic relapses, residual symptoms between relapse, and disability accrual. Subclinically, changes in the CNS can be seen on MRI. Acute damage in the brain from the disease appears as enhancing lesions. Chronically, several measures can be monitored to assess the long-term damage of MS, including T2 lesion burden, T1 "black holes", and atrophy. Some people have a relapse and get 100 percent better and others don't get all the way better. Even when the neurons get repaired, the repair does not appear to be optimal. Neurons can also die off over time, resulting in brain atrophy.

As shown in Exhibit 2, early in the disease process there are a lot of relapses, even more events on MRI, and inflammation. It is thought that for every clinical relapse there are as many as 10 active CNS events that can be seen on MRI (subclinical disease). Over time, there can be fewer relapses and less inflammation but increasing CNS deterioration and accumulating disability. All of the current disease-modifying medications work during the inflammatory phase.

MS is a costly disease. The direct health care costs are estimated at $10 billion annually. This is an average of $47,000 per patient per year and $12,000 for a relapse event. The indirect health care costs are also significant. Total annual indirect costs are estimated at $5,769 versus $1,417 for people without MS. MS patients have a mean of almost 30 disability days annually. The annual disability cost for an employer with an employee with MS is $3,858 compared to $414 for those without MS.[4]

Disability from MS is significant and increases over time. After having the disease for five years, about 10 percent of patients will be wheelchair bound.[5] At 25 years, over 50 percent will be. So for someone diagnosed at 20, they may be wheelchair bound at 45. As disability increases, there is a significant drop-off in employment.

There are numerous ways to measure disability and track it over time. One way is to measure how fast someone can walk. Walking ability is directly related to the ability to conduct activities of daily living. In one study, the timed 25-foot walk (T25FW) of 6 to 7.99 seconds was associated with a change in occupation due to MS, occupational disability, walking with a cane, and with needing "some help" with instrumental activities of daily living; time greater than 8 seconds was associated with collecting Supplemental Security Income and government health care, walking with a walker, and with the inability to do instrumental activities of daily living.[6]

The goal of treatment in MS is to prevent re-

Exhibit 2: Natural History of Relapsing MS Clinical and MRI Measures

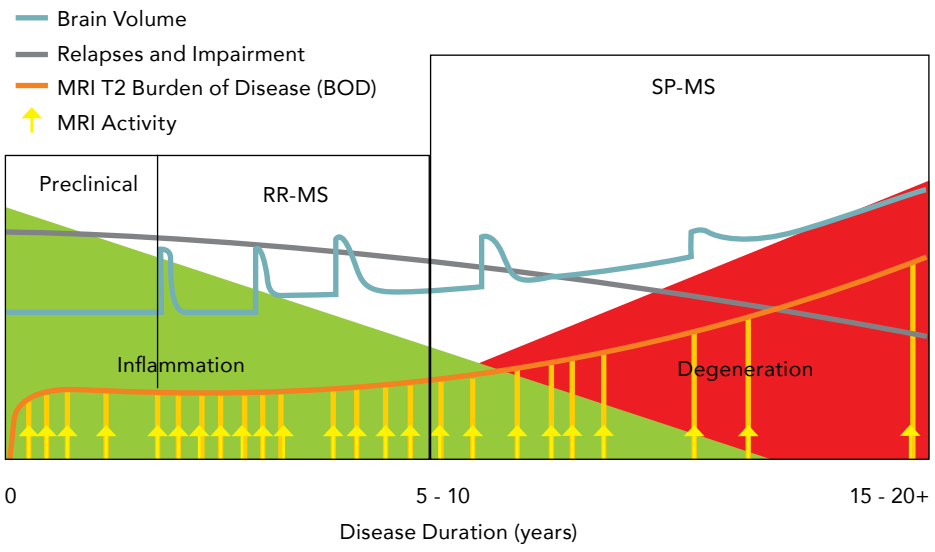


Exhibit 3: Agents to Reduce Risk of Relapse in MS

Name	Administration	FDA Indication
Dimethyl Fumarate (Tecfidera)	120 à 240 mg PO twice daily	Relapsing Forms
Fingolimod (Gilenya)	0.5mg PO daily	Relapsing Forms
Glateramer Acetate (Copaxone)	20mg SQ daily	Relapsing Forms
Interferon-beta 1a (Avonex)	30mcg IM weekly	Relapsing Forms
Interferon-beta 1a (Rebif)	22 or 44mcg SQ three times weekly	Relapsing Forms
Interferon-beta 1b (Betaseron, Extavia)	250mcg SQ every other day	Relapsing Forms
Mitoxantrone (Novantrone)	12mg/m^{2}IV q3M; Max dose140mg/m^2	Worsening RRMS, SPMS, PRMS
Natalizumab (Tysabri)	300mg IV every 4 weks	Relapsing Forms
Teriflunomide (Aubagio)	7 or 14 mg PO daily	Relapsing Forms

lapses, subclinical events, and progressive disability. Preventing relapses is done with one of the disease-modifying medications listed in Exhibit 3. All the agents but mitoxantrone are only approved for relapsing forms of MS. Mitoxantrone has fallen out of favor due to delayed blood dyscrasias and cardiac issues.

Natalizumab (Tysabri®) is an agent that has generated a great deal of press and was temporarily removed from the U.S. market, but is now available. It is a monoclonal antibody, which essentially works by preventing lymphocytes from crossing the blood-brain barrier. This agent is effective in reducing relapses and damage on MRI but can rarely cause a major adverse effect - progressive multifocal leukoencephalopathy (PML).

As of April 2013, 347 total PML cases out of 112,181 patients treated with natalizumab worldwide have been reported.[7] The mortality in those cases has been 23 percent. Natalizumab-associated

PML has improved survival compared with PML in other populations. Residual disability from PML has been mild in 13 percent, moderate in 50 percent, and severe in 37 percent.

PML is a reactivation of JC virus inducing a lytic infection of oligodendrocytes, resulting in demyelination. The factors leading to viral activation are not fully understood but risk factors for PML include JC virus positivity, duration of natalizumab therapy, and previous immune suppressive therapy. Eighty percent of adults harbor JC virus, thus people have to be screened for positivity before starting natalizumab. Presenting symptoms can include impaired cognition, cortical blindness, hemiparesis, and seizure (17%). Although some of these symptoms could also suggest a MS relapse, seizures do not usually occur as part of a relapse. Thus, new onset seizures in a patient on natalizumab should be assumed to be PML until proven otherwise.

Treatment of PML involves discontinuing natalizumab and three to five plasma exchange treatments. Immune Reconstitution Inflammatory Syndrome (IRIS) can occur and is the primary reason for mortality with PML. This is treated with high-dose intravenous corticosteroids.

There have been several oral therapies approved for MS. Fingolimod (Gilenya®), a sphingosine-1-phosphate receptor agonist/modulator, was the first oral therapy approved. This agent blocks the egress of lymphocytes out of the lymph nodes. It results in a 50 percent reduction in annualized relapse rate compared with interferons or glatiramer.[8] The most common adverse effects with this agent are asymptomatic bradycardia, headache, elevated liver function tests, and reversible macular edema. Thirty-one deaths thought to be secondary to fingolimod therapy have occurred in the 32,000 patients treated to date. Several of these deaths appeared to be cardiovascular related. The FDA now recommends an electrocardiogram be done at baseline and six hours after the first dose. Some sites do a 23-hour cardiac monitoring on patients with known underlying cardiovascular disease or sleep apnea.

Teriflunomide (Aubagio®) was the second oral agent approved for MS. This is the active metabolite of leflunomide, an agent approved several years ago for rheumatoid arthritis. Teriflunomide appears to work by blocking pyrimidine synthesis and decreasing antigen presenting cell activity. It results in a 31 percent relative reduction in annualized relapse rate compared with placebo.[9] The adverse effects of concern with this agent are hepatotoxicity and teratogenicity.

Dimethyl fumarate (Tecfidera®) is the most recent oral agent to reach the market. A different formulation of this (Fumaderm) has been used in Germany to treat severe psoriasis. The mechanism of action in MS is uncertain, but it has effects on T- and B-cells in the immune system and on dendritic, endothelial and glial cells in the CNS. The most common adverse effects are headache, mild infections, gastrointestinal symptoms, increased liver function tests, and flushing. In trials of this agent, there was a 44 to 53 percent reduction in ARR over two years compared to placebo and a 29 percent reduction versus glatiramer.[10,11] Three cases of PML thought to be related to the psoriasis product have been reported. No cases have been reported in 2,600 patients using the MS approved formulation for up to four years.

Although there are 10 effective disease-modifying treatments for MS, there are definitely limitations with current therapies. One limitation is the cost of these agents which can be significant. Another limitation is the partial effectiveness; none of them prevent every relapse. Additionally, significant adverse effects can occur. For individual agents, the optimal dose of most is uncertain.

The biggest challenge in choosing therapy is that comparative efficacy of all the agents is unknown. The oral agents have been compared with some of the injectable agents and the injectables have been compared with each other. The interferons and glatiramer appear to have similar efficacy, resulting in a 30 percent reduction in ARR in the randomized double blind- trials. More recent open-label trials have shown higher rates of reduction, but this may be the effect of less severe disease in the study subjects or the lack of blinding. Fingolimod and dimethyl fumarate lead to a lower annualized relapse rate compared to interferons or glatiramer, but these oral agents have not been compared to each other. Teriflumonide appears to have a similar efficacy to the injectable agents. None of the oral agents have been compared to natalizumab, which appears to be most effective in reducing ARR. Thus, clinicians have an array of effective medications, but the optimal order in which the agents should be used is unknown.

Conclusion

Although a devastating disease, there are effective disease- modifying medications for MS. Although not ideal, the use of disease-modifying therapy can reduce annual relapses around 30 percent and maybe more with some of the newer oral agents. It is hoped that in the near future there will be better data to help clinicians select the most effective agent at the most effective dose for a given patient.

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References

1. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol*. 2001;50(1):121-7.

2. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011;69(2):292-302.

3. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology*. 1996;46(4):907-11.

4. Mathis AS. Managed care aspects of managing multiple sclerosis. *Am J Manag Care*. 2013;19(2 Suppl):S28-34.

5. Richards RG, Sampson FC, Beard SM, Tappenden P. A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models. *Health Technol Assess*. 2002;6(10):1-73

6. Goldman MD, Motl RW, Scagnelli J, et al. Clinically meaningful performance benchmarks in MS: timed 25-foot walk and the real world. *Neurology*. 2013;81(21):1856-63.

7. Vermersch P, Kappos L, Gold R, et al. Clinical outcomes of natalizumab-associated progressive multifocal leukoencephalopathy. *Neurology*. 2011;76(20):1697-704.

8. Bergvall N, Makin C, Lahoz R, et al. Comparative effectiveness of fingolimod versus interferons or glatiramer acetate for relapse rates in multiple sclerosis: a retrospective US claims database analysis. *Curr Med Res Opin*. 2013;29(12):1647-56.

9. O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med*. 2011;365(14):1293-303.

10. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med*. 2012;367(12):1098-107.

11. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med*. 2012;367(12):1087-97.