

## Response to: 'Statin therapy now more common than steroids in clinical practice' by Pareek and Chandurkar

We appreciate the interest shown by Pareek and Chandurkar<sup>1</sup> concerning our recent study on diabetes mellitus (DM) risk associated with disease-modifying antirheumatic drugs and statins in patients with rheumatoid arthritis (RA).<sup>2</sup> They pointed out that statin-associated DM risk in patients with RA might be a more important concern than the risk attributed to glucocorticoids (GCs) due to longer treatment durations.<sup>1</sup>

We agree that statin treatment is potentially continued for a longer duration than GC when initiated in patients with RA, as in the case of our cohort (median (IQR) duration for statins: 13 (6–26) months vs GC: 7 (0–17) months). However, GCs are more frequently used in patients with RA than statins (GC: 65% vs statins: 25% in our cohort), and the DM risk increase starts at the first month of treatment and continues to increase as the duration increases.<sup>3</sup> Although there are no data regarding timing of statin-associated risk increase, studies from the general population suggest that DM risk further increases with longer duration of statin use<sup>4</sup> and intensive regimens.<sup>5</sup> These factors were not accounted for in our study and may partially explain the higher HR observed with statins compared with GC. However, we also like to emphasise that statins' effects on DM risk might be potentiated by the chronic inflammation of RA along with the use of other medications influencing DM risk. The JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial showed in patients with slightly elevated C reactive protein ( $\geq 2$  mg/L) a relatively greater DM risk increase (HR (95% CI)=1.26 (1.04 to 1.51)) than in other statin trials.<sup>6,7</sup> Although this risk might be partly attributed to the potency of rosuvastatin, it is likely that even low-grade inflammation might influence DM risk given the non-significant DM risk increase (HR (95% CI) 1.14 (0.84 to 1.55)) observed in another rosuvastatin trial in patients with heart failure (a well-known diabetogenic state).<sup>8</sup> Lastly, despite the anti-inflammatory effects of both GCs and statins, the potency of this effect might also modify the insulin resistance and DM risk emerged by these medications.

Pareek and Chandurkar<sup>1</sup> also highlight that concomitant hydroxychloroquine (HCQ) use with statins or GCs might attenuate the DM risk increase associated with both medications. This therapeutic advantage of HCQ was also demonstrated in our study<sup>2</sup> (see table 1) as shown by Pareek *et al*<sup>9</sup> for statins, despite the differences in patient characteristics, statin and HCQ doses and durations. This is an important point since both statins and GCs play essential roles in RA and cardiovascular risk management and cannot be avoided because of DM

**Table 1** Risk of incident diabetes by concomitant hydroxychloroquine use with either glucocorticoids or statins

	No of events/ No of exposure	Adjusted HR* (95% CI)	p Value
Concomitant hydroxychloroquine treatment			
With glucocorticoids	48/2078	0.69 (0.51 to 0.93)	0.014
With statins	45/1012	0.92 (0.68 to 1.25)	0.604

\*Adjusted for age, sex, disease duration, socioeconomic status, ethnicity, smoking, hypertension, comorbidity index, body mass index, Health Assessment Questionnaire Score, non-steroidal anti-inflammatory drug usage and year of entry.

risk. Concomitant HCQ use might be considered in patients with RA who are on these medications and at high risk for DM. However, for DM risk reduction with HCQ in RA, longer treatment durations may be required (~2 years+) than in those without inflammatory diseases.<sup>2,10–12</sup>

To conclude, despite the DM risk increase with statins and treatment duration concern pointed out by Pareek and Chandurkar,<sup>1</sup> we believe that statins exert beneficial cardiovascular effects with more complex interactions in patients with RA than in the general population. We hope to elucidate the net risk/benefit ratio of statins in our ongoing research on statins in additional RA cohorts.

Gulsen Ozen,<sup>1,2</sup> Sofia Pedro,<sup>3</sup> Kaleb Michaud<sup>1,3</sup>

<sup>1</sup>Department of Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA

<sup>2</sup>Faculty of Medicine, Marmara University, Istanbul, Turkey

<sup>3</sup>National Data Bank for Rheumatic Diseases, Wichita, Kansas, USA

**Correspondence to** Dr Kaleb Michaud, Department of Medicine, University of Nebraska Medical Center, Omaha, 68198–6270 NE, USA; kmichaud@unmc.edu

**Competing interests** None.

**Provenance and peer review** Commissioned; internally peer reviewed.

**To cite** Ozen G, Pedro S, Michaud K. *Ann Rheum Dis* Published Online First: [please include Day Month Year] doi:10.1136/annrheumdis-2016-210906

Received 8 December 2016

Accepted 10 December 2016



► <http://dx.doi.org/10.1136/annrheumdis-2016-210858>

*Ann Rheum Dis* 2016;0:1. doi:10.1136/annrheumdis-2016-210906

### REFERENCES

- Pareek A, Chandurkar N. Statin therapy now more common than steroids in clinical practice. *Ann Rheum Dis* 2016. doi: 10.1136/annrheumdis-2016-210858. [Epub ahead of print 23 Dec 2016]
- Ozen G, Pedro S, Holmqvist ME, *et al*. Risk of diabetes mellitus associated with disease-modifying antirheumatic drugs and statins in rheumatoid arthritis. *Ann Rheum Dis* 2016. doi: 10.1136/annrheumdis-2016-209954. [Epub ahead of print 11 Nov 2016]
- Movahedi M, Beauchamp ME, Abrahamowicz M, *et al*. Risk of incident diabetes mellitus associated with the dosage and duration of oral glucocorticoid therapy in patients with rheumatoid arthritis. *Arthritis Rheumatol* 2016;68:1089–98.
- Macedo AF, Douglas I, Smeeth L, *et al*. Statins and the risk of type 2 diabetes mellitus: cohort study using the UK clinical practice research datalink. *BMC Cardiovasc Disord* 2014;14:85.
- Preiss D, Seshasai SR, Welsh P, *et al*. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA* 2011;305:2556–64.
- Ridker PM, Danielson E, Fonseca FA, *et al*. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195–207.
- Sattar N, Preiss D, Murray HM, *et al*. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010;375:735–42.
- Kjekshus J, Apetrei E, Barrios V, *et al*. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007;357:2248–61.
- Pareek A, Chandurkar N, Thulaseedharan NK, *et al*. Efficacy and safety of fixed dose combination of atorvastatin and hydroxychloroquine: a randomized, double-blind comparison with atorvastatin alone among Indian patients with dyslipidemia. *Curr Med Res Opin* 2015;31:2105–17.
- Mercer E, Rekedal L, Garg R, *et al*. Hydroxychloroquine improves insulin sensitivity in obese non-diabetic individuals. *Arthritis Res Ther* 2012;14:R135.
- Wasko MC, McClure CK, Kelsey SF, *et al*. Antidiabetogenic effects of hydroxychloroquine on insulin sensitivity and beta cell function: a randomised trial. *Diabetologia* 2015;58:2336–43.
- Solomon DH, Garg R, Lu B, *et al*. Effect of hydroxychloroquine on insulin sensitivity and lipid parameters in rheumatoid arthritis patients without diabetes mellitus: a randomized, blinded crossover trial. *Arthritis Care Res (Hoboken)* 2014;66:1246–51.