8-14-2010

The Efficacy of Statins in Treating Relapse-Remission Multiple Sclerosis

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The Efficacy of Statins in Treating Relapse-Remission Multiple Sclerosis

Abstract
Background: Multiple sclerosis (MS) is believed to be an autoimmune disease that creates an inflammatory process that breaks down the blood brain barrier (BBB) allowing the immune system to attack the myelin sheaths of the central nervous system (CNS). MS can be treated with a variety of disease modifying drugs (DMD) that decrease the immune system's attack on the myelin sheaths of the CNS. In the past few decades, three-hydroxy-three-methylglutaryl coenzyme A reductase inhibitors, known as statins, have been suggested to have anti-inflammatory effects that will reduce the permeability of the BBB. This review is to investigate the trials that have been done involving the use of statins as monotherapy, or in combination with an interferon DMD, as treatment in relapse-remitting MS (RRMS).

Methods: An extensive review of MEDLINE, CINAHL, Web of Science, and MDConsult, was performed to find human trials that used statins with or without beta interferons to treat RRMS. The research also looked for the trials that measured the number of contrasted enhanced lesions on T1 sequenced magnetic resonance imaging.

Results: The three trials reviewed had differing results. The Birnbaum et al trial concluded that statins may have an adverse effect on the disease activity of RRMS and should be used with caution. The Paul et al trial concluded that statins were safe, well tolerated, and had possible benefits in treating RRMS. The Rudick et al trial concluded that statins did not affect the treatment of RRMS.

Conclusion: The question of how effective statins are in the treatment of RRMS, is yet to be resolved. There is a need for large population trials with of long duration that focus their outcomes on the clinical aspect of treating RRMS.
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The Efficacy of Statins in Treating Relapse-Remission Multiple Sclerosis

Todd Erickson

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 14, 2010

Faculty Advisor: Mary Von MS, PAC
Clinical Graduate Project Coordinators: Annjanette Sommers MS, PAC & Rob Rosenow PharmD, OD
Todd Erickson was born in Montana, and raised in Wyoming, which he currently calls home. He is married with three children. He started working as a radiologic technologist in 1982 and graduated from Casper College in 1984 with a degree in radiologic technology. He was certified in radiology in 1984. In 1990, he was the first technologist in Casper, WY, and among the first in the United States to be certified in cardiovascular interventional technology. Then, in 2004, he received certification in magnetic resonance imaging. He took a leave of absence from radiology in 1995 for mission work in the Eastern European country of Albania, returning to radiology in 1998. In 2002, his oldest son graduated from Casper College with a degree in computer science. Then, in 2005, his youngest son graduated from Casper College with a degree in music and joined the Marines. His daughter received her Master’s Degree in mathematics from the University of Kentucky in 2007. With the children independent, he was free to pursue his dream of becoming a Physician Assistant, at Pacific University of Oregon and he intends to graduate in August 2010.
**Abstract**

**Background:** Multiple sclerosis (MS) is believed to be an autoimmune disease that creates an inflammatory process that breaks down the blood brain barrier (BBB) allowing the immune system to attack the myelin sheaths of the central nervous system (CNS). MS can be treated with a variety of disease modifying drugs (DMD) that decrease the immune system’s attack on the myelin sheaths of the CNS. In the past few decades, three-hydroxy-three-methylglutaryl coenzyme A reductase inhibitors, known as statins, have been suggested to have anti-inflammatory effects that will reduce the permeability of the BBB. This review is to investigate the trials that have been done involving the use of statins as monotherapy, or in combination with an interferon DMD, as treatment in relapse-remitting MS (RRMS).

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**Keywords:** Multiple Sclerosis, Statins, and magnetic resonance imaging
Acknowledgements

First and foremost I would like to give praise to God, who has blessed me with a loving wife, family, and friends.

I would like to give special thanks to my wife who has put up with my whining, my bad moods, and my insecurities. She has been my inspiration, always encouraging me to continue on, and most of all, she has worked hard to support me without complaint, even with the long months of separation.

To my children Bradley, Shawnasie, and Beau, who were all married in the years while I was in school. They dealt with my time schedule as well as my lack of funds without complaint.

To the rest of my family for the support and prayers they gave me throughout the time before and during school.

And finally, thanks to Drs. Pedemonte and Rosenow for their enthusiasm, Professors Von, Ortiz, Sommers, and Randolf for their encouragement and help in getting me through classes, Professor Ferguson for his humor and enthusiasm, Professors Reddy and Hill for the work that they do to maintain the clinical sites, and especially to Diane for all the work she does for our clinical rotations. You’re the best.
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List of Abbreviations

BBB……………………………………………………………………blood brain barrier
CN………………………………………………………………….central nervous system
DMD……………………………………………………………...disease-modifying drugs
EAE…………………………………………experimental autoimmune encephalomyelitis
EDSS…………………………………………………….Expanded Disability Status Scale
FDA………………………………………………………….Federal Drug Administration
IM…………………………………………………………………………...inter-muscular
INF-β……………………………………………………………………..…beta-interferon
MP……………………………………………………………………..methylprednisolone
MS………………………………………………………………………..multiple sclerosis
RCT……………………………………………………………….randomized control trial
RRMS………………………………………………relapse-remitting multiple sclerosis
SC…………………………………………………………………………….subcutaneous
The Efficacy of Statins in Treating Relapse-Remission Multiple Sclerosis

BACKGROUND

Multiple Sclerosis

Multiple sclerosis (MS) is an incurable disease of the central nervous system (CNS) and, possibly, one of the most frequently diagnosed neurological diseases in young adults. As of May 2009, there are about 400,000 individuals in the US with MS and about 10,000 newly diagnosed cases every year.\textsuperscript{1} Although MS is not terminal, it can be debilitating to the point that the patients are unable to care for themselves.

MS is believed to be an autoimmune disease in which the leukocytes that are meant to fight disease begin to attack the myelin sheaths of the nerves within the CNS.\textsuperscript{1} Normally the blood brain barrier (BBB) will provide immune privileges and homeostasis to the CNS, but an immunological event, early in MS, breaks down the BBB and allows transmigration of antigen and non-antigen specific leukocytes as well as immunological mediators.\textsuperscript{2,3} Once across the BBB, the leukocytes begin to attack, causing an inflammatory process that will eventually lead to the destruction of the myelin sheaths.

There are several diagnostic subcategories for MS (Table 1), and they are based on a state of progression versus relapse-remitting. The primary and secondary progressive states deal with accumulation of symptoms that changes the baseline of the patient’s disability. The relapse-remitting state is an exacerbation that will remit back to the patient’s disability base line from before the exacerbation. There are patients who can have aspects of both progressive and relapse-remitting multiple sclerosis (RRMS).\textsuperscript{1}
MS is treated with a variety of disease-modifying drugs (DMD). Glatiramer acetate, motroxantrone, beta-interferons (INF-β), and natalizumab are DMDs that have been proven to reduce relapse, and have been FDA approved for RRMS. Even though these can help to reduce relapse, they do not stay the progression of MS. The downside to these drugs, the need for treatment for duration of life and the side effects, can cause many patients to refuse long-term adherence to the treatment. DMDs are used to reduce the immune system’s attack on the myelin sheaths. Researchers are continually looking for drugs that will either improve the remitting time or stay the progression.

**Statins**

Three-hydroxy-three-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, known as statins, were first approved by the FDA in August of 1987. In 1995, Kobashigawa et al. reported that post cardiac transplant patients had improved outcomes when treated with pravastatin. These findings led to studies that extensively explored statins and their potential in the treatment of autoimmune diseases.

Experimental autoimmune encephalomyelitis (EAE), a model developed in mice that simulates human MS, and in vitro studies, suggest that statins have an immunomodulatory effect on both T cells and monocytes of immunocompetent cells. An in vitro study, reported in 2006, reproduced human BBB derived endothelial cells and tested the diffusion of bovine serum albumin and [14C]-sucrose across the barrier. The study described a 2.39 to a 2.45 fold reduction in permeability of BBB derived endothelial cells with the use of statins, as compared to the permeability of BBB derived endothelial cells without statins.
There was a small open-label trial, conducted in 2003, which used 20mg of lovastatin in seven MS patients with active disease. Magnetic resonance imaging (MRI) results from these patients indicated a decrease in inflammation with statin treatment. A second small open-label trial, conducted in 2004, used 80mg of simvastatin over a six month trial that resulted in a decrease in gadolinium (Gd) enhanced lesions. In 2005, a study showed that the use of statins with glatiramer acetate (GA) or INF-β resulted in a decrease in T-cell production. These trials concluded with the fact, that statins need further testing as an adjunct treatment for MS.

**Purpose of Study**

This topic gives rise to a variety of research that looks at varying outcomes; therefore, this study evaluates the results and the quality of the studies in the past four years to determine if there could be definitive conclusions drawn regarding the question of the efficacy of the use of statins in treating RRMS.

Ideally, a double blind randomized control trial (RTC) with a large population might provide answers to the efficacy of statins in prolonging the time between relapses in MS, but the trials available have small sample sizes and explore varying measured outcomes. The trials also vary between animal trials, human RCT, and a post hoc study.

This systematic review is designed to look at the human trials and discern what would be helpful in a clinical situation, and review the animal trials for background information.

**Clinical Question**

What is the efficacy of statins in treating relapse-remission multiple sclerosis in humans?
METHODS

Search Strategy

A systematic review was done by performing an extensive evaluation of literature for articles that discuss the use of statins as a treatment for RRMS. Trials considered were those published in the last 4 years in which one arm of the study was given a statin and the other arm was either given no treatment or a standard MS treatment. Both prospective and retrospective studies, published in English, were considered, with a focus on human trials.

Four databases were searched: MEDLINE, CINAHL, Web of Science, and MDConsult. Since this review was for clinical purposes, the key words used were multiple sclerosis, statins (MeSH term 3-hydroxy-3-methylglutaryl coenzyme A), and MRI.

Exclusion

Vollmer et al\textsuperscript{8} was excluded because of the date, but also because reviews\textsuperscript{7,11,13-16} and editorials\textsuperscript{14,15} in the last four years discuss the results. These discussions all lead to the same conclusion; there is a need for further trials. Also, there is a more recent trial, Paul et al\textsuperscript{3} that agrees with Vollmer et al, and it has been included in this review.

RESULTS

The Summary Matrix of Reviewed Articles gives a brief look at the three studies used for this systematic review, including their set-up and conclusions (See Table 2). Detailed results of each study are found in this section with a discussion of the findings appearing in the next section.
**Trial One**

The Birnbaum et al\textsuperscript{17} trial was a randomized double blind trial. Patients with definite RRMS were initially chosen using either Poser criteria (Table 3) or MacDonald criteria (Table 4). Participants were then further limited to those on 44µg subcutaneous (SC) INF-β three times a week and had been clinically stable for at least 6 months prior to selection.\textsuperscript{17}

The trial was set-up with three arms. Group one was administered a placebo, the second was administered 40mg of atorvastatin, and the third was administered 80mg of atorvastatin. The following is a list of the mean values of the clinical and demographic characteristics of group one, two and three, respectively:\textsuperscript{17}

- **Age (SD):** 40.1 (9.2), 38.4 (7.5), 45.1 (6.3)
- **Duration of disease in years:** 7.7 (7), 6.4 (6.7), 7.2 (5.9)
- **EDSS at inclusion (SD, range):** 2.3 (1.4, 1-5.5), 2.1 (0.6, 1.5-3), 2.0 (0.7, 1.5-3.5)
- **No. relapses for 12 months prior to treatment:** 1, 0, 0

The groups were randomized by giving each participant two unmarked bottles of drugs. The groups were instructed to take one pill from each bottle daily. Group one was given two bottles of placebo. Group two was given one bottle placebo and one bottle 40mg atorvastatin. The final group was given two bottles of 40mg atorvastatin. All study personnel were unaware as to what each participant received.\textsuperscript{17}

The trial started with a pool of 29 individuals. One individual failed due to drug related rash, one to a relapse at the time of screening and a third was a voluntary withdraw. After screening, only 26 participants entered the randomization for the 9
month trial. Of the 26 that entered, 4 participants were discontinued. After 1 month, a participant from group three left due to muscle cramps followed by a relapse that did not respond well to steroids. After two months, 1 participant from group 3 left for an unknown reason and was lost to follow-up. A participant from group 3 was withdrawn after three months due to persistent elevated transaminases. After five months a participant from group 1 left due to elevated creatine kinase. All participants that were discontinued from the study were accounted for in the analysis.\textsuperscript{17}

Participants received treatment for 6 months and were evaluated with MRI and EDSS at 0, 3, 6, and 9 months. The neurologists performing the evaluations were also blinded. Baseline MRI found one participant with one contrast enhanced lesion (CEL) in groups one and two. Group three had two participants with adverse outcomes, one with one CEL and one with two CELs.\textsuperscript{17}

This trial used analysis of variance (ANOVA) to compare continuous baseline covariates. The p-values for the baseline demographics vary from 0.19 for age to 0.91 for disease ratio, meaning there is no statistical significance in the baseline demographics of the three groups. The trial looked at three outcomes: new CEL on MRI, clinical relapse, and both CEL with relapse.\textsuperscript{17}

The likelihood of experiencing a CEL, or having a relapse, was determined through survival analysis between the placebo and the combined atorvastatin groups. Compared to the placebo group, the combined atorvastatin group demonstrated a greater risk for experiencing one or more adverse outcomes with a statistically significant p-value of 0.019. The trial demonstrated that atorvastatin treatment had a hazard ratio of 8.25 (p=0.044, 95% CI 1.06-64.2).\textsuperscript{17}
At the end of nine months, the combined atorvastatin group had more adverse outcomes than the placebo group. The placebo group had no subjects with CEL only, no subjects with a clinical relapse only, but one subject did have both a CEL and a clinical relapse. The atorvastatin group, taking 40mg, had two subjects with CEL only, one subject with a clinical relapse only, and one subject that had both a CEL and a clinical relapse. The final group of atorvastatin, taking 80mg, had four subjects with CEL only, one subject with a clinical relapse only, and one subject that had both a CEL and a clinical relapse.17

Of the 17 participants in the combined atorvastatin group, 10 had one or more adverse outcomes compared to 1 participant from the 9 placebo subjects (p=0.022). Some of the relapses experienced by the participants were the first experienced by that participant in years and some were significant enough for steroidal treatment.17

This trial concluded that although well tolerated, atorvastatin significantly increased the risk of MS disease activity. The trial addresses the facts that lower doses, other statin agents, and larger population groups need to be tested to give a more accurate picture, but suggests that patients on an interferon and a statin should be monitored closely for disease activity and should possibly be changed to another cholesterol lowering agent.17

**Trial Two**

The Paul et al5 trial was a baseline to treatment study that looked specifically at atorvastatin in the treatment of RRMS. The study assessed 80 RRMS patients for certain study prerequisites. The patients did not have to have clinically active disease, but they needed to fulfill the panel criteria for clinically definite MS including an EDSS (Table 5)
score between 0-6, an age between 18-55, and at least one contrast enhanced lesion (CEL) on MRI.  

The trial was divided into two groups. Group one was treated with atorvastatin and no DMD and group two was treated with atorvastatin and INF-β. The following is a list of the mean values of the clinical and demographic characteristics of group one and group two, respectively:

- Age: 37.9 (26-48), 33.9 (19-51)
- Duration of disease in months: 116.3 (26-317), 63.4 (2-229)
- EDSS at inclusion (SD, range): 2.50 (1.5, 0-6), 1.14 (1.1, 0-4)
- Total relapses since disease onset (SD, range): 5.75 (2.6, 3-12), 3 (2.1, 1-10)
- Relapses 12 months prior to treatment (SD, range): 1.63 (1.3, 0-4), 1.4 (1.0, 0-4)

The participants were placed in a group according to their history of DMD use. Group one had received DMD with either IFN-b-1a 22 mg SC 3 times weekly or IFN-b-1b SC every other day for at least 6 months, the mean being 48 months. Group two had not received DMD for at least six months prior to the screening date. Group two was not treated with DMDs throughout the study, while group one’s treatment continued for the duration of the study.  

Of the 80 original participants, 39 were excluded pre-trial due to the lack of a CEL on the qualifying MRI. Group two contained 25 participants that were allocated to using atorvastatin only and group one contained 16 participants that were allocated to atorvastatin with their INF-β scheduled treatments. Group two did not lose any participants to follow-up, although they had one patient discontinue therapy due to active disease. That patient was not included in the analysis. Group one lost one patient to
follow-up because of a change in residency. Three participants from group one discontinued the study, two from active disease, and one from a sustained increase in creatine kinase. These four participants were not included in the analysis.

All the participants were seen 13 times throughout the trial, and received monthly MRIs with EDSS evaluations every 3 months. Relapses were treated with 3-5 days of 1mg of methylprednisolone (MP) administered intravenously, and atorvastatin treatment was continued during MP administration.

Statistically, trial two was a two factorial MANOVA design used for a direct exploratory comparison, the results of which showed no real statistical difference (p=0.274) between group one and group two of the trial. The trial compared several outcomes, but the focus of this review is on the MRI and EDSS results.

Both arms showed improvement of CEL number on T1 MRI with p-values: 0.003 for the whole group, 0.060 for group one, and 0.170 for group two. The trial showed improvement of CEL volume with p-values: 0.008 for the whole group, 0.062 for group one, and 0.140 for group two. The T2 lesion count, on MRI, increased with p-values: <0.001 for the whole group, 0.008 for group one, and 0.002 for group two. T2 lesion volumes also increased, with p-values: 0.008 for the whole group, 0.003 for group one, and 0.053 for group two. EDSS evaluations showed with p-values: 0.665 for the whole group, 0.712 for group one, and 0.502 for group two.

Trial two concluded that 9 months of high-dose atorvastatin is safe and well tolerated in RRMS patients, with or without INF-β co-medication. Therefore, the results did not suggest statins combination therapy as a superior treatment to the statin monotherapy. Also, based on MRI surrogate measures, there is a possible benefit from atorvastatin on
lesion formation. The immunomodulatory effects on RRMS that are observed here remain to be investigated in future trials. 5

**Trial Three**

The Rudick et al 18 trial was a post hoc analysis of the SENTINEL 18 study. The SENTINEL study included participants that had experienced at least one relapse during the past 12-months, then randomized them to receive continued interferon beta-1a in combination with 300mg of natalizumab (589 patients) or placebo (582 patients) intravenously every 4 weeks for up to 116 weeks. Over a period two years, they looked at the rate of clinical relapse per year as well as disability progression sustained for 12 weeks as measured by EDSS.14 The study also recorded other medications the participants were taking, Rudick et al, therefore, looked at the placebo arm of 582 participants and found that 40 of them were on routine statins of various types.18

The post hoc study did not involve any further contact or information gathering from the participants. The placebo arm of the SENTINEL study was divided into two arms for this study. Group one was 542 participants on intramuscular (IM) INF-β without statins, and group two was 40 participants on IM INF-β and statins. The following is a list of the mean/median values of the clinical and demographic characteristics of group one and two, respectively:18

- Mean age(SD): 38.7 (7.56), 44.0 (7.15)
- Median duration of disease in years (range): 8 (1-34), 8 (1-31)
- Mean EDSS at inclusion (SD): 2.5 (1.13), 2.6 (1.13)
- Mean no. relapses for 12 months prior to treatment (SD): 1.5 (0.72), 1.4 (0.71)
- Median CEL per patient (range): 0 (0-16), 0 (0-2)
Of the 40 participants in group two, one participant had an unknown statin start date, 19 started after the first INF-β was given, and 20 were taking statins prior to the randomization date. These start dates lead to a median duration of statin administration at 657 days with most participants taking atorvastatin (n=26) or simvastatin (n=4) and five participants taking multiple statins. Participants in the statin group had a mean age of 5.3 years older than those in the placebo group; other than the age difference, the participants were matched at baseline between the two groups.\textsuperscript{18}

Statistically, the cumulative probability of sustained disability progression was calculated using the Kaplan-Meier model. Treatment effect was analyzed with the Cox proportional hazards model. EDSS was analyzed with an ANOVA model. A Poisson regression was used to annualize the relapse rate and the CEL results were analyzed with a rank-based ANOVA.\textsuperscript{18}

The two year clinical outcomes reveal that groups one and two had no significant differences. The adjusted annualized relapse rates are 0.67 for group one and 0.66 for group two (p = 0.937). The cumulative probability of sustained disability progression at two years had a p-value of 0.438, while the change in EDSS score from baseline had a p-value of 0.716. CEL count per patient at one year resulted in a p-value of 0.842, and at two years, 0.788.\textsuperscript{18}

The trial concluded that statins do not have an effect on the efficacy of INF-β. This trial compared itself to trial one, and concluded that because of a larger population in both arms of the instant trial, it was more accurate.\textsuperscript{18}
DISCUSSION

Trial One

The strength of the Birnbaum et al\textsuperscript{17} trial lies in its randomization and the blinding of both participants and study personnel. It also took into account the various doses of atorvastatin, using the doses commonly given to lower cholesterol. The trial tracked all of the participants and gave a good history as to why they were discontinued. It also included all of the participants that started treatment in its outcome analysis.

The weaknesses of this trial were that it only tested atorvastatin, it used a small population, and it was of short duration. Although it varied the statin dose, it failed to give a good picture of the full dose responsiveness of atorvastatin. The demonstrated outcomes had the appearance that 80mg was more harmful than 40mg. If 40mg is less harmful than 80mg, then would 20mg or even 10mg be less harmful and have a positive effect on RRMS?

As to the efficacy of statins in treating RRMS, this trial suggested that at these dosage levels they are harmful. There is a thought that statins block the STAT1 phosphorylation pathway of the interferon.\textsuperscript{19} Beta interferon and statins affect the immune system along different pathways, some of which may be antagonistic to each other. This hypothesis is also worthy of further investigation.

Trial one disclosed honoraria for several of those conducting the trial from multiple sources, and several were above $10,000.

Trial Two

The Paul et al\textsuperscript{5} trial’s strengths are in its clinical and demographic characteristics. First of all, the trial did well in recording the pretrial condition of the participants,
providing a clear picture of both groups and where they were in the disease process. Secondly, it covers what happened to those participants that were discontinued. Even though they were not included in the analysis, the trial mentioned when they were discontinued and what their results were up to the time of leaving. Thirdly, it compared its results to previous trials that either agreed with or contradicted its findings. Vollmer, et al\textsuperscript{8} had similar findings and is discussed in several editorials\textsuperscript{14,15} and reviews.\textsuperscript{7,11,13-16} The Birnbaum et al\textsuperscript{17} trial above, contradicted the findings.

The Paul et al\textsuperscript{5} trial had its weaknesses. Participants were not randomized. The participants were grouped solely by where they are in their disease progression, which can be seen in the demographic characteristics of the trial. This placed those participants that are further along in their disease progression into the INF-β group. The trial was not blinded, which may have impacted EDSS evaluations of the patients and the neurologist’s interpretation of the MRIs. This may not affect the outcomes by a large margin, since all participants were taking atorvastatin, but there is room for bias, which should be taken into consideration. Only one type of statin was used and only at one dosage. Statins have differing pharmacological properties,\textsuperscript{17} therefore their interactions with INF-β may vary. It is interesting that Paul et al found 80mg to not be harmful, when Birnbaum et al found 80mg to be more harmful than 40mg.

Finally, the duration and total number of participants were weaknesses. Trial two was larger than trial one, but it still only had 41 participants and was just a nine month study.

As to the efficacy of statins in treating RRMS, this trial suggests that they are effective. It is notable that there are different results from this trial compared to trial one. Why are the outcomes of these trials the exact opposite?
Trial two disclosed honoraria for several of the people conducting the trial from multiple sources, but no amounts were disclosed.

**Trial Three**

The Rudick et al\(^{18}\) trial was strong in places that other two trials are weak. It was conducted over a two year period and had a larger population of participants. The study was post hoc, but the original study was randomized. Although the placebo group contained 542 participants and the statin group contained 40, the groups were well matched at baseline for disease severity. Since, the statin group was taking various statins in different doses as prescribed by their personal physicians for cholesterol therapy, this helped in providing a more complete look at the effect of statins on INF-\(\beta\), but there was no real control over what type of statin was used or in what dose. Even though the original trial was randomized, the determination of which participants would take statins was not randomized.

As to the efficacy of statins in treating RRMS, this trial suggested that they are not effective.

Trial three did not list any disclosures.

**CONCLUSION**

The decision of how effective statins are as a DMD in the treatment of RRMS has not been resolved. There have been many advances contributing to the knowledge of the cellular and humoral immune responses and their relationship to MS. The use of statins to target elements of the immunological cascade could be advantageous over currently available drugs.\(^{13}\)
In response to the clinical question of this paper, these three studies have completely different answers. The sample sizes and duration of the trials can be large contributors to the disparities of the results, but the varying statin dosages and the assorted types of statins may also be contributors. Trial one used varying dosages of atorvastatin, trial two used only 80mg of atorvastatin, and trial three had varying dosages of assorted statins.

Financing and other limitations can also alter the trial. Avoiding bias from drug companies can lead to small trials with a short duration, but clinically, there is no substitute for a large, randomized controlled trial that takes 2-3 years.

When looking at the weaknesses of the trials, the conclusion would be a need for one or more trials that are based on the idea of the use of statins as a DMD in RRMS. These differing trials can provide a unique opportunity to setup a new trial.

The ultimate trial would have an extremely large sample size, with each arm having between 200 and 300 participants. It would need to be randomized and double blinded. The patients would also have to have an extensive inclusion and exclusion criteria. The patients would need to be at about the same place in their RRMS disease state. The Poser or MacDonald criteria, used in trial two, would be a good evaluation tool for the patient’s disease state determination.

Since MS is a cyclic relapse – remitting disease, a three to five year study would also be advantageous. RRMS patients have differing disease cycles. During short time duration trials, it is difficult to distinguish the cause of a patient’s relapse. Is the relapse due to an adverse reaction to the treatment being tested or is it due to their natural RRMS cycle?
There would be multiple arms in such a trial. One arm would be a true placebo group that received no treatments at all. This would help to determine what outcomes will possible occur in the natural progression of the RRMS patient. There would also need to be multiple arms at each of the statin types, and each of the statin dosages, with multiple arms for the INF-β. This would mean two arms per dose, per type of statin. There would be an arm for INF-β by itself, and one with each statin, at each dosage. Lastly, there would be an arm for each statin at each dose, without INF-β.

The outcomes would also need to be controlled. Since the ultimate goal is for clinical treatment of RRMS patients, the outcome should measure disease progression. The patient cares most about quality of life, therefore; the EDSS score is a good place to start. The next logical outcome would be number of relapses over the study’s duration. Relapses are one of the ways that patients determine progression of disease, and it is after a relapse that the patient’s disability baseline may shift. Finally CEL on MRI is a good outcome. Although this is not directly related to a relapse, the total number of CELs on MRI is a hallmark for future progression of MS.

There are more trials in progress that are attempting to address some of these issues. For example, the Orefice, G. et. al. trial is conducting a 2 year study with 20mg of atorvastatin in conjunction with INF-β that should be out sometime in 2010.20, 21 With the difficulties of the current DMDs for RRMS, the search for something safer and more affective will continue.
REFERENCES


Table 1 – Diagnostic description of the types of Multiple Sclerosis

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>Only a few attacks with little or no disability after 20 years</td>
</tr>
<tr>
<td>Primary – Progressive Multiple Sclerosis (PPMS)</td>
<td>Gradual, but steady accumulation of neurological deficits from onset</td>
</tr>
<tr>
<td>Secondary – Progressive Multiple Sclerosis (SPMS)</td>
<td>Progressive worsening of symptoms with or without superimposed relapses</td>
</tr>
<tr>
<td>Progressive – Relapsing Multiple Sclerosis (PRMS)</td>
<td>Progressive coarse from the onset, sometimes combined with occasional acute symptom flare-ups</td>
</tr>
<tr>
<td>Malignant or Fulminant Multiple Sclerosis</td>
<td>Rapidly progressive disease coarse</td>
</tr>
</tbody>
</table>
Table 2 – Summary of matrix

<table>
<thead>
<tr>
<th>Author/ Title/ Journal</th>
<th>Yr. pub</th>
<th>Patients/ Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome(s)</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birnbaum et al(^\text{13})</td>
<td>2008</td>
<td>Dx RRMS Adults, on standard high-dose subcutaneous interferon beta-1a</td>
<td>INF-B, 40mg or 80mg Atorvastatin</td>
<td>INF-B only</td>
<td>CEL on MRI only, Relapse only, and both</td>
<td>RCT</td>
</tr>
<tr>
<td>Paul et al(^3)</td>
<td>2008</td>
<td>DX RRMS Adults age 18-55, EDSS 0-6, at least one CEL on MRI</td>
<td>INF-B and 80mg of Atorvastatin</td>
<td>80mg Atorvastatin</td>
<td>EDSS and MSFC scores, CEL on MRI, CBC, electrolytes, creatinine, creatinine kinase, and lipids</td>
<td>baseline-to-treatment trial was designed to evaluate the safety, tolerability and efficacy of orally administered atorvastatin in patients with RRMS</td>
</tr>
<tr>
<td>Rudick et al(^\text{14})</td>
<td>2009</td>
<td>DX RRMS Adults taking IM IFN-B-1a</td>
<td>Statins</td>
<td>No statins</td>
<td>2-year endpoints, including cumulative probability of sustained disability progression as defined in the SENTINEL study(^4); rate of clinical relapse; number of new or enlarging T2-hyperintense lesions; and number of gadolinium-enhancing (Gd ) lesions.(^4)</td>
<td>post hoc analysis of data from the Safety and Efficacy of Natalizumab in Combination With IFN -1a in Patients With Relapsing-Remitting Multiple Sclerosis (SENTINEL) study</td>
</tr>
</tbody>
</table>
Table 3 – Poser criteria\textsuperscript{22} used to give a diagnostic level to MS

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically probable MS</td>
<td>• 2 attacks and clinical evidence of 1 lesion, or</td>
</tr>
<tr>
<td></td>
<td>• 1 attack and clinical evidence of 2 separate lesions, or</td>
</tr>
<tr>
<td></td>
<td>• 1 attack, clinical evidence of 1 lesion, and paraclinical evidence of another separate lesion</td>
</tr>
<tr>
<td>Laboratory supported probable MS</td>
<td>• 2 attacks and CSF abnormalities</td>
</tr>
<tr>
<td>Clinically definite MS</td>
<td>• 2 attacks and clinical evidence of 2 separate lesions, or</td>
</tr>
<tr>
<td></td>
<td>• 2 attacks, clinical evidence of one and paraclinical evidence of another separate lesion</td>
</tr>
<tr>
<td>Laboratory supported Definite MS</td>
<td>• 2 attacks, either clinical or paraclinical evidence of 1 lesion, and cerebrospinal fluid (CSF) immunologic abnormalities, or</td>
</tr>
<tr>
<td></td>
<td>• 1 attack, clinical evidence of 2 separate lesions &amp; CSF abnormalities, or</td>
</tr>
<tr>
<td></td>
<td>• 1 attack, clinical evidence of 1 and paraclinical evidence of another separate lesion, and CSF abnormalities</td>
</tr>
</tbody>
</table>
Table 4 – McDonald criteria\textsuperscript{23} used to give standards for making a diagnosis

<table>
<thead>
<tr>
<th>Relapses</th>
<th>Clinical Lesions</th>
<th>Additional requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or more</td>
<td>2 or more</td>
<td>None; clinical evidence will suffice (additional evidence desirable but must be consistent with MS)</td>
</tr>
<tr>
<td>2 or more</td>
<td>1</td>
<td>Dissemination in space, demonstrated by MRI, or a positive CSF and 2 or more MRI lesions consistent with MS, or further clinical attack involving different site</td>
</tr>
<tr>
<td>1</td>
<td>2 or more</td>
<td>Dissemination in time, demonstrated by MRI, or second clinical attack</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Dissemination in space by demonstrated by MRI, or positive CSF and 2 or more MRI lesions consistent with MS and Dissemination in time demonstrated by MRI, or second clinical attack</td>
</tr>
<tr>
<td>An insidious neurological progression suggestive of MS</td>
<td></td>
<td>Positive CSF and Dissemination in space demonstrated by MRI evidence of 9 or more T2 brain lesions, or 2 or more spinal cord lesions, or 4-8 brain and 1 spinal cord lesion, or positive visually evoked response (VEP) with 4-8 MRI lesions, or positive VEP with &lt;4 brain lesions plus 1 spinal cord lesion and Dissemination in time demonstrated by MRI, or continued progression for 1 year</td>
</tr>
</tbody>
</table>
### Table 5 – Expanded Disability Status Scale (EDSS) \(^\text{24}\)

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>Normal neurological exam.</td>
</tr>
<tr>
<td>1.0</td>
<td>No disability, but minimal signs in one functional system (FS) are present.</td>
</tr>
<tr>
<td>1.5</td>
<td>No disability, but minimal signs in more than one FS are present.</td>
</tr>
<tr>
<td>2.0</td>
<td>Minimal disability in one FS is present.</td>
</tr>
<tr>
<td>2.5</td>
<td>There is mild disability in one FS or minimal disability in two FS.</td>
</tr>
<tr>
<td>3.0</td>
<td>There is moderate disability in one FS or mild disability in three or four FS. However, the person is still fully ambulatory.</td>
</tr>
<tr>
<td>3.5</td>
<td>The person is fully ambulatory, but has moderate disability in one FS and mild disability in one or two FS; or moderate disability in two FS; or mild disability in five FS.</td>
</tr>
<tr>
<td>4.0</td>
<td>The person is fully ambulatory without aid, and is up and about most of the day (12 hours) despite relatively severe disability. He or she is able to walk 500 meters without aid or rest.</td>
</tr>
<tr>
<td>4.5</td>
<td>The person is fully ambulatory without aid, and is up and about much of day. He or she is able to work a full day, but may otherwise have some limitations of full activity or require minimal assistance. This is considered relatively severe disability. Able to walk 300 meters without aid.</td>
</tr>
<tr>
<td>5.0</td>
<td>The person is able to walk 200 meters without aid or rest. Disability impairs full daily activities, such as working a full day without special provisions.</td>
</tr>
<tr>
<td>5.5</td>
<td>The person is able to walk 100 meters without aid or rest. Disability precludes full daily activities.</td>
</tr>
<tr>
<td>6.0</td>
<td>The person needs intermittent or unilateral constant assistance (cane, crutch or brace) to walk 100 meters with or without resting.</td>
</tr>
<tr>
<td>6.5</td>
<td>The person needs constant bilateral support (cane, crutch or braces) to walk 20 meters without resting.</td>
</tr>
<tr>
<td>7.0</td>
<td>The person is unable to walk beyond five meters even with aid, and is essentially restricted to a wheelchair. However, he or she wheels self and transfers alone, and is active in wheelchair about 12 hours a day.</td>
</tr>
<tr>
<td>7.5</td>
<td>The person is unable to take more than a few steps and is restricted to wheelchair, and may need aid to transfer. He or she wheels self, but may require a motorized chair for a full day's activities.</td>
</tr>
<tr>
<td>8.0</td>
<td>The person is essentially restricted to bed, a chair or a wheelchair, but may be out of bed much of day. He or she retains self care functions and has generally effective use of arms.</td>
</tr>
<tr>
<td>8.5</td>
<td>The person is essentially restricted to bed much of day, but has some effective use of arms and retains some self care functions.</td>
</tr>
<tr>
<td>9.0</td>
<td>The person is confined to bed, but still able to communicate and eat.</td>
</tr>
<tr>
<td>9.5</td>
<td>The person is totally helpless and bedridden and is unable to communicate effectively or eat and swallow.</td>
</tr>
<tr>
<td>10.0</td>
<td>Death due to MS.</td>
</tr>
</tbody>
</table>