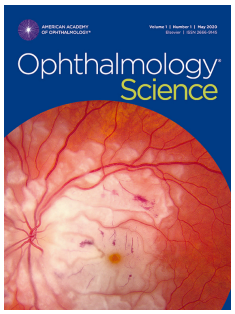

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Can simvastatin reduce the need for immunomodulatory drugs to treat uveitis? A prospective, randomized, placebo-controlled trial

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Abstract

Objective: To assess the efficacy of simvastatin 80mg/day versus placebo in patients with non-infectious non-anterior uveitis receiving prednisolone ≥10mg/day.

Design: Randomized, double-masked, controlled trial

Subjects: Adult patients with non-infectious non-anterior uveitis on oral prednisolone dose of ≥10 mg/day.

Methods: Patients were randomly assigned at a 1:1 ratio to receive either simvastatin 80mg/day or placebo. 32 patients were enrolled (16 in each arm) all of whom completed the primary endpoint and 21 reached the two-year visit (secondary end points).

Main outcome measures: The primary endpoint was mean reduction in the daily prednisolone dose at 12 months follow-up. Secondary end points were mean reduction in prednisolone dose at 24 months, percent of patients with a reduction in second-line immunomodulatory agents, time to disease relapse and adverse events.

Results: Our results show that simvastatin 80mg/day did not have a significant corticosteroid-sparing effect at 12 months (estimate: 3.62, 95% CI: -8.15 to 15.38; p=0.54). There was no significant difference between the groups with regards to prednisolone dose or change in dose at 12 and 24 months. There was no difference between the two groups in percent of patients with reduction in second-line agent by 24 months. Among patients who achieved disease quiescence the median time to first relapse was longer for those receiving simvastatin (8.7 months, 95% CI 3.2-14.19) than placebo (3.2 months, 95% CI 0.17-6.23), though this was not statistically significant. There was no significant difference in adverse events or serious adverse events between the two groups.

Conclusions: Simvastatin 80mg/day did not have an effect on the dose reduction of corticosteroids nor conventional immunomodulatory drugs at one and two years. The results suggest that it may extend the time to disease relapse among those that achieve disease quiescence.

Systemic corticosteroids represent the mainstay treatment for patients with uveitis, particularly those with systemic involvement or bilateral disease. While treatment is very effective in controlling the intra-ocular inflammation, long-term systemic side effects limit their use, so that ophthalmologists continually aim to reduce the dose to ≤10mg/d.[1] To achieve this, other immunomodulatory agents can be added to enhance and maintain inflammatory control. While they are effective in the majority of cases,[2-5] they are not without their own risks of complications and can affect hepatic, renal and gastrointestinal function, as well as increase the risk for opportunistic infections.

Statins are routinely prescribed to reduce serum cholesterol levels and improve clinical outcomes in patients with cardiovascular diseases. They are considered an effective treatment with a low risk of systemic side effects, primarily myalgia and rhabdomyolysis. Studies have shown that they also have pleiotropic immunomodulatory effects, both *in vitro* and *in vivo*.[6] In animal models of uveoretinitis statins reduced the clinical and histological scores of inflammation and inhibited T lymphocyte recruitment into the retina.[7] Two large observational population-based studies also showed a protective effect of statins against the development of uveitis.[8 9] Clinical studies in multiple sclerosis patients showed a positive effect from simvastatin on brain atrophy, suggesting these drugs cross the blood-brain barrier and can play a role in controlling disease activity.[10] In rheumatoid arthritis, statins led to improvement in disease activity scores and reduced the numbers of tender and swollen joints.[11] A study on the effect of statins among patients with sarcoidosis, demonstrated an increased time to disease flare among patients with mild-moderate disease.[12] Given the relatively safe side effect profile of statins, they would be a suitable treatment option for patients with uveitis, as well as reducing serum cholesterol levels and improving the cardiovascular outcomes in patients on long-term corticosteroid therapy.

The aim of this study was to prospectively examine in a randomized double masked clinical trial the additional anti-inflammatory effect and safety of simvastatin in patients with uveitis and to determine if their addition could reduce the amount of corticosteroid or number/ dose of additional immunomodulatory agents required to keep the uveitis controlled.

Methods

This study was a prospective, randomized, placebo-controlled, double-masked clinical trial in patients with intermediate, posterior and panuveitis who required systemic prednisolone at 10mg/day or above to control their intraocular inflammation with or without the addition of a 2nd-line immunomodulatory agent. The study was conducted at Moorfields Eye Hospital, London, UK, and subjects were selected from patients treated in the uveitis service. The study was approved by the regional ethics committee (REC reference: 15/LO/0084) and adhered to the Tenants of the Declaration of Helsinki (Protocol number: 14/0172; EudraCT number: 2014-003119-13; IRAS project ID: 156966). All participating patients were included after providing written informed consent. Patients were included if they were between the ages of 18-80; were diagnosed with non-infectious intermediate, posterior or panuveitis; were treated with a dose of prednisolone greater than 10mg/day with or without a 2nd-line immunosuppression agent. Patients of both genders were included, though premenopausal female patients were required to use two methods of contraception. For exclusion criteria see table S1.

The study was designed to compare the effect of simvastatin 80mg once daily versus placebo on prednisolone dose at 12 months follow-up. The primary outcome measure was the change in prednisolone dose at 12 months. Secondary outcomes included: mean change in prednisolone dose at 24 months; change in percent of patients requiring 2nd-line immunosuppression at 24 months; rate of disease relapses at 24 months; blood cholesterol and lipids levels at 24 months; safety of simvastatin.

Patients were assigned randomly using a blocked randomization method to ensure balanced sample sizes. Patients were randomly allocated using an online system to receive either simvastatin or placebo (1:1). A total of 32 patients (16 in each arm) were randomized (Figure S1). For all patients prednisolone and 2nd-line immunosuppression doses were decided based on clinical findings and disease activity at each study visit. When inflammation was found to be inactive, prednisolone dose was reduced using a weekly reduction regimen down to <10mg/d. Prednisolone reduction regimen followed accepted clinical practices, for doses between 60-30mg/day a weekly reduction of 10mg, between 30-15mg/day a weekly reduction of 5mg and <15mg/day a weekly reduction of 2.5mg.[13] Once a

prednisolone dose <10mg/d was achieved, 2nd-line immunosuppression was reduced in monthly decrements until stopped. All patients were followed-up in the trial every three months for 12 months, although seen routinely as required, and 21 completed 24 months follow-up.

At each study visit patients had their vital signs checked, full ophthalmic assessment including visual acuity, intraocular pressure, slit lamp examination with dilated biomicroscopic fundal examination. The level of inflammatory activity was assessed against the SUN criteria,[14] and a macular optical coherence tomography scan (Heidelberg Spectralis, Heidelberg Engineering inc., Germany) was performed. Blood tests were taken including full blood count, serum lipids, creatinine kinase (CK) enzyme, liver and kidney function tests and pregnancy tests for females of childbearing potential. At each trial visit a review of concomitant medications and compliance with trial drug administration was done, as well as recording any adverse reactions. Disease quiescence was defined as a follow-up visit where no intra-ocular inflammation was noted. Disease relapse was defined as a subsequent recurrence of intraocular inflammation requiring any increase or addition of immunosuppression treatment.

Statistical analysis

The sample size of 32 patients (16 per arm) was calculated to detect a difference of 2.5 mg between arms in terms of the primary outcome, prednisolone reduction after 12 months, assuming a standard deviation of 2.5mg, 5% statistical significance and 80% power. To allow for a possible 10% dropout, the sample size was increased to 36 patients.

The full analysis population included all subjects who met the study eligibility criteria and were subsequently randomized to one of the two groups. Continuous variables were summarized using either mean (SD) or median (interquartile range) as appropriate. Normality was assessed using normal probability plots. Categorical variables were summarized by number (percentage).

The primary analysis estimates the difference in mean prednisolone dose at 12 months between patients randomized to simvastatin and placebo using a linear regression model that adjusts for baseline prednisolone dose (ANCOVA analysis).

Patients were analysed according to the groups to which they had been randomized (intention to treat).

Use of 2nd-line immunosuppression at 24 months was analysed using a chi-squared test, as was the number of disease relapses by 24 months. Time to first relapse was estimated using the Kaplan-Meier estimator and differences between the groups were compared using the log-rank test. Blood cholesterol and lipids at 24 months were analysed descriptively.

Results

The study included 35 patients who were assessed for eligibility, of which 32 were randomized to receive either simvastatin 80mg daily or placebo (Figure S1). Two patients were found not to be eligible and a third passed away (due to an unrelated cause). The first subject was recruited in September 2015 and the final trial visit was in July 2018. All patients completed the primary outcome at 12 months and 21 patients completed the 24 months follow-up visit. The baseline demographic data were comparable between the two groups (Table 2). Average (±SD) age at baseline was 44.4±7.8 years for the simvastatin group and 48.3±11.2 years for the placebo group. Average dose of prednisolone at baseline was 15.0±8.7mg for the simvastatin group and 16.7±9.5mg for the placebo group (Table 3).

All patients were included in the primary analysis. The mean difference of oral prednisolone from baseline was calculated for the placebo and simvastatin groups (Table 3). There was a trend of reduction in daily oral prednisolone dose in the simvastatin group, but it was not significant. The mean prednisolone dose at 12 months was 16.2±19.6mg/day for patients in simvastatin group and 12.4±11.2mg/day for patients in placebo group (Table 3, Figure 2). At 12 months there was no difference in the mean change in prednisolone dose between the two groups (delta change between simvastatin and placebo groups was 3.62mg, 95% CI: -8.15 to 15.38, p=0.54). There was an increase in the percentage of patients requiring a prednisolone dose <10mg/day with 50% (n=8) of patients in the simvastatin group and 37.5% (n=6) of those in the placebo group. By 24 months there was no difference in the change in prednisolone dose with an average of

7.7±6.2mg/day and 7.8±2.5mg/day for the simvastatin and placebo groups, respectively (delta change between simvastatin and placebo groups was -0.34mg, 95% CI: -4.71 to 4.03, p=0.87). The percentage of patients using a prednisolone dose <10mg/day was 45.5% (n=5) of patients in the simvastatin group and 50% (n=5) of those in the placebo group. There was no difference in the time to reach a prednisolone dose <10mg/day and the median was 52 weeks (95% CI 12-66) and 26 weeks (95%CI 12-∞) for the simvastatin and placebo groups respectively (p=0.62).

At baseline 12 patients were receiving a 2nd-line agent in addition to prednisolone, 6 in the simvastatin group and 6 in the placebo group. Of these 10 were using mycophenolate mofetil and 2 methotrexate. By 24 months there was no difference in the percent of patients able to reduce or stop their 2nd-line agent treatment with 33.3% in the simvastatin group and 50% in the placebo group (p=0.56).

Disease activity

Disease activity scores at each study visit were analysed for all patients. At baseline 6 (37.5%) patients in the placebo group and 8 patients (50%) in the simvastatin group had active disease (Figure 3). By three months the number of patients with active disease increased to 9 patients (56.3%) in the placebo group and decreased to 7 patients (43.8%) in the simvastatin group. This remained steady throughout follow-up and by 12 months 10 patients (62.5%) in the placebo group and 9 patients (56.3%) in the simvastatin group had active disease. At 24 months there was disease activity data regarding 21 patients (11 in the simvastatin group and 10 in the placebo group). The proportion of patients who had active disease was higher, but not significantly, in the simvastatin group (5/11, 45.5%) compared to the placebo group (1/10, 10%, p=0.07).

By 24 months, disease quiescence was noted for 31 patients and relapse had occurred in 26 cases (13 patients in each group), with a median time to relapse of 6 months (95% CI 2.11-9.89). Median time to relapse for the placebo group was 14 weeks (95% CI 12-52) compared to 38 weeks (95% CI 14-54) for the simvastatin group (Figure 4). Although the time to first relapse was longer in the simvastatin group, it was not significant.

Safety of simvastatin

Simvastatin was safe and was well tolerated by most patients. Table 4 describes the change in blood cholesterol and lipid levels from baseline to 24 months. In the simvastatin group there was a reduction in total cholesterol levels from 5.29±1.01mmol/L to 4.56±1.48mmol/L. In the placebo group the cholesterol levels remained stable from 5.59±1.08mmol/L to 5.42±0.77 mmol/L, though there was no significant difference between the groups in the average change in cholesterol levels.

There was no difference in the reduction in low-density lipoproteins (LDL) between the groups (p=0.25) or any significant difference in the change in high-density lipoprotein (HDL) levels. Creatinine kinase levels were measured at each follow-up visit and average levels at baseline were 128.632±78.88Umol/L for the simvastatin group and 136.38±100.16Umol/L for the placebo group. By 24 months there was no significant difference in the change in average CK level between the simvastatin (221.7±198.21Umol/L) and placebo groups (130.43±74.0Umol/L, p=0.25). Similarly, there was no significant difference in liver enzyme levels s between the two groups.

There was a total of 127 adverse events recorded throughout the trial, 51 in the placebo group and 76 in simvastatin group: Among these 5 were serious adverse events, and those were not related to the trial investigational medicinal product. In the placebo group, two sickle cell crises occurred, and the last attack ended in the death of that patient. In the simvastatin group, two serious adverse events were reported, and both were unrelated elective surgeries. During the trial one patient reported she had become pregnant and was immediately removed from the trial. Her information was unblinded and she was found to have received the placebo. She was continually followed and delivered a healthy chid. Myalgia and arthralgia were reported 11 times in the placebo group and 22 times in the simvastatin group, these were mild and transient and none of the patients had to stop their trial medication or withdraw from the trial.

Discussion

This study aimed to examine the safety and efficacy of adding simvastatin 80mg/d to the systemic immunosuppression treatment of patients with non-infectious intermediate, posterior and panuveitis. At 12 months follow-up there was no significant cortico-steroid sparing effect compared to placebo. Furthermore, there was no significant difference in the use of 2nd-line immunosuppression drugs or the rate of disease quiescence, though there was a trend towards an extended time to disease relapse among patient in the simvastatin group. Simvastatin was well tolerated and resulted in a significant reduction in total cholesterol and LDL levels.

Studies using *in vitro* models and animal models suggest that statins modulate the immune system through alterations in cell surface molecules, cellular interactions, signalling proteins and nuclear factor expression and function [15]. The immunomodulatory effect of statins is exerted either directly on cells, such as interfering with T lymphocyte proliferation [16, 17], inhibiting the expression of co-stimulatory molecules CD80 and CD86 on B cells [18], or through inhibition of cellular interactions and signalling molecules such as tumour necrosis factor α (TNF-α) [19], a potent pro-inflammatory cytokine that induces apoptosis of retinal cells [20]. By influencing the cytokine balance from pro-inflammatory to anti-inflammatory, statins modulate the immune response and achieve an immunomodulatory effect [18 21]. Additionally, statins block the intercellular adhesion molecule 1 (ICAM1) pathway which is responsible for the interaction between the vascular endothelium and lymphocytes, therefore statins interfere with transvascular migration of lymphocytes [22], thereby reducing the number of lymphocytes reaching the sites of inflammation.

Previous studies reported on the immunomodulatory effect of statins in uveitis. In a retrospective population-based study, the use of statins was found to have a protective effect on uveitis development, throughout two years [8]. The study identified 108 incident cases of uveitis with an incidence of 19% among statin users, compared to 30% in patients not treated with statins. Shirinsky et al. randomized fifty patients with non-infectious uveitis to receive conventional immunomodulatory treatment with or without the addition of simvastatin 40mg for two months.[23] While the study was open-labelled, they found the addition of simvastatin resulted in significantly lower

anterior chamber inflammation and visual acuity, with no serious systemic adverse events. Another study also reported a twofold reduction in the risk of ocular inflammatory disease in male patients who used statins, compared to a control group, over five years [9]. Although these findings did not reach statistical significance, the risk reduction was higher with longer duration of statin use. While these were not randomized, blinded, controlled trials and had a variably short follow-up, they were able to demonstrate at least a short term effect on reducing the dose of concomitant systemic corticosteroids. In our study we were also able to show that up to nine months of follow-up there was a trend towards a reduction in systemic corticosteroids, though it was not demonstrated at the 12 months primary endpoint. Furthermore, despite choosing a very small difference in treatment effect (a 2.5mg difference in daily dose) the lack of a significant difference between the two treatment arms does not support a clear advantage for this treatment. It is possible that this result reflects a moderate immunomodulatory effect for simvastatin that does not result in a sustained impact compared to that of systemic corticosteroids. This study was limited by including active patients already receiving systemic corticosteroids and 2nd-line immunosuppression. Their robust effect may have overshadowed that of simvastatin and the primary outcome. A larger sample size or a different primary outcome, such as a dichotomous outcome (percent of patients achieving a daily dose below 10mg/day), may have demonstrated a clearer result. Alternatively, the isolated effect of simvastatin could be explored on time to relapse among quiescent patients receiving no treatment. Our results do offer some support for quiescence maintaining role, as seen in the extended time to relapse seen in our study.

Systemic immunosuppression with corticosteroids in uveitis is known to increase patient's risk of cardiovascular disease [24-26]. Patients with chronic ocular inflammatory disease taking systemic immunosuppression are also at risk of developing cardiovascular diseases (CVD). Given the long-term exposure to corticosteroids and second-line immunomodulatory agents required in patients with sight threatening uveitis, this would warrant treatment to reduce high serum cholesterol particularly LDL and minimise the risk of CVD. In our study, the mean total cholesterol was higher than normal, with 60% of patients having high serum

cholesterol at baseline. Simvastatin reduced total cholesterol and LDL, which supports the well-established action of simvastatin on serum lipids, adding an additional indication to treatment in such patients who are expected to continue using corticosteroids and immunosuppression drugs for many years.

While the results of this study were unable to support the use of simvastatin 80mg/day as a significant immunomodulatory agent, the results offer support for its role as an adjunctive treatment, potentiating the effect of other agents in prolonging the time to relapse and protecting patients for some of the systemic side effects linked to long term corticosteroid use. This study supports the safety of simvastatin in uveitis patients and its role in maintaining quiescent disease.

Acknowledgements

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Figure Legends

Figure 2- Mean dose of prednisolone for simvastatin and placebo groups from baseline up to 12 months with 95% confidence intervals.

Figure 3- Portion of patients with active disease for simvastatin (A) and placebo (B) groups at baseline up to 12 months

Figure 4- Survival to first relapse for simvastatin and placebo groups.

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Table 2- Baseline demographics for patients in simvastatin and placebo groups

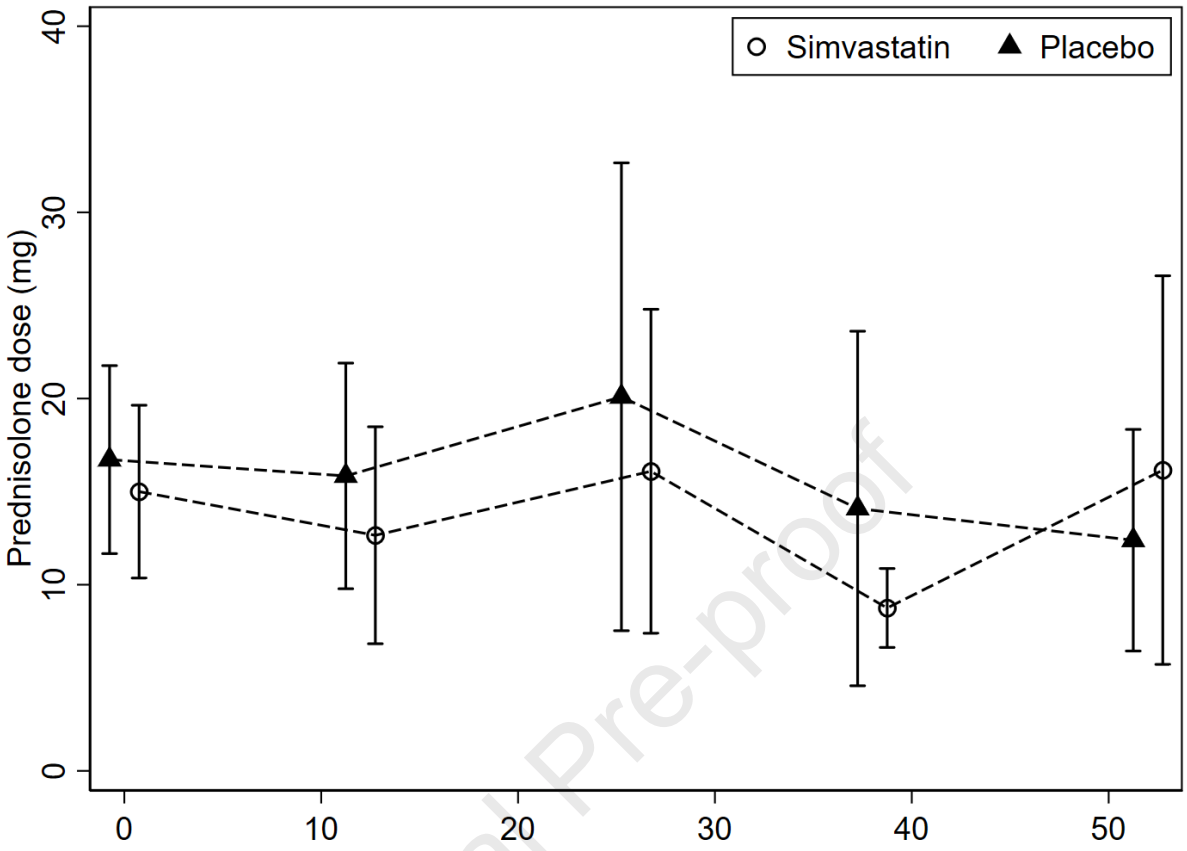
Baseline criteria	Simvastatin	Placebo	P-Value
Age (yrs)	44.4±7.8	48.3±11.2	0.264
Female gender, n (%)	10 (62.5)	10 (62.5)	1.000
Duration of uveitis,(yrs)	6.8±4.7	10.8±9.3	0.135
Bilateral disease, n (%)	13 (81.3)	15 (91.8)	0.600
Anatomical location, n (%)			
Intermediate uveitis	8 (50)	6 (37.5)	
Posterior uveitis	3 (18.8)	3 (18.8)	0.894
Panuveitis	5 (31.3)	7 (43.8)	
Associated systemic disease, n (%)	7 (43.8)	3 (18.8)	0.127
Prednisolone Dose (mg)	15±8.7	16.7±9.5	0.505

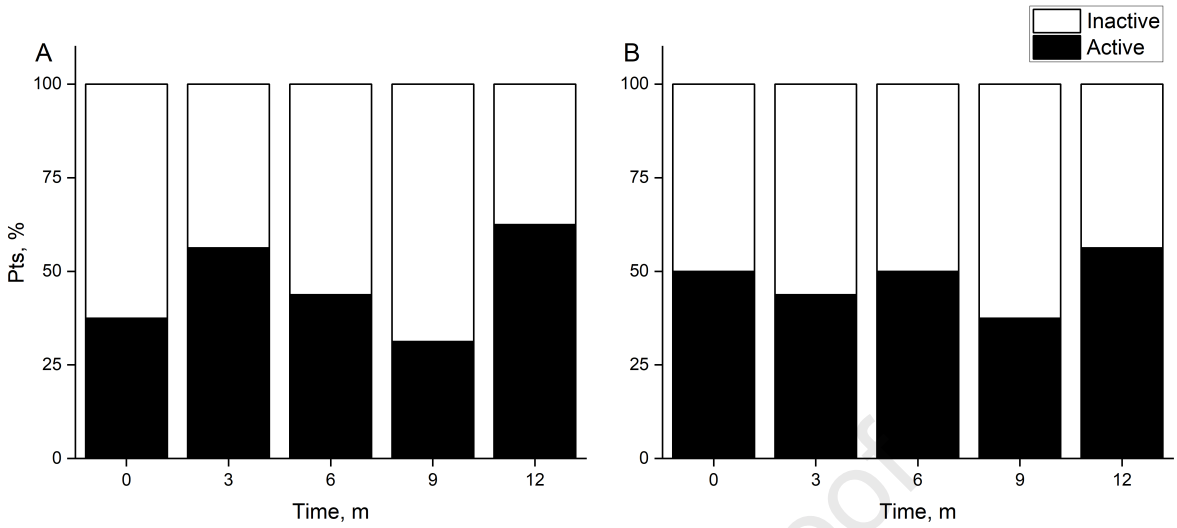
Table 3- Prednisolone dose for patients in simvastatin and placebo groups from baseline up to 12 months

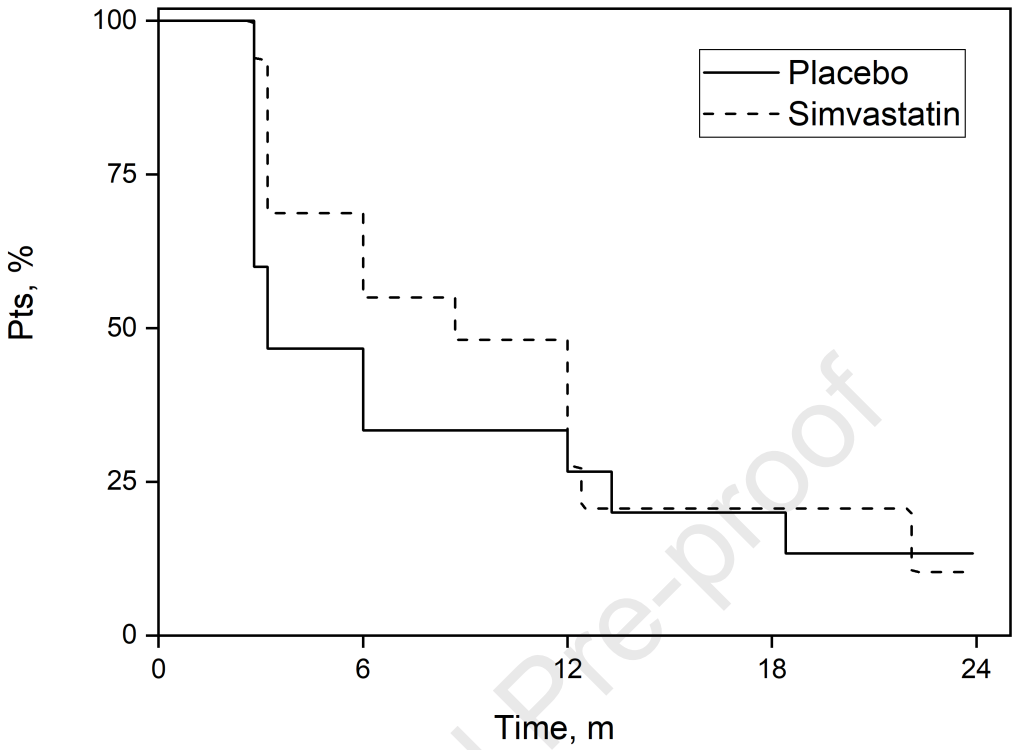
	Prednisolone dose, mg, mean±SD		Patients with prednisolone <10mg/day, n(%)	
Week	Simvastatin	Placebo	Simvastatin	Placebo
0	15±8.7	16.7±9.5	0	0
12	12.7±10.9	15.8±11.4	7 (43.8)	6 (37.5)
26	16.1±16.3	20.1±23.6	6 (37.5)	6 (37.5)
38	8.8±4.0	14.1±17.9	6 (37.5)	7 (43.8)
52	16.2±19.6	12.4±11.2	8 (50)	6 (37.5)

Table 4- Blood tests for patients in simvastatin and placebo groups for baseline and 24 months

	Baseline, mean±SD		24 months, mean±SD		**P**
	Simvastatin	Placebo	Simvastatin	Placebo	
RBG, mmol/L	6.68±3.39	5.25±1.09	5.29±1.12	5.71±2.94	0.400
HbA1c, mmol/mmol (%)	6.21±1.77	5.76±0.33	6.16±1.06	5.63±0.41	0.504
Total cholesterol, mmol/L	5.29±1.01	5.59±1.08	4.56±1.48	5.42±0.77	0.172
LDL, mmol/L	2.88±0.68	3.07±0.75	2.14±1.31	2.63±0.86	0.253
HDL, mmol/L	1.76±0.62	1.89±0.61	1.7±0.67	1.84±0.64	0.713
Triglyceride, mmol/L	1.42±0.53	1.4±0.58	1.59±1.01	2.15±0.9	0.278
Creatinine kinase, umol/L	128.63±78.88	136.38±100.16	221.7±198.21	130.43±74.0	0.246







Treatment of patients with non-infectious non-anterior uveitis with simvastatin 80mg/d did not influence the dose of corticosteroids or conventional immunomodulatory drugs at twelve or twenty-four months. Time to first relapse was extended among quiescent patients.