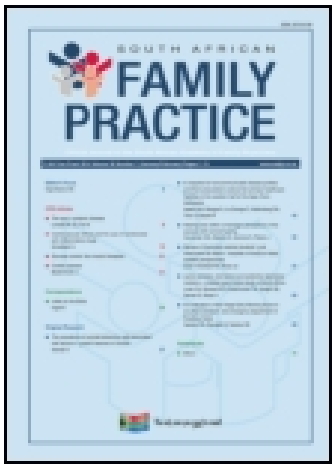

South African Family Practice
Publication details, including instructions for authors and subscription information:
http://medpharm.tandfonline.com/loi/ojfp20

The anti-inflammatory properties of simvastatin can benefit statin-naïve rheumatoid arthritis patients with associated risks for cardiovascular disease

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Published online: 16 Feb 2015.

To cite this article: AO Komolafe, MMTM Ally, JJ Van Tonder & OBW Greeff (2015) The anti-inflammatory properties of simvastatin can benefit statin-naïve rheumatoid arthritis patients with associated risks for cardiovascular disease, South African Family Practice, 57:1, 28-30, DOI: 10.1080/20786190.2014.995919

To link to this article: http://dx.doi.org/10.1080/20786190.2014.995919

South African Family Practice 2015; 57(1):28–30
http://dx.doi.org/10.1080/20786190.2014.995919

S Afr Fam Pract
ISSN 2078-6190 EISSN 2078-6204

RESEARCH

The anti-inflammatory properties of simvastatin can benefit statin-naïve rheumatoid arthritis patients with associated risks for cardiovascular disease

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Background: The anti-inflammatory properties of statins are well documented. The aim of this study was to determine if statins may offer therapeutic benefits in rheumatoid arthritis (RA) patients that are also at risk for cardiovascular disease.
Methods: Patients with moderately active RA, despite being on maximum disease-modifying anti-rheumatic drugs (DMARDs) therapy, and that were at risk for cardiovascular disease, were screened for inclusion. Eligible patients were randomised into two groups. In this open-label, cross-over design patients in group 1 received simvastatin treatment (20 mg/day) for a period of 3 months in addition to their usual DMARDs, after which they stopped simvastatin treatment and were followed up for a further 3 months while on their usual DMARDs only. Those in group 2 were allowed to continue on their usual DMARDs without simvastatin treatment for the first 3 months of the study, after which they received 20 mg/day simvastatin for a period of 3 months in addition to their usual DMARDs.
Results: The addition of 20 mg simvastatin to conventional DMARDs produced significant improvements in all of the evaluated parameters. These include significant improvements in DAS28 score, tender joint count, swollen joint count, CRP levels and ESR, while patients were receiving simvastatin treatment.
Conclusions: The addition of 20 mg simvastatin to conventional DMARDs in statin-naïve RA patients at risk for cardiovascular disease may add benefit, apart from modifying lipid profiles, by modulating immune function and suppressing disease activity.

Keywords: anti-inflammatory, cardiovascular disease, disease-modifying anti-rheumatic drugs (DMARDs), rheumatoid arthritis, statins

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory polyarthritis, affecting at least 1% of the world's population and 2% to 3% of people over the age of 60 years.[1] It is one of the most debilitating diseases that is associated with marked local and systemic inflammation. The mortality rate in RA patients is higher, compared with normal healthy individuals, as is the incidence of cardiovascular and other systemic complications.[2] Advances in the field of molecular biology allowed for the development of more efficacious drugs for the treatment of RA. Despite these innovations, optimal disease control and prevention of disease progression remains difficult in many patients. As a consequence, characteristic RA complications like reduced life expectancy and poor long-term prognosis persist.[3] The biologic and non-biologic disease-modifying therapies that are currently available sometimes yield limited responses and occasionally fail to induce any remission of the disease.[2] Hence the continued search for alternative treatment strategies that may improve patients' outcomes.

Non-biologic forms of treatment that are still being investigated include the use of statins as an adjunct therapy due to their reported anti-inflammatory and immunomodulatory properties. The majority of these properties may be independent of the lipid-lowering effects of statins and are thought to be the result of interrupted inflammatory signalling pathways. Amongst other effects, *in vitro* experiments have demonstrated that statins curb the secretion of pro-inflammatory cytokines like IL-6, IL-8[4] and IFN-γ[5], as well as inhibit T cell proliferation and activation.[6,7]

Statins can serve a dual purpose in view of their documented anti-inflammatory effect and long-established lipid lowering effect in RA patients with associated risks for cardiovascular disease.[8] Such a dual effect has been hypothesised for statins in systemic lupus erythematosus, another multisystem autoimmune disease associated with accelerated atherosclerosis.[9] Recent clinical studies have shown that statin use in patients with RA help in reducing disease activity score and swollen joint count in addition to lowering cardiovascular risk. These improvements in disease activity and swollen joint count are accompanied by some improvement in plasma markers of inflammation, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).[10] Increasing evidence of the anti-inflammatory effect of statins warrants further research exploring the potential of these agents in the management of RA, a chronic disease marked by high levels of inflammation. This study investigated the effect of statin therapy on some clinical outcomes of rheumatoid arthritis in a South African population of patients with associated risks for cardiovascular disease, using simvastatin as the investigational product.

Methods and procedures

An open-label, randomised, controlled, cross-over study was conducted. Participation in the study was voluntary and all participants provided informed consent. Ethical approval was granted by the University of Pretoria, Faculty of Health Sciences Research Ethics Committee (Protocol No. 129/2011) prior to commencement of the study. The study was conducted according to ICH GCP, SA GCP and the Declaration of Helsinki for medical research involving human subjects.

Patients with moderately active RA despite being on maximum DMARD therapy and having associated cardiovascular risks were screened at the Rheumatology Clinic of Steve Biko Academic Hospital. Eligible patients were randomised into two groups and each patient was seen over three visits at the Rheumatology

Clinic of Steve Biko Academic Hospital. Patients in the first group received simvastatin treatment (20 mg/day) for a period of 3 months in addition to their usual DMARDs, after which they stopped simvastatin treatment and were followed up for 3 months while receiving DMARDs only. Patients in the second group were allowed to continue on their usual DMARDs without simvastatin treatment for a period of 3 months, after which they received simvastatin (20 mg/day) for a period of 3 months in addition to their usual DMARDs. The anti-inflammatory effect of simvastatin was assessed by monitoring the inflammatory variables, ESR and CRP. The effect of statin therapy on clinical outcomes was evaluated through joint counts and disease activity scores. Assessment of the rheumatoid arthritis disease activity was done at each visit of the study by an independent joint assessor who is a physician at the Rheumatology Clinic of Steve Biko Academic Hospital. Blood samples were collected at each visit for analysis.

Statistical analysis

Observations from the two arms of the cross-over design were pooled according to treatment, i.e. with or without statin therapy. Results are reported in terms of the median and range. The sample size (n = 12) restricted statistical analyses to non-parametric techniques. The primary endpoint, change in DAS28 score, as well as all secondary endpoints were evaluated using Wilcoxon signed rank tests for paired samples to compare groups. A p-value of < 0.05 was considered statistically significant.

Results

A total of 27 patients with rheumatoid arthritis were screened, of whom 12 with risks for cardiovascular disease were eligible and randomised into the two arms of the study. There were three men and nine women with a median age of 59 years (range 40–72) enrolled in the study. The median duration after the diagnosis of RA was 5 years (range 1–27). Ten (83.3%) of the patients had positive rheumatoid factor status and two (16.7%) had sero-negative RA. All the patients had received at least two DMARDs, including methotrexate (n = 12), chloroquine (n = 7), sulfasalazine (n = 4) and leflunomide (n = 2). Of the 12 enrolled patients, 10 were on corticosteroid pharmacotherapy (prednisone).

The primary endpoint, DAS28 score, was significantly reduced when simvastatin was included in the patient treatment regime (Table 1). All of the secondary endpoints also improved during periods when patients received simvastatin. Of the discrete variables, both swollen joint count and tender joint count improved significantly. The same trend was observed with the serum markers of inflammation, CRP and ESR, which decreased significantly while patients were on statin therapy, compared with when they were not.

Discussion

Despite improved control of inflammation, cardiovascular risk among the RA patient population remains high. This increased prevalence of cardiovascular risk in RA patients was also observed in this study, with 44.4% of the RA patients screened for the study having associated risks for cardiovascular disease, which qualified them for inclusion in the study. The observed prevalence from the present study is supported by a comprehensive meta-analysis of published mortality studies of patients with RA, which showed a 50% increased risk of cardiovascular death in RA, when compared with the general population.[11] These figures indicate that a high number of RA patients would be eligible for this treatment regime because a large proportion of RA patients are expected to have associated cardiovascular risks that would justify statin therapy.

In this study, there was a marked improvement in disease activity in patients with rheumatoid arthritis presenting with moderately active disease, despite existing DMARD therapy. The primary endpoint of this study was change in the DAS28 disease activity score. Generally utilised because of its practical ease and good correlation with scores that consider far more joints, like the 66/68 joint count, the DAS28 is an excellent tool for tracking disease progression and to discriminate between patients with high and low disease activity.[12] It is postulated that serial measurements of DAS28 may be used to predict physical disability and radiographic disease progression.[13] The statistically significant improvement in DAS28 score observed forms the most conclusive evidence from the present study that indicate an improvement of diseased state of patients while they received statin therapy in addition to their routine pharmacotherapy. This evidence is supported by statistically significant improvements in both swollen and tender joint counts while participants were on simvastatin co-therapy. These observations are corroborated by previous reports with similar findings.[14] Joint counts are the most characteristic features of RA. They are directly related to disease severity and current disease activity, which is why these measures comprise the major contributors to disease activity scores.[13] It is therefore essential that any new treatment regime intended to improve clinical outcomes of RA bring about significant reductions in swollen and tender joint counts, since these are the types of measures that can make a difference to patients, subjectively, in contrast to other measures like CRP and ESR.

High-grade systemic inflammation and its interplay with traditional CV risk factors appear to play a major role in increased mortality observed in RA.[15] Evidence of improvements in clinical outcomes described above is further supported by a significant reduction in CRP, a serum marker of systemic inflammation. Similar results have been reported by other researchers.[14] A significant reduction was also observed with ESR, a non-specific

Table 1: Observed disease activity and inflammatory outcomes in patients receiving/not receiving simvastatin in addition to their current RA pharmacotherapy

Outcome	Without simvastatin		With simvastatin		*p*-value*
	Median	Range	Median	Range	
DAS28 score	5.25	3.76–6.21	4.16	2.67–6.02	< 0.01
Swollen joint count	5.25	5–14	3	1–8	< 0.01
Tender joint count	5	2–9	2	1–9	< 0.05
CRP (mg/l)	8.75	1.9–69.5	6.55	1–30	< 0.05
ESR (mm/h)	38	10–108	34	4–80	< 0.05

*Values based on Wilcoxon signed rank tests, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate

marker of inflammation. Together these observations provide functional evidence of change at a systemic level. The exact mechanism of immunomodulation is beyond the scope of this study, but results from the present study aligns with previous reports that statin therapy reduces systemic markers of inflammation.[16]

The significant reduction in DAS28 score, as well as supportive evidence from secondary endpoints, suggest that statins may offer therapeutic benefit to RA patients with associated risks for cardiovascular disease. Results from the present study is supported by previous studies that reported that the addition of simvastatin to conventional immunosuppressive therapies improved clinical, biological, and immunological parameters in RA patients.[14,17–19]

One limitation of the study was the small number of participants, which necessitated the cross-over design. A drawback of this study design is the possibility of therapeutic carry-over between treatment periods. But, even with the possibility of elevated background noise, parameters were still found to be significantly improved. Another limitation was the open-label design, which may have biased participants/investigators who were involved in the trial.

Conclusion

The influence of statins on immune mechanisms is well-established from *in vitro* studies and *in vivo* models of autoimmune disorders. Their ability to switch Th1 to Th2-type response, to support regulatory T-lymphocyte activity, and to inhibit Th17 cell functions together with concomitant inhibition of plethora of effector immune mechanisms, independent on lipid-lowering effects, justify the attempt of their potential implementation in the treatment of autoimmune diseases such as RA.[20] Previous clinical studies have reported favourable results in this regard.[14,17–19]

In the present study simvastatin treatment reduced DAS28 score, swollen joint count, tender joint count and serum CRP levels, as well as ESR. In conclusion, the addition of 20 mg simvastatin to conventional DMARDs in statin-naïve RA patients at risk for cardiovascular disease may add benefit, apart from modifying lipid profiles, by modulating immune function and suppressing disease activity.

Acknowledgements — This research was funded by the Department of Pharmacology at the University of Pretoria. The authors declare that there is no financial or personal relationship(s) that may have inappropriately influenced the writing of this paper.

References

1. Chopra A, Abdel-Nasser A. Epidemiology of rheumatic musculoskeletal disorders in the developing world. Best Pract Res Clin Rheumatol. 2008;22(4):583–604. http://dx.doi.org/10.1016/j.berh.2008.07.001
2. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365(23):2205–19. http://dx.doi.org/10.1056/NEJMra1004965
3. Wolfe F, Mitchell DM, Sibley JT, et al. The mortality of rheumatoid arthritis. Arthritis Rheum. 1994;37(4):481–94. http://dx.doi.org/10.1002/(ISSN)1529-0131
4. Sakoda K, Yamamoto M, Negishi Y, et al. Simvastatin decreases IL-6 and IL-8 production in epithelial cells. J Dent Res. 2006 Jun;85(6):520–3. http://dx.doi.org/10.1177/154405910608500608
5. Leung BP, Sattar N, Crilly A, et al. A novel anti-inflammatory role for simvastatin in inflammatory arthritis. J Immunol. 2003;170(3):1524–30. http://dx.doi.org/10.4049/jimmunol.170.3.1524
6. Steimle V, Siegrist CA, Mottet A, et al. Regulation of MHC class II expression by interferon-gamma mediated by the transactivator gene CIITA. Science. 1994 Jul 1;265(5168):106–9. http://dx.doi.org/10.1126/science.8016643
7. Kurakata S, Kada M, Shimada Y, et al. Effects of different inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, pravastatin sodium and simvastatin, on sterol synthesis and immunological functions in human lymphocytes *in vitro*. Immunopharmacology. 1996 Aug;34(1):51–61. http://dx.doi.org/10.1016/ 0162-3109(96)00108-7
8. Costenbader KH, Coblyn JS. Statin therapy in rheumatoid arthritis. South Med J. 2005;98(5):534–40; quiz 541, 572. http://dx.doi.org/10.1097/01.SMJ.0000161755.22998.F7
9. Tu H, Li Q, Xiang S, et al. Dual effects of statins therapy in systemic lupus erythematosus and SLE-related atherosclerosis: the potential role for regulatory T cells. Atherosclerosis. 2012 May;222(1):29–33. http://dx.doi.org/10.1016/j.atherosclerosis.2012.02.023
10. Paraskevas KI. Statin treatment for rheumatoid arthritis: a promising novel indication. Clin Rheumatol. 2008;27(3):281–7. http://dx.doi.org/10.1007/s10067-007-0806-8
11. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, et al. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum. 2008;59(12):1690–7. http://dx.doi.org/10.1002/art.v59:12
12. Smolen JS, Breedveld FC, Eberl G, et al. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. Arthritis Rheum. 1995;38(1):38–43. http://dx.doi.org/10.1002/(ISSN)1529-0131
13. Pala O, Cavaliere LF. Joint counts. In: Bartlett SJ, editor. Clinical care in the Rheumatic Diseases. 3rd ed. Atlanta, GA: Association of Rheumatology Health Professionals; 2006. p. 39–41.
14. Abud-Mendoza C, De la Fuente H, Cuevas-Orta E, et al. Therapy with statins in patients with refractory rheumatic diseases: a preliminary study. Lupus. 2003;12(8):607–11. http://dx.doi.org/10.1191/0961203303lu429oa
15. Stevens RJ, Douglas KM, Saratzis AN, et al. Inflammation and atherosclerosis in rheumatoid arthritis. Expert Rev Mol Med. 2005;7(7):1–24.
16. Ridker PM, Morrow DA, Rose LM, et al. Relative efficacy of atorvastatin 80 mg and pravastatin 40 mg in achieving the dual goals of low-density lipoprotein cholesterol <70 mg/dl and C-reactive protein <2 mg/l. J Am Coll Cardiol. 2005 May 17;45(10):1644–8. http://dx.doi.org/10.1016/j.jacc.2005.02.080
17. Kanda H, Yokota K, Kubo K, et al. Simvastatin reduces the disease activity in patients with rheumatoid arthritis. Arthritis Rheum. 2004;50Suppl 9:S387.
18. Prevoo ML, Van'T Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995 Jan;38(1):44–8. http://dx.doi.org/10.1002/(ISSN)1529-0131
19. Cojocaru L, Rusali AC, Şuţa C, et al. The role of simvastatin in the therapeutic approach of rheumatoid arthritis. Autoimmune Dis. 2013;2013:326258.
20. Chalubinski M, Broncel M. Influence of statins on effector and regulatory immune mechanisms and their potential clinical relevance in treating autoimmune disorders. Med Sci Monit. 2010;16(11):245–51.

Received: 29-09-2014 Accepted: 01-12-2014