OXFORD JOURNAL
OF STUDENT
SCHOLARSHIP

Systematic Literature Review of Treatment of Multiple Sclerosis

Audrey Praisoody
audreypraisoody@gmail.com

ABSTRACT

Multiple Sclerosis (MS) is a chronic immune-mediated neurodegenerative disease with no cure. Currently, there are a multitude of different strategies that aim to prevent the disease's progression. However, none have proven to be reliable. This systematic literature review aims to compare clinical trials from the past 5 years to evaluate the impact of MS treatments on relapse rates, lesion severity, disability progression, and brain atrophy. A comprehensive search was conducted in Pub-med for published randomized controlled trials conducted within the past 5 years. Keywords such as"Multiple Sclerosis," "brain atrophy," and, "motor function.," were used to conduct the search. A total of 9 records were reviewed for this paper. However, five were not used due to repetitive methods, and small sample sizes. The following records were chosen in order to maximize diversity between trials to provide a more comprehensive review. Each trial analyzed was peer-reviewed and reported quantitative data regarding relapse rates and brain atrophy. In total 5 trials were analyzed. Of the five trials, there was one phase I trial, two phase II trials, and two phase III trials. Three trials tested monoclonal antibodies in relapsing remitting multiple sclerosis (RRMS) and primary progressive multiple sclerosis PPMS. Of the 3, 2 were anti-CD20 antibodies (Ofatumumab and Ublituximab) and 1 was anti-CD40 (Frexalimab). One tested neural stem cells in recovering cognitive function, and the last tested teriflunomide in the earliest stage of MS radiologically isolated syndrome (RIS). All trials were conducted with the end purpose of reducing the annual relapse rate (ARR) and number of gadolinium-enhancing lesions GELs in patients. Ublituximab, Frexalimab, Ofatumumab and TERIS all met their primary endpoints with $p<0.001$. Recent advances in MS therapies have improved disease control. However the majority of new treatments, including the five treatments analyzed in this review, require more long-term data. Monoclonal antibodies such as Ublituximab, Frexalimab, and Ofatumumab have proven to be promising treatments for RRMS. Those with PPMS and SPMS require more intense treatments, and treatment methods such as using stem cells should be further investigated. Early treatment of MS has been found to delay disease progression in the TERIS trial.

INTRODUCTION

Multiple Sclerosis (MS) is an auto-immune neurodegenerative disease that causes neurologic disability in adults. MS is characterized by immune-mediated attacks on the myelin sheath, axons, and their supporting cells, resulting in demyelination and inflammation throughout the central nervous system. This causes severe brain atrophy and reductions in motor skills, both of which impacts a patient's independence and long-term prognosis. MS is classified into 3 different types: relapsing remitting (RRMS), secondary progressive (SPMS), and primary progressive (PPMS). RRMS is the most common form of MS, patients typically experience clearly defined relapses or neurological systems followed by remission. Inflammation flares is a distinguishing symptom of RRMS, therefore, most early treatments suppress immune activity. However, this causes a major problem throughout a patient's body as their immune system is significantly less active making them more vulnerable to external factors. The primary goal of anti-inflammatory methods is to reduce the amount of lesions patients experience. Immune suppressants do little to recover cognitive function or brain volume. Additionally in the secondary and primary progressive stages of MS inflammation is chronic and located within the CNS tissue. Most immunomodulatory treatments for RRMS prevent delimitation, however this is irrelevant in treating the progressive stages due immune response already being embedded within the tissue. PPMS and SPMS both require more rigorous and effective treatments than RRMS. All of which necessitates treatments that are more effective than immune suppressants. This systematic literature review aims to evaluate existing clinical trials to compare treatments for MS. The primary goal of this review is to assess how different treatments affect brain atrophy and motor functions in patients with MS.

Ublituximab versus Teriflunomide in Relapsing Multiple Sclerosis

This was a double blind, phase III, double-dummy, clinical trial that compared the effects of Ublituximab and Teriflunomide in treating MS. This lab consisted of 2 trials (ULTIMATE I and ULTIMATE II), each with around 545 participants, and 4 tested groups: placebo (oral), placebo (intravenous), ublituximab, and teriflunomide. (1) The Ublituximab group received 150 mg on day 1, followed by 450 mg on day 15 and at weeks 24, 48, and 72 intravenously. The Teriflunomide group took a 14mg dose orally once a day. Ublituximab is an antibody that targets the CD20 protein (found on the surface of B cells) and results in cellular cytolysis (breaking of the B cell membrane). Teriflunomide is a chemical compound that targets the DHODH enzyme, which inhibits pyriminde synthesis and prevents immune cells from multiplying. Prior trials proved that Ublituximab was "25 to 30 times the antibody-dependent cellular cytolysis potential" than any other drug. The primary goal of this trial was to reduce the annualized relapse rate by comparing the efficiency and safety of intravenous ublituximab and oral teriflunomide. There were also 6 hierarchical secondary goals. The first was reducing the quantity of GELs, second was reducing hyperintense lesions and the 3rd was decrease in worsening of disability at 12 weeks. The tertiary goal was worsening of disability at 24 weeks. The primary end point was proven significant with ublituximab performing better than teriflunomide (annualized relapse rate over a period of 96 weeks was 0.08 in the ublituximab group and 0.19 in the teriflunomide group, $P<0.001$). The 1st secondary endpoint was also significant (0.02 in the ublituximab group and 0.49 in the teriflunomide group, $P<0.001$). Neither

ublituximab nor teriflunomide proved significant in preventing hyperintense lesions, therefore the 3rd secondary endpoint was not tested. The tertiary endpoint was slightly significant up to 12% of the ublituximab group and 6% of teriflunomide reported lessening of disability. However, this did decrease to 9.6% and 5.1% by week 24. Ublituximab proved to be promising in the treatment of MS, as it proved to prevent relapses and lesions. It should be further investigated for long term usage and treatment of disability.

Frexalimab in MS

This phase II, double blind clinical trial aimed to inhibit CD40L with the Frexalimab antibody. (2) CD40 and CD40L help regulate the initiation of adaptive and innate immune responses when activated on T cells. Infiltrating CD40L+ T cells have been identified to act as drivers of CD40-mediated inflammatory responses potentiating the progression of MS lesions and overall disease progression. Frexalimab is a second generation monoclonal antibody designed to remove CD40, and therefore is believed to have potential to be a suitable treatment for MS. Phase I of this trial was terminated presumptuously due to severe symptoms, however prior to this phase Frexalimab had been edited to avoid this. This trial consisted of 125 participants and was conducted over the span of 12 weeks. In this trial there were 4 groups, 2 of which were placebo, the ratio of placebo to experimental was 4:4:1:1. One of the experimental groups received a 1200 mg dose intravenously every 4 weeks and the other received a 300 mg dose. The primary goal of this trial was to reduce the quantity of new gadolinium-enhancing T1-weighted lesions at week 12 relative to week 8. Secondary endpoints include the number of new or enlarging T-2 weighted lesions at week 12 relative to week 8. Trial results showed that the adjusted mean number of new GELs at week 12 relative to week 8 was 0.2 (95% confidence interval [CI], 0.1 to 0.4) in the group that received 1200 mg of frexalimab intravenously and 0.3 (95% CI, 0.1 to 0.6) in the group that received 300 mg of frexalimab subcutaneously, as compared with 1.4 (95% CI, 0.6 to 3.0) in the pooled placebo group. Additionally at the end of the trial period 85% of the participants in the 1200mg group and 84% of the participants in the 300mg had no new GELs, as compared with 50% in the placebo group. Showing that the primary endpoint was met with Frexalimab reducing the number of GELs. Secondary endpoints were also met with The adjusted mean number of new or enlarging T2-weighted lesions at week 12 was 0.3 (95% CI, 0.1 to 0.6) in the group that received 1200 mg of frexalimab intravenously, 0.5 (95% CI, 0.2 to 1.0) in the group that received 300 mg of frexalimab subcutaneously, and 3.5 (95% CI, 1.6 to 7.9) in the pooled placebo group. Frexalimab was also shown to reduce biomarkers that indicate neuroaxonal damage and inflammatory activity. No major side effects were shown to have occurred due to this drug. Frexalimab has been shown to be a promising therapy for patients with MS, however more research is required to determine the long-term effects of this drug.

Ofatumumab

ALITHIOS

ALITHIOS is a phase III clinical trial measuring the effects of ofatumumab in multiple sclerosis during a 4 year time period. (3) Ofatumumab is an anti-CD20 monoclonal antibody. Two prior clinical trials were conducted, comparing the effectiveness of ofatumumab and teriflunomide. In both trials ofatumumab proved to be more effective in reducing the annual relapsing rate and amount of GELs, leading to the creation of ALITHIOS to investigate the long-term effects of ofatumumab. In ALITHIOS there were 2 test groups, one group having switched from teriflunomide to ofatumumab (consisting of 677 participants) and one continuously using ofatumumab (consisting of 690). Results showed that ofatumumab was generally well tolerated over the 4 year treatment, however they also showed infection, immune suppression and maligency risks. Around 58.35% of patients experienced an infection of some degree and 3% of patients experienced severe infections. Immunoglobulins were below the average amount and caused discontinuation in 3.1% of patients, however for the majority this side-effect was not concerning. Low immunoglobulin amounts were not correlated with the infection rate. The continuous ofatumumab group maintained a low ARR for up to 4 years: adjusted ARRs in the core and extension periods were 0.11 (95% confidence interval (CI): 0.08–0.13) and 0.05 (95% CI: 0.04–0.07), respectively (49.4%; $p < 0.001$), corresponding to an adjusted rate of one relapse every 20 years during the extension period. For the newly switched ofatumumab group, the ARR was reduced by 71.7% in the extension versus core period ($p < 0.001$); adjusted ARRs were 0.23 (95% CI: 0.18–0.28) and 0.06 (95% CI: 0.05–0.09), respectively. Additionally, ofatumumab reduced the number of GELs. The adjusted mean number of Gd+ T1 lesions per scan in the core and extension periods was: 0.02 (95% CI: 0.02–0.03) and 0.01 (95% CI: 0.00–0.02), respectively; a reduction of 65.0% ($p = 0.003$). For the newly switched ofatumumab group, the adjusted mean number of Gd+ T1 lesions per scan reduced from 0.55 (95% CI: 0.47–0.65) in the core period, to 0.01 (95% CI: 0.01–0.02) in the extension period; a reduction of 97.4% ($p < 0.001$). This study showed that ofatumumab is suitable for long-term treatment, can help fight disease progression, and improve patients quality of life.

Neural stem cell transplantation in patients with progressive multiple sclerosis

STEMS was a prospective, therapeutic exploratory, non-randomized, open-label, single-dose-finding phase 1 clinical trial, aiming to treat patients with PPMS. (4) The trial tested the effects of neural stem cells from terminated fetuses in 15 patients. Despite advancements in several effective treatments for MS (such as monoclonal antibodies), their advantages are mainly seen in patients with RRMS, leaving the needs of patients with PPMS and SPMS unmet. PPMS and SPMS require therapeutic methods that combine neuroprotection, immunomodulation and regeneration to hamper irreversible disability progression. Treatments for PPMS and SPMS are very limited with the only FDA approved drug for PPMS being Ocrelizumab, however this medication does not treat disability progression. Other available treatments are Siponimod and BTK Inhibitors. However, Siponimod is only for patients experiencing active SPMS, does not provide any neuroregeneration, and only reduces risk of disability progression by 21%. BTK inhibitors are also not widely available and are currently undergoing more research. Neural stem/precursor cells (NPC) are mitotically activated and selfrenewing, they also have the ability to locate

damaged areas on their own, hypothetically leading to a more precise treatment, and neuroregeneration. Previous trials completed in rodents and non-human primates with MS have shown potential for NPCs to be an effective neuralprotective and regenerative treatment. The primary goal of this study was to determine whether NPC treatment was safe for human use. With secondary exploratory goals being cognitive progression and longitudinal changes in: Motor-evoked potentials (MEP), Somatosensory-evoked potentials (SEP), Visual-evoked potentials (VEP), Optical coherence tomography (OCT). Results determined that NPCs were safe for treatment with the only serious adverse event occurring being non-related to the trial and all other adverse events being grade 1 or 2. Exploratory results determined that changes in disability using EDSS and the amount of GELs were non-significant. However, there was a significant decline in gray and white matter atrophy. During this trial cerebrospinal fluid was used for biochemical, microbiological and immunological analysis. Results showed an increase in neuroprotective proteins linked to axon development, neurogenesis, synapse organization, cell migration, and extracellular matrix remodeling. These findings support the speculation that hfNPCs can modulate CNS pathways towards repair and neuroprotections. Results also discovered an upregulation in cytokines and chemokines, which typically are pro-inflammatory. However, these molecules have been shown to exert pro regenerative functions. These molecules and other inflammatory responses could have caused the increase in GM-CSF. Additionally patients showed a significant improvement in SDMT scores, a test used to determine cognitive processing speed. And while not significant EDSS findings showed a small positive slope. However it is important to note that this trial was non-randomized and the EDSS findings could be a result of an inclusion bias. All results were more significant in the higher dosage patients. Due to the small population of this trial it is hard to draw any solid conclusions for the exploratory endpoints. However, we can conclude that NPCs have potential to treat certain aspects of PPMS (specifically brain atrophy). STEMS require longer and more in depth research and the higher dosage should be further researched for a potential treatment for PPMS.

TERIS

TERIS was a multicenter, double-blinded, randomized (1:1), phase II clinical trial testing the effects of teriflunomide, an approved treatment for MS, in patients with RIS. (5) The trial was conducted over a course of 96 weeks during which patients took a 14mg dose of teriflunomide daily. Radiologically isolated syndrome (RIS) is the earliest detectable preclinical stage of MS. A diagnosis of MS requires proof of clinical symptoms consistent with acute or progressive CNS injury detectable by an MRI. When a patient does not express symptoms of MS but a MRI scan reveals anomalies highly suggestive of demyelinating plaques given their size, location, and shape in the absence of symptomatology explained by these lesions, they can be diagnosed with RIS. Teriflunomide has been proven to help delay the progression of MS, and is used as a suitable treatment of RRMS in over 80 countries. Therefore, the primary goal of this study was to extend the time til the first neurologic event resulting from CNS demyelination. This event typically marks the transition from RIS to MS. Secondary outcomes included reductions in the quantity and volumes of T2-weighted hyperintense lesions and gadolinium-enhancing

(Gd+) lesions. During the the study 124 patients were assessed for eligibility, 89 entered the trial, 45 in the placebo group, and 44 in the teriflunomide group. 9 participants discontinued their involvement, 3 discontinued due to adverse events. Teriflunomide caused a risk reduction of 72% relative to placebo in preventing the first clinical event. In the teriflunomide group 8 participants experienced a clinical event at a mean time of 128.2 weeks. 6 led to RRMS and 2 led to PPMS. In the placebo group 20 participants experienced a clinical event at a mean time of 109.6 weeks (18 RRMS, 2 PPMS). Secondary goals were not met with the number and volume of T2-weighted hyperintense lesions and GELs (Gd+) not being statistically significant. From this study we can infer that disease-modifying treatments such as teriflunomide can help delay the progression of MS even before official diagnosis. We can also infer that the earlier treatment is started the longer patients are able to remain clinically stable.

DISCUSSION

This systematic literature review analyzed a total of five studies attempting to treat MS using different methods. A major limitation of all of these studies was their duration period. Ublituximab, TERIS, and STEMS all lasted over a period of 96 weeks, which is not sufficient enough to provide evidence on the long term effects of these drugs. Frexalimab was a phase II trial which inherently provided less information, but it also only lasted 12 weeks which would affect the results of the trial. Frexalimab met both their primary and secondary endpoints which would suggest that it is a promising treatment, however we do not know how it would perform over a longer period of time, necessitating more research. Additionally another major limitation of Frexalimab, TERIS, and STEMS was its small population size. Which should be considered when determining the validity of their findings. When determining their participants TERIS was unable to ensure each participant met the accepted risk factors for their trial, which would have affected their findings. STEMS being a phase I trial, and having a small sample size would not have provided enough evidence to meet any of their exploratory endpoints. Due to the method having potential to be a treatment of MS, and STEMS meeting the primary endpoint of safety, more research should be conducted to determine the effectiveness of this treatment. Ofatumumab being conducted over a longer period of time and having a larger sample size reduced limitations, however the study coincided with the global pandemic of COVID-19 which could have affected their infection rates. Additionally, more research should be conducted in order to determine the effectiveness of the drug over a longer period of time. When determining the effectiveness of Ublituximb the study only compared it to Teriflunomide, in order to more accurately compare the drugs performance, more research should be done comparing it to other drugs.

At the end of the study, ofatumumab managed to reduce the ARR to 0.05 and reduce the quantity of lesions by around 88%, with a lesion per scan rate of 0.02. The study had the longest follow-up period of 4 years. When compared to other monoclonal antibodies, ublituximab matched its effectiveness in reducing GELs, however ublituximab had a higher ARR at 0.08. It is important to note that the ublituximab trial only was conducted in roughly half the amount of time of ofatumumab which could have contributed to the higher ARR. It is also worth noting that ofatumumab has more side effects than ublituximab. Overall both of these trials are very promising and similar to one another. Frexalimab was a phase II trial, inherently providing less information about the drug compared to ublituximab and

ofatumumab. The trial's main goals were to reduce the quantity of lesions in patients, which it did by reducing the amount of lesions by up to 90%. The end ratio of the lesions were 0.11, meaning participants in the frexalimab trial experienced more lesions than ublituximab and ofatumumab at the end of the trial. However, the frexalimab trial only lasted 12 weeks, so it could only test its effectiveness in treating MS in the short term. Frexalimab was only a phase II trial so there are many unknowns about this treatment, but it has proved to be very promising in reducing GELs. STEMS was only a phase I so there is very limited information about this method. However, while STEMS was proven to be safe it failed to meet any of its exploratory endpoints. The trial did show potential towards meeting those endpoints, however very little is known about how stem cells can treat MS and more research is needed for it to be considered an effective treatment. TERIS should be considered an effective treatment, with it delaying disease progression by 72%. TERIS also indicated that the most effective method for treating MS or RIS is early intervention. While the analyzes of these results come with limitations, including the retrospective nature of studies and data variability, future research should be focused on early stages of the disease.

Treatment	Sample Size	Duration	Main outcomes	ARR	Reduction of new GEL
Ublituximab	545	96 weeks	Reduction of ARR	0.08	0.02
Frexalimab	125	12 weeks.	Reduction of new GELs	NA	0.2
Ofatumumab	1367	4 year	Reduction of ARR	0.05	0.01
STEMS	15	96 weeks	Safety	NA	0.38
TERIS	89	96 weeks	Prevention of RRMS/ PPMS	NA	0.33

CONCLUSION

This systematic literature review analyzed five different trials for the treatment of MS. A major limitation of this systematic paper was its sample size due to only five trials being analyzed. Additionally, variability among trials, differences in sample sizes, MRI protocols, or assessment tools, could have affected comparisons. Of the five three were targeted towards treating RRMS (Ublituximab, Ofatumumab, and Frexalimab), one was targeted towards PPMS and SPMS (STEMS), and one was targeted towards treating RIS (TERIS). Both Ublituximab and Ofatumumab managed to significantly reduce the ARR of their patients, however more research is required for both of these to determine the long term effects of the drugs. Frexalimab effectively reduced the number of new GELs meeting their primary and secondary endpoints, and proved Frexalimab as a potential treatment for RRMS. However, the trial lasted for a short period of time, and had a relatively small sample size, necessitating more research. STEMS was trial aiming to create a more intense treatment primarily for patients with PPMS and SPMS, they met their primary goal of safety, however did not meet any of their exploratory endpoints regarding the effectiveness of this treatment. This trial was extremely small and needs more research for the long term effects of the treatment, and for the effectiveness of the treatment overall. TERIS aimed to research the effects of treating RIS with teriflunomide and its potential to prevent disease progression into RMS. They met their primary endpoint, however faced limitations due to their sample size, and potential population bias. Overall, longer trials should be conducted for all of these treatments with a larger population size.

REFERENCES

1. Genchi, Angela, et al. "Neural stem cell transplantation in patients with progressive multiple sclerosis: an open-label, phase 1 study." *Nature Medicine* 29.1 (2023): 75-85.
2. Hauser, Stephen L., et al. "Efficacy and safety of four-year ofatumumab treatment in relapsing multiple sclerosis: The ALITHIOS open-label extension." *Multiple Sclerosis Journal* 29.11-12 (2023): 1452-1464.
3. Lebrun-Frénay, Christine, et al. "Teriflunomide and time to clinical multiple sclerosis in patients with radiologically isolated syndrome: the TERIS randomized clinical trial." *JAMA neurology* 80.10 (2023): 1080-1088.
4. Steinman, Lawrence, et al. "Ublituximab versus teriflunomide in relapsing multiple sclerosis." *New England Journal of Medicine* 387.8 (2022): 704-714.
5. Vermersch, Patrick, et al. "Inhibition of CD40L with frexalimab in multiple sclerosis." *New England Journal of Medicine* 390.7 (2024): 589-600.