Multiple Sclerosis
First Line Therapy Treatments

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Interferons (IFNs) and glatiramer acetate have become the standard of care for first line treatment of relapsing, remitting multiple sclerosis (RRMS).[1] Results from short-term pivotal treatment studies indicate that these drugs reduce relapses and delay disability progression in RRMS patients.[2-4] They also delay progression from clinically isolated syndrome (CIS) to definite MS with a second demyelinating event.[5] These drugs have been available in Canada now for nearly two decades, allowing for the analysis of long-term efficacy and safety data. In this brief review, the long-term efficacy and safety of these therapies are presented, as well as the use of these medications in CIS.

Interferons

There are three interferons currently available: IFNß-1a administered intramuscularly weekly, IFNß-1a administered subcutaneously three times a week, and IFNß-1b subcutaneously q.o.d.

IFNß-1b has the longest follow-up period — 16 years. IFNß-1b administered continuously for 16 years showed sustained reduction in the annualized relapse rate (ARR) when compared with subjects who had never taken IFNß-1b or discontinued it during the follow-up period.[6] Longer exposure to IFNß-1b correlated with delayed progression to requiring a walking aid and a significant reduction of disease activity on MRI. Furthermore, there were no new safety issues being identified compared with the original trial.[4]

The 15-year follow-up study of IFNß-1a intramuscularly demonstrated lower disability and delayed time to requiring a walking aid in the treated cohort, compared to those not receiving therapy.[7] Adverse events observed in the extension study, such as flu-like reactions at the time of injection, skin reactions, and changes in white blood cell count or liver enzymes, were similar to those in the pivotal trial.[2]

In the eight-year follow-up study for IFNß-1a subcutaneously, ARR was significantly lower and disability progression was also slower in subjects originally randomized to treatment compared to the placebo group. Subjects in the higher dose treatment group (44 µg) had a significantly smaller percentage change in total T2 lesion volume on MRI compared to the placebo group.[8] Again, no new adverse events or safety concerns compared to the original treatment trial.[3]

Glatiramer Acetate

The 10-year follow-up with glatiramer acetate (GA) demonstrated a reduced ARR to approximately one relapse every five years with only

11% requiring a walking aid after 10 years. The 15-year analysis also demonstrated a continued reduction in ARR. No new adverse events were reported.

Clinically Isolated Syndrome

It is now known that patients presenting with Clinically Isolated Syndrome (CIS), with silent inflammatory lesions on MRI, have a higher risk of developing MS and have a greater progression of disability later in the course of the disease. All the above mentioned treatments have been shown to delay conversion to definite MS.

In the pivotal CIS study with IFNß-1b, the risk reduction for a second demyelinating event compared to placebo was 47% and 43% for a new silent inflammatory lesion on MRI. The study was designed such that subjects in the placebo group who converted to MS (had a second demyelinating event) started treatment with IFNß-1b.[9] After trial completion, all subjects were eligible to enter a follow-up phase with open-label IFNß-1b for five years after randomization. This study demonstrated that the risk for definite MS was lower in the early treatment group (46%) compared to the delayed treatment group (57%).[10] Furthermore, the early treatment group developed fewer new lesions on MRI than the delayed treatment group. However, the difference between early and delayed treatment regarding disability progression over five years was not statistically significant.

In the pivotal CIS study with IFNß-1a IM, the probability of conversion to MS after three years was lower in the treated group than in the placebo group (35 vs. 50%) and there were fewer new or enlarging lesions found on MRI scans.[11] Similar to the IFNß-1b CIS study, once subjects in the placebo group were diagnosed with MS, they were treated with IFNß-1a intramuscularly. After five years, the cumulative probability of conversion to MS was lower in the early treatment group compared to the delayed treatment group. The number of new or enlarging lesions on MRI was also lower in the early treatment group.[12] The 10-year follow-up was recently published, again demonstrating a lower conversion rate to MS in the early treatment group compared to the delay treatment group with only 6% of all subjects requiring a walking aid after 10 years.[13] In this study, there were no significant differences between the early treatment and the delay treatment groups for any MRI outcomes. No new safety issues were found in any of these studies.

There is currently no long-term data available on CIS outcomes for IFNß-1a subcutaneously or glatiramer acetate.

Conclusion

The first line therapies, interferons and glatiramer acetate, have demonstrated continued efficacy and safety for more than 15 years after the pivotal treatment trials — reducing relapses, delaying disability progression, and decreasing the number of new silent MRI lesions. These drugs can be used with confidence in CIS or MS patients for the long-term.

Possible Questions

1) What are the common side effects with interferons?

Interferons, both IFNß-1a and IFNß-1b, can cause flu-like symptoms at the time of injection, such as fatigue, general malaise, body aches, headaches, and sometimes a low-grade fever. These symptoms respond well to treatment with acetaminophen and/or ibuprofen before injection and four-hours later. Usually these symptoms resolve after the first six months of treatment. There is a risk that interferons can worsen depression. Skin reaction at injection sites can appear, but they usually diminish with time. Long-term scarring can also occur. Finally, these medications can also lower white blood cell counts, increase liver enzymes, or affect thyroid function; blood work should be performed at baseline, one, three, and six months after initiating treatment and yearly thereafter.

2) What are the common side effects with glatiramer acetate?

Unlike interferons, there are no flu-like side effects or monitoring blood work required. There is a low possibility of an anxiety attack-like event post-injection that lasts about 20 minutes; this is a paradoxical reaction that can not be predicted by how long the medication has been used. Additionally, glatiramer acetate also causes localized skin reactions that abate with time, but it is more likely than the interferons to cause scarring.

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