Clinical Record:

A 61-year-old Caucasian man was admitted with fever, dizziness, unsteady gait and slurred speech of three days duration in the context of self-medicating on carbamazepine up to 900mg per day, which was prescribed for trigeminal neuralgia three weeks previously. He has a history of hypertension, controlled on felodipine 10mg and enalapril 20mg daily for 5 years, gout on allopurinol 100mg daily for 10 years, depression and diet-controlled diabetes. Rosuvastatin 10mg daily was started 6 months previously for dyslipidaemia. Over the preceding 12 months, he was treated for left facial pain with non-steroidal anti-inflammatory medications and oxycodone. He was subsequently trialled on carbamazepine 100mg TDS. On presentation, his temperature was between 38.1 - 39.9°C. He had horizontal nystagmus, incoordination and a maculopapular rash on the trunk. Investigations revealed mild anaemia (Hb 112L g/L), mild lymphopenia ($0.56 \times 10^9/L$), high C-reactive peptide (CRP) (100 mg/L) and lipase (450IU/L), and deranged liver functions (ALP 163 IU/L; GGT 384 IU/L; ALT 48 IU/L). Sepsis, autoimmune disease and hepatitis infection were excluded.

Discontinuation of carbamazepine resulted in resolution of neurological symptoms and signs over 2 days but he remained febrile (Fig. 1). On further questioning, he admitted having intermittent fever for 6 months and had received several empirical courses of antibiotics (amoxycillin + clavulanate and clindamycin). Investigations prior to presentation were remarkable for mild anaemia and fluctuating CRP. Rosuvastatin was ceased on day 7 with resolution of fever within a day (Fig.1). His haemoglobin, CRP and liver functions normalised over the subsequent months. Persistence of trigeminal neuralgia required reinstitution of carbamazepine on day 8, but he remained afebrile. Subsequently he was diagnosed with multiple sclerosis as the cause of his trigeminal neuralgia. As hyperlipidaemia was modest patient was not considered for alternative lipid lowering therapy.

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Discussion:

Drug fever is a diagnosis of exclusion with fever coinciding with the administration of the drug and disappearing after its discontinuation³. The presence of skin rash or eosinophilia aids the diagnosis, although present in only 20% of cases³.

Rosuvastatin is well tolerated and less than 4% of patients have treatment withdrawal due to side effects⁸. Fever associated with rosuvastatin is extremely uncommon. To date, 2 cases of drug reaction with eosinophilia and systemic symptoms (DRESS) have been described with statins – a case each with atorvastatin² and pravastatin⁴. Although eosinophilia was absent in our patient, the constellation of fever, lymphopenia, abnormal liver and pancreatic functions, and skin rash make DRESS probable based on the RegiSCAR, the DRESS validation score⁶. Carbamazepine is a well-recognised cause of DRESS and the risk has been shown to increase significantly in those with HLA-A3101 and HLA-B1502 alleles⁹. However, the latter is associated mostly with severe skin hypersensitivity reactions and occurs almost exclusively in patients with Asian ancestry⁹. In any case, carbamazepine induced DRESS appears less likely in this case as its rechallenge was free of any clinical sequelae. Furthermore, the overall clinical picture particularly features of neurotoxicity in the setting of the patient self-medicating on carbamazepine, favours toxicity more than hypersensitivity, although serum drug concentrations were not available.

In addition to hypersensitivity reactions, it is important to consider the role of pharmacokinetic drug interactions in the patient's clinical presentation. Drug interactions between HMG-CoA reductase

inhibitors and medications that either induce or inhibit, or are metabolised by the cytochrome P450 system are well known¹. However, as rosuvastatin is mostly cleared by the kidneys unchanged and only less than 10% is metabolised by CYP2C9 and CYP2C19, drug interactions due to CYP system would appear less likely in this case. Furthermore, as carbamazepine is an inducer of CYP2C9 and CYP2C19, one would expect a reduction in the serum levels of rosuvastatin. However, an increase in serum rosuvastatin concentration due to genetic polymorphism in OATP1B1 and BCRP transporter proteins cannot be ruled out⁷.

The Naranjo scale⁵, a validated tool for assessing the probability of adverse drug reaction, estimated the association of rosuvastatin with fever in this case as 'probable' rather than 'certain,' with a score of 7. However, the Naranjo scale probably underestimated this association because of weightings for variables such as previous reporting of similar events and serum drug concentrations, which are not applicable to rosuvastatin. The temporal association of fever with rosuvastatin, both the onset and resolution, and the uneventful clinical course post cessation of rosuvastatin strengthens the likely aetiological association of rosuvastatin with fever. The rechallenge of carbamazepine further validates this association by excluding carbamazepine as a potential cause of fever. Although the clinical and laboratory features suggest a probable diagnosis of rosuvastatin induced DRESS, the intercurrent use of carbamazepine confounds the clinical picture; thus makes elucidation of the pathophysiology of fever challenging - DRESS versus isolated drug fever.

References

1. Martin J. et al. Cytochrome P450 drug interactions within the HMG-CoA reductase inhibitor class: are they clinically relevant? *Drug Saf* 2003; 26(1): 13-21.
2. Gressier L. et al. Atorvastatin-induced drug reaction with eosinophilia and systemic symptoms (DRESS). *Ann Dermatology Venereol* 2009; 50-3.
3. Mackowiak PA, LeMaistre CF. Drug fever: a critical appraisal of conventional concepts. An analysis of 51 episodes in two Dallas hospitals and 97 episodes reported in the English literature, *ANN Intern Med* 1987; 106:728
4. Bezalei S et al. A case of pravastatin-induced DRESS syndrome. *Journal of the American Academy of Dermatology* 2014; 70(5): AB114.
5. Naranjo CA et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30: 239-245.
6. Kardaun SH et al. Variability in the clinical pattern of cutaneous side effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *British Journal Dermatology* 2007; 156: 609-611
7. AstraZeneca 2015, CRESTOR® product information, genetic polymorphism, viewed 4 March 2016, <http://www.astrazeneca.com.au/healthcare-professionals/product-information>
8. Rosuvastatin. *Australian Prescriber* 2006; 29:167-71.
9. McCormack M et al. HLA-A3101 and carbamazepine-induced hypersensitivity reactions in Europeans *N Engl J Med*. 2011 March 24; 364(12): 1134–1143.

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TITLE:

Pyrexia of unknown origin associated with Rosuvastatin

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Abstract:

A case of pyrexia of unknown origin in a 62 year old man associated with Rosuvastatin is described. He was initially admitted with features of carbamazepine toxicity, which was commenced three weeks previously for trigeminal neuralgia. Rosuvastatin was started six months ago for his hyperlipidaemia. Further history revealed that patient was having intermittent fever since the start of Rosuvastation. Omission and subsequent rechallenge excluded Carbamazepine as the cause of fever. Extensive investigations excluded infective and collagen vascular disorders as the cause for fever. Ceasing of Rosuvastatin resulted in resolution of fever.

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