

Haemolytic anaemia complicating the concurrent use of allopurinol & azathioprine after kidney transplantationCatherine Hanna^{1*}, Neeraj Dhaun¹, Maria Squires², Simon Watson¹

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ABSTRACT

Gout is a common problem in renal transplant recipients but often difficult to treat. Allopurinol can be combined with azathioprine but clinicians should be aware of the need for dose reduction, the potential to measure azathioprine breakdown products and the possible side effects of this combination. Leucopenia is a known side effect but this case report shows that haemolytic anaemia can also occur.

Keywords: Allopurinol, Azathioprine, Transplantation, Haemolytic anemia

INTRODUCTION

Elevated serum uric acid (sUA) is common in kidney transplant recipients.¹ It is an important risk factor for reduced graft survival² and incident cardiovascular disease³ and may lead to the development of the painful arthropathy 'gout'. Importantly, emerging clinical data show that lowering sUA has both cardiovascular and renal benefits⁴, as well as reducing the frequency of gout episodes.

Xanthine oxidase inhibitors such as allopurinol effectively lower sUA. Their use in transplant recipients is limited by their inhibition of the metabolism of the immunosuppressive agent azathioprine. Co-administration of allopurinol and azathioprine leads to accumulation of potentially toxic thiopurine metabolites (TM) which cause leucopenia.⁵ Co-prescription can be done but with care. Here we describe another important but less well-known side effect of concomitant azathioprine and allopurinol use.

CASE REPORT

A 56 year-old gentleman with end-stage renal failure due to reflux nephropathy received a kidney transplant from a living related donor 15 years earlier. Maintenance immunosuppression was ciclosporin 100mg twice daily and azathioprine 100mg daily. He suffered frequent attacks of gout with sUA persistently over 0.42mmol/l (0.12 – 0.42). Allopurinol 100mg daily was commenced and azathioprine was replaced with mycophenolate mofetil (MMF) to avoid TM accumulation. Unfortunately, MMF was not tolerated due to severe skin rash and mouth ulceration and so allopurinol was stopped to allow re-introduction of azathioprine. Colchicine was used for gout control but this was poorly tolerated due to diarrhoea. In the following two years the patient experienced increasingly disabling gout and eventually allopurinol was re-introduced alongside a 50% reduction in the dose of azathioprine.

Over the next three months the patient developed symptomatic anaemia with a fall in haemoglobin (Hb)

from 120 to 87g/l (135 – 180) (Figure 1). There was no evidence of blood loss. Mean corpuscular volume rose from 91 to 107 fl (78 – 98) and bilirubin from 13 to 37 μ mol/l (3 – 21). Serum vitamin B₁₂, folic acid and iron studies were normal and there was no change in the serum creatinine, white cell or platelet counts. Further investigations revealed evidence of haemolysis with low

haptoglobins (<0.1g/L, normal 0.2 – 2.6 g/L), a reticulocytosis (115 x10⁹/L, normal 25 - 85), and a rising lactate dehydrogenase concentration (213 U/L, normal 125 – 220 U/L). A blood film showed macrocytosis, polychromasia and anisochromia. A direct Coombs test was negative.

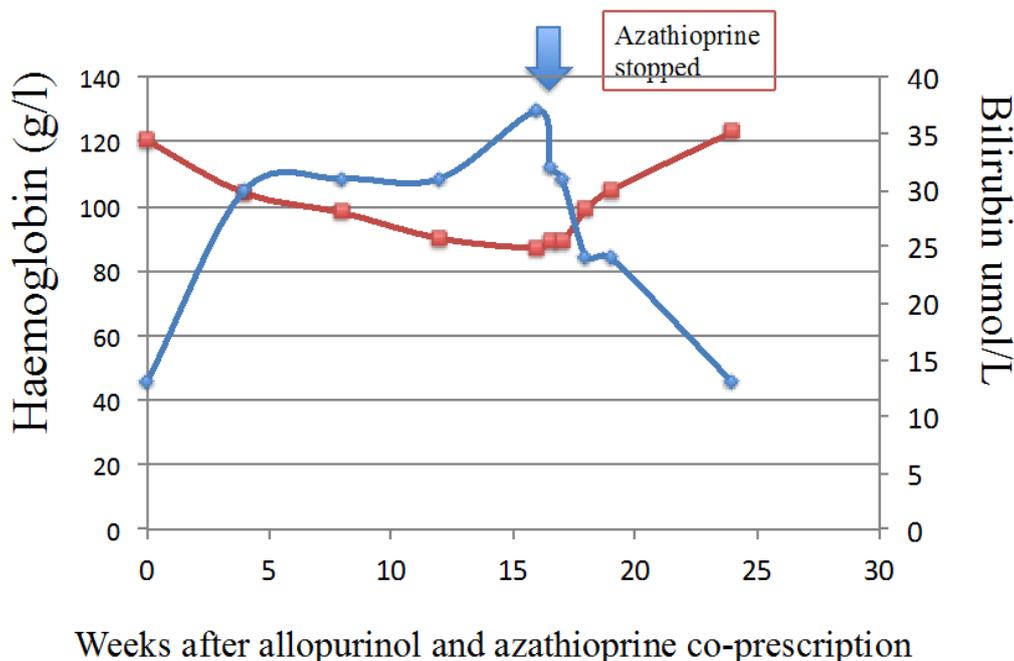


Figure 1: Trend in haemoglobin and bilirubin after azathioprine and allopurinol co-prescription.

DISCUSSION

Azathioprine is an inactive pro-drug and its immune suppressant activity is dependent upon metabolism to 6-thioguanine metabolites (6-TGN) by a series of multi-enzyme processes. Two routes of inactivation limit this: oxidation by xanthine oxidase to 6-thiouric acid and thiol methylation by thiopurine methyltransferase (TPMT) to form 6 methylmercaptopurine (6-MMPN), a metabolite which in high concentrations causes hepatotoxicity. When co-administered, allopurinol inhibits xanthine oxidase activity and leads to the preferential formation of 6-TGN. Intuitively it would be anticipated that 6-MMPN concentrations would also rise, however there is in fact a dramatic reduction in these concentrations, the mechanism of which is unknown.⁵ In accordance with this, measurement of azathioprine metabolites in this patient revealed a high 6-TGN (844 pmol/8 x10⁸ erythrocytes, normal 235 – 450) and a low 6-MMPN concentration (<100pmol/8 x 10⁸ erythrocytes). Azathioprine was stopped and within one month there was nearly complete normalization of serum markers (Figure 1). Ongoing immunosuppression consisted of prednisolone and ciclosporin only. Allopurinol was continued for gout control.

Transplant clinicians see many cases of gout. Although xanthine oxidase inhibitors can provide excellent control of symptoms an awareness of the potential for toxic interaction with azathioprine is important. We believe it is equally important for clinicians to appreciate that TM toxicity can result in haemolytic anemia⁶, as well as leucopenia.

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