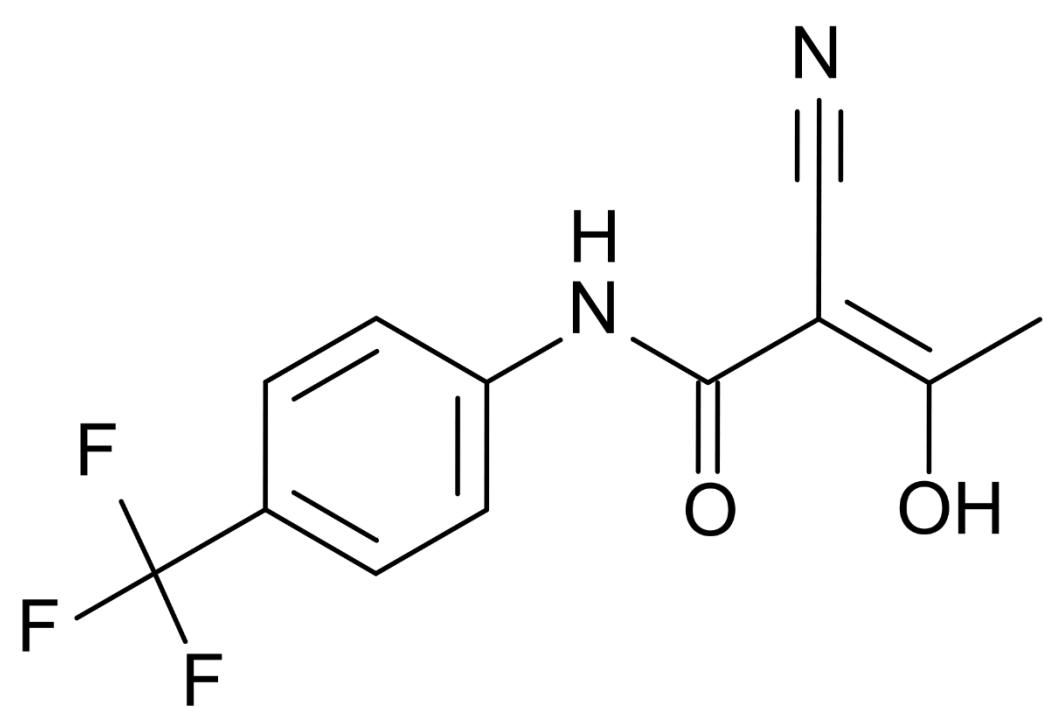




Teriflunomide is the Safest and Most Effective Diseases Modifying Therapy for the Treatment of Relapsing Remitting Multiple Sclerosis

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Abstract

Multiple Sclerosis is a demyelinating degenerative disease that is rising in prevalence. Relapsing Remitting Multiple Sclerosis is a type of MS in which patients experience an onset of neurological symptoms followed by complete or partial recovery. Provided is a review of the efficacy and safety of Teriflunomide for the treatment of Relapsing Remitting Multiple Sclerosis using clinical studies, reviews, and comparative studies. The results show that Teriflunomide is one of the preferred medications prescribed for RRMS because of its ability to significantly reduce relapse rates, disability progression, and its’ suppression of active inflammatory lesions. When considering the type and number of adverse events encountered with all treatments in addition to the efficacy Teriflunomide becomes the clear choice.

Introduction

Multiple Sclerosis is a chronic, progressive, immune mediated disease of the central nervous system. The pathological hallmarks of Multiple Sclerosis include inflammation, demyelination, axon degeneration, gliosis, and dysfunction resulting from dysregulation of the immune system. Multiple Sclerosis affects over 2.5 million people worldwide, and over 400,000 in the United States. Each week there are approximately 400 new cases diagnosed in the United States (1). It is primarily diagnosed in people between the ages of 20 and 40 and is approximately three times more common in women. Multiple Sclerosis is the leading cause of disability in young adults and can substantially affect the quality of life.

There are four clinical subtypes of Multiple Sclerosis: relapsing-relmitting, primary-progressive, secondary-progressive, and progressive-relapsing. Approximately 85% of diagnosed cases are relapsing-relmitting. Relapsing-relmitting MS is characterized by stable periods with intermittent episodes of new or worsening symptoms. Symptoms for MS include: visual disturbances, numbness, fatigue, weakness, loss of balance, poor coordination, tremors, slurred speech, problems with memory and concentration, paralysis and more.

Subcutaneous Injection	Oral
Interferon β -1a	Fingolimod
Interferon β -1b	Teriflunomide
Glatirmaer Acetate	Dimethyl Fumarate

Mechanism of Action

- Selectively reversible inhibitor of dihydroorotate dehydrogenase
- Blocks de novo pyrimidine synthesis in rapidly proliferating cells
- Reduces activity of proliferating T and B lymphocytes
- Diminishes the inflammatory response
- Inhibits protein tyrosine-kinases
- Alters cytokine production
- Modulates the expression of cell surface adhesion molecules
- This all contributes to the observed immunomodulatory effects (7)

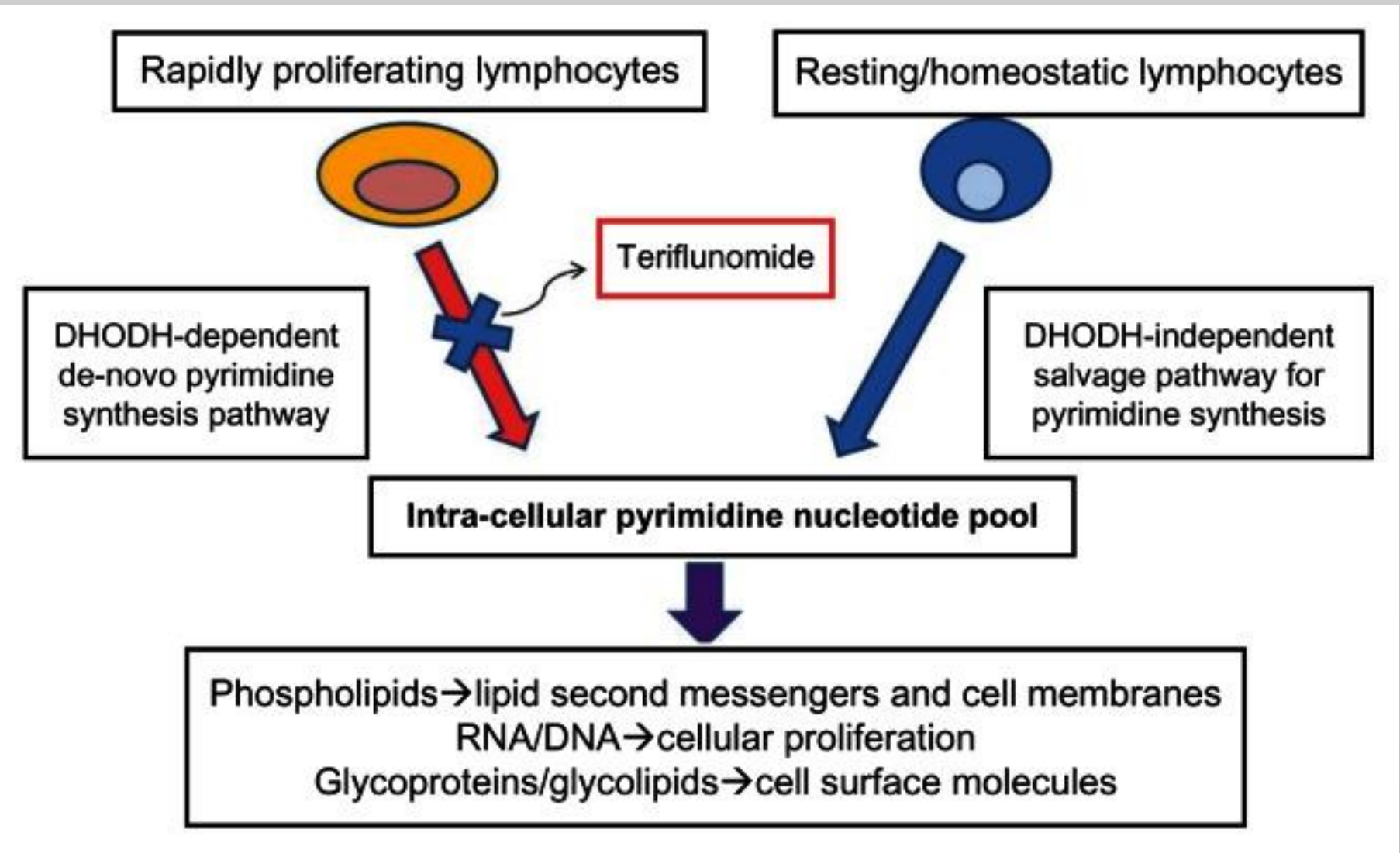


Figure 1: This picture depicts the mechanism of action that Teriflunomide works through. It acts to selectively and reversibly inhibit the DHODH enzyme. However, it does not inhibit normal cell growth because there is a salvage pathway for the formation of pyrimidines. (6).

Efficacy

The efficacy of Teriflunomide was determined through a number of clinical trials before its’ approval by the FDA. The Phase II trial entitled: Treatment of MS with Teriflunomide Monotherapy (2006) found that a daily 7 mg or a 14 mg dose significantly reduced the number of cumulative unique active lesions. In addition, there was a significant reduction in the number of T1 gadolinium-enhancing lesions and T2 lesions. There was also a dose dependent trend toward fewer relapses (3). The TEMSO study was a phase III trial that found a significantly lower annualized relapse rate, reduced total lesion volume, and fewer gadolinium-enhanced lesions. However, only the 14 mg dosage group had a significantly reduced disability progression and hazard ration (5). The phase III TOWER study found a significantly lower annualized relapse rate in both study groups. While only finding the 14 mg dose to reduce the risk of sustained accumulation of disability (4). TOPIC a phase III study found that Teriflunomide significantly increased the time to relapse (2).

In Teriflunomide v Placebo with Glatiramer Acetate a phase III study it was found that the use of Teriflunomide significantly reduced the number and volume of lesions compared to Glatiramer Acetate (3). In addition, in Teriflunomide v Placebo added to Interferon β another phase III trial it was found that there was an acceptable tolerability for these two medications to be used in conjunction. In addition, there were significantly fewer adverse events and a reduced number of T1 lesions in the Teriflunomide study group (3).

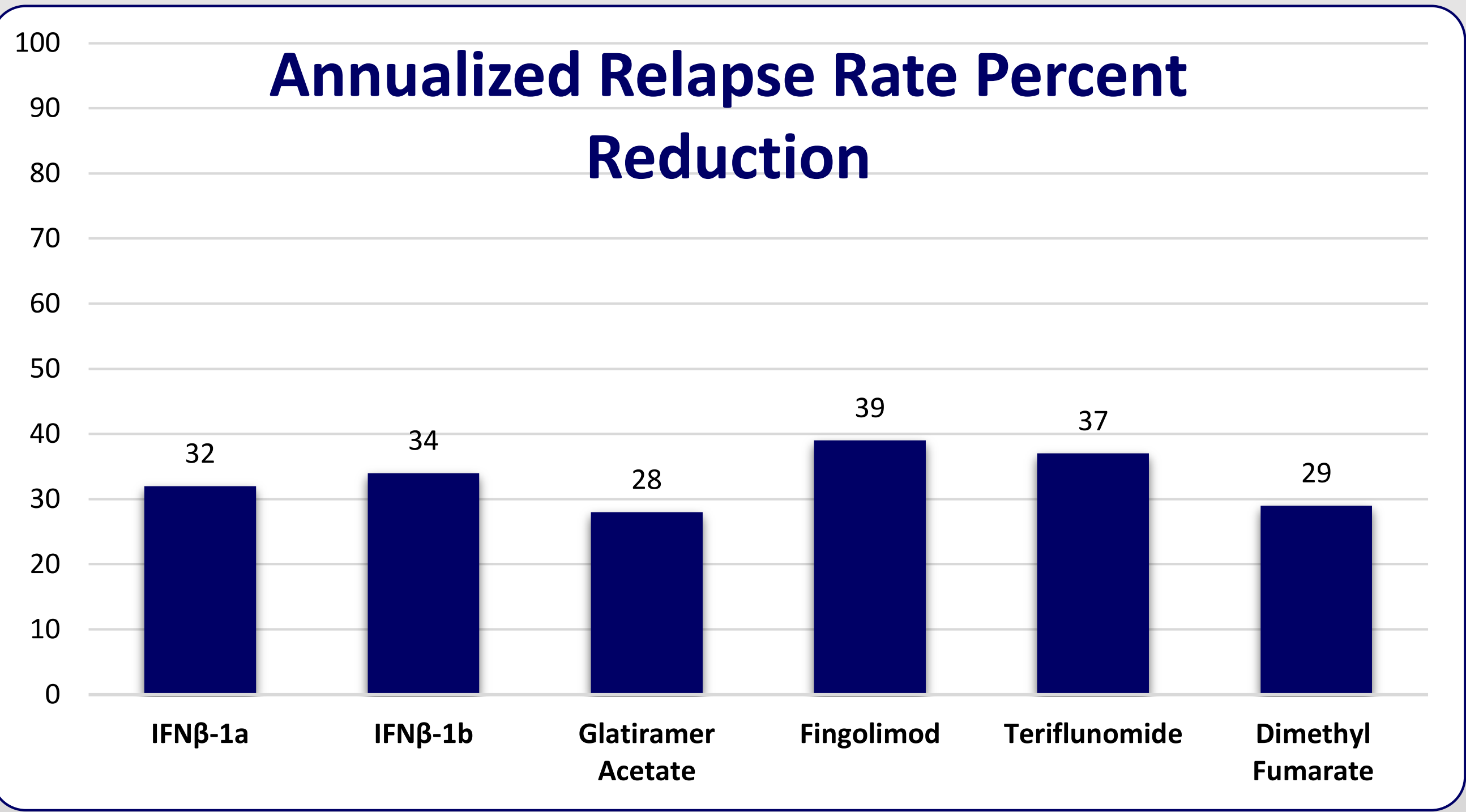


Figure 2: This graph depicts the percent decrease in annualized relapse rates over two years while taking a disease modifying therapy. The percentages shown are the statistically significant decreases when compared to the placebo in their own phase III randomized controlled trials (1).

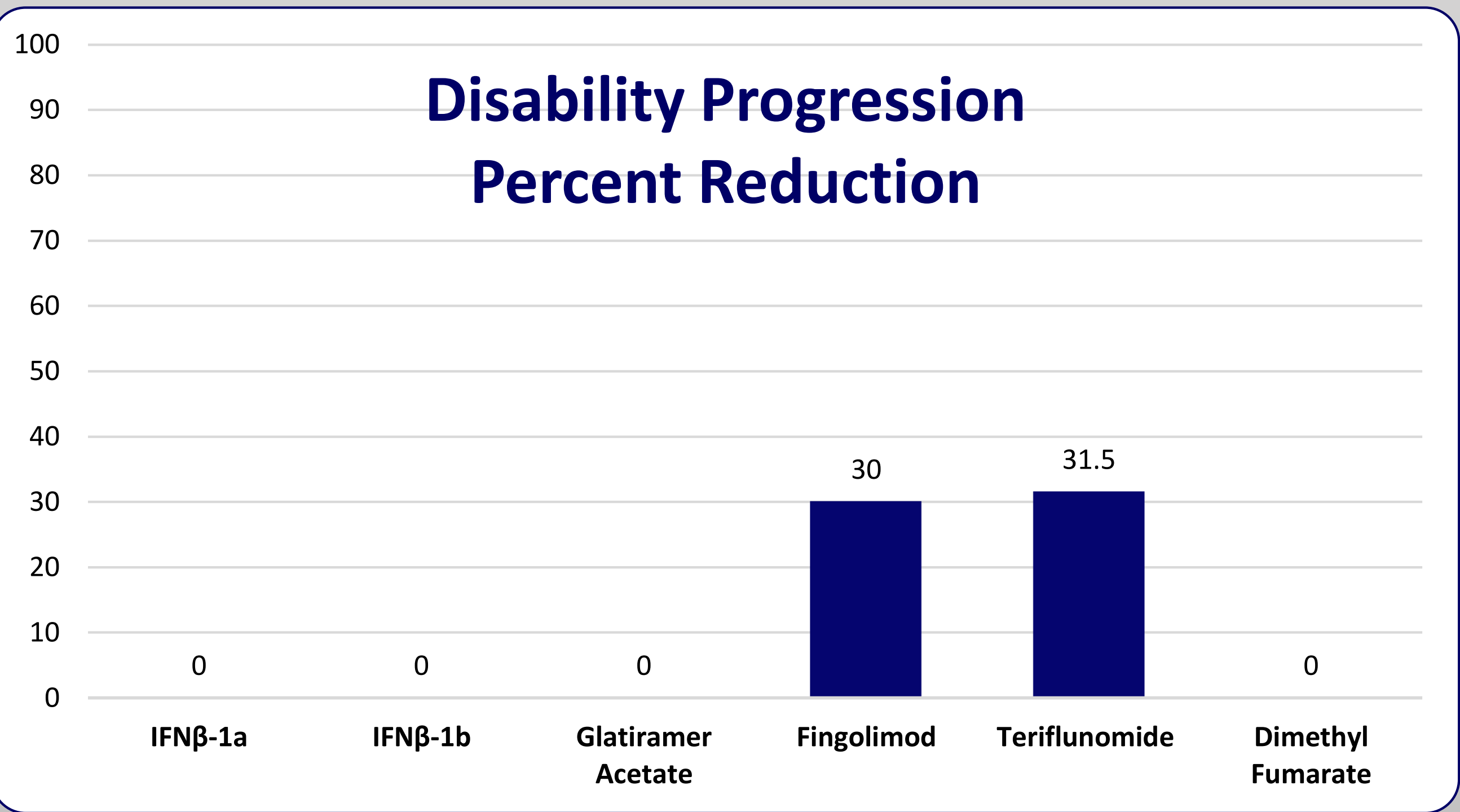


Figure 3: This figure shows the percent decrease in disability progression during the treatment of MS over two years. There are drugs with no data because not all drugs display any significant impact on disability progression (1).

Side Effects

Side Effects					
IFN β -1a	IFN β -1b	Glatiramer Acetate	Fingolimod	Teriflunomide	Dimethyl Fumarate
<ul style="list-style-type: none">• Injection Site Reactions• Flu-Like Symptoms• Lipoatrophy• Fatigue• Hematopoietic Abnormalities• Hepatic Enzyme Abnormalities• Myalgia	<ul style="list-style-type: none">• Injection Site Reactions• Flu-Like Symptoms• Lipoatrophy• Fatigue• Hematopoietic Abnormalities• Hepatic Enzyme Abnormalities• Myalgia	<ul style="list-style-type: none">• Injection site Reaction• Lipoatrophy• Allergic Reactions	<ul style="list-style-type: none">• Heart Failure• Cardiac Abnormalities• Hypertension• Hepatic Enzyme abnormalities• Infections• Respiratory changes• Dyspnea• Macular Edema	<ul style="list-style-type: none">• Hepatic Enzyme Abnormalities• Alopecia• Diarrhea• Nausea• Teratogenicity	<ul style="list-style-type: none">• Flushing• Diarrhea• Nausea

Table 1: This table summarizes the most common adverse events associated with available Disease-Modifying Therapies for Multiple Sclerosis. (8).

Conclusion

It has been found the Teriflunomide is both a safe and efficacious agent for treating relapsing-relmitting multiple sclerosis. Through clinical trials Teriflunomide has demonstrated its’ ability to significantly reduce the annualized relapse rate for patients. In addition at a dosage of 14 mg it has also proven to significantly reduce disability and disease progression. Using MRI markers it has demonstrated the capacity to reduce both the number and volume of T1 and T2 active inflammatory lesions in the brain. Because multiple sclerosis is typically diagnosed between the ages of 20 and 40 its’ ability to slow disease progression greatly improves the quality of life for patients. Of course Teriflunomide does have adverse events due to its use. These effects are primarily mild to moderate and there are rarely serious adverse events. When compared to other similar disease modifying therapies Teriflunomide has more mild and tolerable adverse effects, making it a better drug candidate for many patients. The convenience of oral administration as opposed to injectable treatments makes this a more attractive therapy for many patients due to the additional negative effects associated with injection therapies and the need for long term use. Of course as with any medication, the proper therapy will need to be assessed on a patient to patient basis with a health care profession as a patients’ medical history may alter the best treatment path. In conclusion, Teriflunomide is the safest and most effective disease modifying therapy for the treatment of Relapsing-Remitting Multiple Sclerosis.

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