Correspondence

The Beneficial Effects of Statin Therapy May Not Apply to All Forms of Crescentic Glomerulonephritis

To the Editor-in-Chief:

We read with interest the manuscript by Fujita et al¹ describing the effect of statin treatment on experimental anti-glomerular basement membrane glomerulonephritis (anti-GBM GN) in WKY rats. In their elegant study, they showed that atorvastatin (20 mg/kg/day p.o.) given three days pre-induction of GN and for up to 10 days markedly reduced the degree of renal injury. They attributed this to reduction in pro-inflammatory M1 macrophages and increase in anti-inflammatory M2 macrophages. The authors propose a therapeutic application for statins in severe glomerulonephritis.

Their results contrast with the effect of simvastatin in rodent experimental autoimmune vasculitis (EAV), an analogous model of crescentic GN induced by immunization with myeloperoxidase (MPO).^{2–3} We gave simvastatin (Rosemont Pharmaceuticals, Leeds, UK) at a similar dose of 25 mg/kg body weight/day p.o. from five days pre-immunization and continued for 56 days. Despite having a potent *in vitro* effect on anti-MPO antibody-induced neutrophil activation, we found that simvastatin did not reduce hematuria, albuminuria, or the degree of crescentic GN.⁴ Taking this in conjunction with a recent case report of vasculitis apparently caused by a statin,⁵ we propose that the effect of statin therapy may not apply to all forms of crescentic glomerulonephritis and advise caution in extrapolating to human disease.

Bahjat Al-Ani
Hamad Al Nuaimi
Caroline Savage

University of Birmingham
Birmingham, UK

Mark A. Little

UCL Centre for Nephrology Royal Free Hospital
London, UK

Author's Reply:

We thank Al-Ani et al for their interest in our recent publication,¹ and we are impressed by the extensive and

important work the group has achieved contributing to the field of crescentic glomerulonephritis (GN) research. As described in their letter, their research model of human myeloperoxidase (MPO)-immunized rodent anti-neutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis is quite interesting and considered one that best resembles human ANCA-associated systemic vasculitides. Their recent study showed that although simvastatin reduced anti-MPO antibody-induced neutrophil degranulation and vWF release from normal human umbilical vein endothelial cells co-cultured with ANCA-stimulated neutrophils, administration of simvastatin did not ameliorate hematuria, albuminuria, or the degree of glomerular injury in rats. We are not surprised by these negative results *in vivo*, given that statin sometimes enhances humoral immune responses and may sometimes be associated with drug-induced autoimmune reactions, including systemic lupus erythematosus as well as ANCA-associated vasculitis.⁶ We speculate that these enhanced immune responses may have occurred via activated Th2-promoting effects,⁷ causing augmentation of humoral immune responses in autoimmune reactions. Evidence suggest that statins are also sometimes capable of inducing proinflammatory responses and acting in a disease-specific manner.⁸ In fact, statin therapy does not seem to benefit giant cell arteritis,⁹ one of the systemic vasculitides.

In contrast, recent observations suggest that statin treatment may have renoprotective effects.^{10–12} The benefits of statins include lipid lowering as well as pleiotrophic effects. The pleiotrophic effects may derive from inhibition of the mevalonate pathway and the synthesis of the isoprenoids (farnesyl pyrophosphate and geranylgeranyl pyrophosphate) involved in cellular signaling, post-translational modification of proteins, and cellular function.¹³ The pleiotrophic effects of statins, such as endothelial protection and anti-inflammatory, oxidative, and thrombotic events, may eventually provide renal benefits.^{10–13}

Our results revealed that atorvastatin can suppress glomerular inflammation via inhibition of macrophage development, reduction of pro-inflammatory M1 macrophages, and augmentation of anti-inflammatory M2 macrophages.¹ In renal glomerular diseases, activated macrophages contribute to the progression of glomerular inflammation.¹⁴ Dendritic cells and T cells are also involved in this process.¹⁵

Statins directly affect multiple cell populations relevant to immune response such as dendritic cells, T cells, regulatory T cells, macrophages, B cells, and endothelial cells, thereby promoting an anti-inflammatory phenotype opposed to pro-inflammatory phenotype.^{12,13,16,17} Based on these findings, it is highly probable that the protective effects of statins, together with their cholesterol-lowering effects, can help treat glomerular diseases. In support of this concept, accumulating evidence has been published using experimental models of renal diseases, including our recent report.^{1,10–12,18} However, renoprotective effects of statins in human renal diseases are not well established.^{10–12,19} Additional prospective, controlled, randomized trials are needed to assess the efficacy of statins in that respect.

We agree that the effect of statin therapy may not apply to all forms of crescentic GN and advise caution in extrapolating to human disease. It is very important that large trial studies be performed to clarify whether statin therapy is truly effective in human severe GN, including crescentic GN and ANCA-associated systemic vasculitis.

Akira Shimizu
 Emiko Fujita
 Shinya Nagasaka

Nippon Medical School
 Tokyo, Japan

References

1. Fujita E, Shimizu A, Masuda Y, Kuwahara N, Arai T, Nagasaka S, Aki K, Mii A, Natori Y, Iino Y, Katayama Y, Fukuda Y: Statin attenuates experimental anti-glomerular basement membrane glomerulonephritis together with the augmentation of alternatively activated macrophages. *Am J Pathol* 2010, 177:1143–1154
2. Little MA, Smyth L, Salama AD, Mukherjee S, Smith J, Haskard D, Nourshargh S, Cook HT, Pusey CD: Experimental autoimmune vasculitis: an animal model of anti-neutrophil cytoplasmic autoantibody-associated systemic vasculitis. *Am J Pathol* 2009, 174:1212–1220
3. Little MA, Smyth CL, Yadav R, Ambrose L, Cook HT, Nourshargh S, Pusey CD: Antineutrophil cytoplasm antibodies directed against myeloperoxidase augment leukocyte-microvascular interactions in vivo. *Blood* 2005, 106:2050–2058
4. Al-Ani B, Al Nuaimi B, Bevins A, Plant T, Savage C, Little M: Inhibition of ANCA-Induced Neutrophil Stimulation by Simvastatin. Manchester, Renal Association, 2010, pp 425
5. Sen D, Rosenstein ED, Kramer N: ANCA-positive vasculitis associated with simvastatin/ezetimibe: expanding the spectrum of statin-induced autoimmunity? *Int J Rheum Dis* 2010, 13:e29–e31
6. Noël B: Lupus erythematosus and other autoimmune diseases related to statin therapy: a systematic review. *J Eur Acad Dermatol Venereol* 2007, 21:17–24
7. Dunn SE, Youssef S, Goldstein MJ, Prod'homme T, Weber MS, Zamvil SS, Steinman L: Isoprenoids determine Th1/Th2 fate in pathogenic T cells, providing a mechanism of modulation of autoimmunity by atorvastatin. *J Exp Med* 2006, 203:401–412
8. Zeiser R, Maas K, Youssef S, Dürr C, Steinman L, Negrin RS: Regulation of different inflammatory diseases by impacting the mevalonate pathway. *Immunology* 2009, 127:18–25
9. Narváez J, Bernad B, Nolla JM, Valverde J: Statin therapy does not seem to benefit giant cell arteritis. *Semin Arthritis Rheum* 2007, 36:322–327
10. Mason JC: The statins-therapeutic diversity in renal disease? *Curr Opin Nephrol Hypertens* 2005, 14:17–24
11. D'Amico G: Statins and renal diseases: from primary prevention to renal replacement therapy. *J Am Soc Nephrol* 2006, 17(4 Suppl 2):S148–S152
12. Campese VM, Park J: HMG-CoA reductase inhibitors and the kidney. *Kidney Int* 2007, 71:1215–1222
13. Greenwood J, Steinman L, Zamvil SS: Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. *Nat Rev Immunol* 2006, 6:358–370
14. Matsumoto K, Fukuda N, Abe M, Fujita T: Dendritic cells and macrophages in kidney disease. *Clin Exp Nephrol* 2010, 14:1–11
15. Kurts C, Heymann F, Lukacs-Kornek V, Boor P, Floege J: Role of T cells and dendritic cells in glomerular immunopathology. *Semin Immunopathol* 2007, 29:317–335
16. Zhang X, Markovic-Plese S: Statins' immunomodulatory potential against Th17 cell-mediated autoimmune response. *Immunol Res* 2008, 41:165–174
17. Kim YC, Kim KK, Shevach EM: Simvastatin induces Foxp3+ T regulatory cells by modulation of transforming growth factor-beta signal transduction. *Immunology* 2010, 130:484–493
18. Eller P, Eller K, Wolf AM, Reinstadler SJ, Tagwerker A, Patsch JR, Mayer G, Rosenkranz AR: Atorvastatin attenuates murine anti-glomerular basement membrane glomerulonephritis. *Kidney Int* 2010, 77:428–435
19. Sandhu S, Wiebe N, Fried LF, Tonelli M: Statins for improving renal outcomes: a meta-analysis. *J Am Soc Nephrol* 2006, 17:2006–2016