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Reminder of important clinical lesson

Successful use of allopurinol in a patient on dialysis

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Summary

We report the case of a man with chronic tophaceous gout who had end-stage renal failure secondary to the Alport syndrome. Following a failed kidney transplant, where urate deposition was a suspected contributor, the patient responded positively to consistent allopurinol therapy and regular haemodialysis sessions. Extensive and destructive tophi receded in size remarkably and the almost constant incidence of acute attacks of gout subsided. The patient has recently received a new kidney transplant and his plasma concentrations of urate are controlled well with allopurinol and he no longer experiences acute attacks of gout. While efficacious, adherence is critical for achieving the therapeutic effects of allopurinol even in end-stage renal disease.

BACKGROUND

Allopurinol is the most commonly used medication for treating hyperuricaemia and gout. It effectively decreases the production of urate by inhibiting the enzyme xanthine oxidoreductase. It acts primarily through its active metabolite, oxypurinol. Both the parent and metabolite are renally cleared.[1] Despite its effectiveness, a substantial proportion of gout sufferers cease allopurinol therapy within 1 year.[2] Further, many patients are underdosed with the drug and, consequently, their plasma urate concentrations do not fall below 0.36 mmol/l, an internationally accepted target concentration.[3] They are, therefore, at risk of recurrent attacks of acute gout and of joint and tissue damage by deposits of monosodium urate.[4] In extreme cases, damage to kidney tissue can result in end-stage renal failure (ESRF).[5]

There is reluctance from many prescribers of allopurinol, most of whom are general practitioners, to increase the dose above 300 mg/day despite advice in the Product Information that supports a maximum dose of 900 mg/day.[6 7] In part, this relates to a concern about an increased risk of allopurinol hypersensitivity syndrome (AHS). AHS has been linked to excessive doses of allopurinol, especially in patients with renal impairment.[8] The most severe forms, Stevens Johnson syndrome and toxic epidermal necrolysis, have significant morbidity and mortality. It is unclear, however, how much these rare, but serious, adverse reactions are related to the dose of allopurinol and the plasma concentration of oxypurinol or indeed renal impairment itself.

We report the use of allopurinol in a patient with very severe and destructive, chronic tophaceous gout on haemodialysis who progressed to ESRF again following the failure of a transplanted kidney. He received a transplant initially because of renal failure secondary to the Alport syndrome, a rare genetic disorder characterised by a failure of type IV collagen production and assembly. We show that allopurinol therapy in a patient with haemodialysis is safe and effective with carefully titrated doses of allopurinol. Further, we show that with encouragement and appropriate monitoring of plasma concentrations of oxypurinol and urate, adherence can be established and the target plasma urate concentrations achieved.

CASE PRESENTATION

A 49-year-old man had his first attack of gout at the age of 34. He was hypertensive and had ESRF secondary to Alport syndrome. His family history was positive for Alport syndrome but not for gout. He was not overweight, had a normal diet and did not drink alcohol excessively. At the age of 26, following peritoneal dialysis and then haemodialysis, he had a kidney transplant and was prescribed cyclosporine, azathioprine and prednisolone. In June 1998, at the age of 35, his plasma urate was 0.71 mmol/l. He was given colchicine prophylactically for recurrent attacks of gout. Allopurinol was not prescribed because of the risk of bone marrow suppression with concomitant azathioprine. In 1999, he suffered recurrent deep vein thrombosis (DVT) and a pulmonary embolism, and was warfarinised prior to starting long-term enoxaparin sodium ('Clexane', low-molecular-weight heparin). In November 2002, analysis of a clot following thrombectomy from his arterio-venous fistula revealed tophaceous material. In 2003, azathioprine was replaced by mycophenalate mofetil, and allopurinol 100 mg/day was prescribed. The latter was increased to 200 mg/day in October 2007, but repeated high plasma urate concentrations, around 0.7 mmol/l, were noted. Variable adherence to allopurinol was admitted and this was related to a lack of confidence that allopurinol could lower the urate concentrations to such a degree that recurrent gout attacks could be eliminated and that tophi could shrink. In November 2007, his tophaceous gout was extensive and extremely debilitating. He was in constant pain from widespread acute attacks and significant damage to his knees. His transplanted kidney was failing and this was suspected to be due to urate

deposition in the graft. He had severe weakness and wasting of his thigh and leg muscles due to urate deposits in muscles. His bilateral soleal vein DVT continued to be symptomatic. His kidney transplant failed in December 2008 and he required 4 h haemodialysis sessions three times a week.

In October 2007, however, prior to his kidney failing, with much encouragement he began responding well to consistent dosing with allopurinol 200 mg/day. His plasma urate concentration dropped from 0.74 to 0.45 mmol/l. After recommencing haemodialysis, an increase in dose of allopurinol to 250 mg/day led to a fall in plasma urate concentration to 0.17 mmol/l post dialysis (table 1). Throughout 2009, however, his plasma urate concentration fluctuated above 0.42 mmol/l and he suffered recurrent acute flares of disease. A poor quality of life was associated with the acute attacks, leading again to variable adherence to the dosing regimens of allopurinol. With encouragement, regular review, monitoring of plasma urate and oxypurinol concentrations and, importantly, with sharing the results with the patient, he began to take the allopurinol consistently. By August 2009, he was taking allopurinol 350 mg/day with a corresponding plasma urate concentration of 0.3 mmol/l pre-dialysis. Plasma oxypurinol concentrations oscillated in the range 9–30 mg/l. The timing of blood samples in relation to dialysis and dosing of the drug varied, however. As the plasma urate concentrations declined, the dose of allopurinol could be maintained at 200 mg/day.

INVESTIGATIONS

Regular measurements of plasma oxypurinol and urate concentrations. Some plasma oxypurinol concentrations were also taken immediately prior to and after haemodialysis sessions.

TREATMENT

For impaired renal kidney function, 3–4 h haemodialysis were undertaken weekly. Allopurinol dose was titrated to plasma urate concentrations.

OUTCOME AND FOLLOW-UP

We were able to show that the drug was significantly cleared by haemodialysis allowing us to give him doses of up to 350 mg daily. Since July 2011, when the patient received a new kidney transplant, he has taken allopurinol 100 mg/day and his plasma urate concentration is 0.42 mmol/l. His tophi, which were extensive, have diminished significantly and he has had no further acute attacks of gout.

Table 1 Allopurinol dosing history and corresponding plasma concentrations of urate, oxypurinol and creatinine

Date	Plasma urate (mmol/l)	Plasma oxypurinol (mg/l)	Plasma creatinine (mmol/l)	Dose (mg)
23/10/2007*	0.74	–	0.22	200
19/03/2008*	0.51	–	0.246	200
15/12/08 PRE†	0.39	–	0.455	250
15/12/08 POST†	0.17	7	–	250
2/07/2009 PRE†	–	16	0.677	300
2/07/2009 POST†	–	10	–	350
5/08/2009 PRE†	0.3	30	0.791	350
5/08/2009 POST†	–	15	–	350
3/09/2009 PRE†	0.3	24.7	–	350
3/09/2009 POST†	–	9.7	–	350
12/11/2010†	0.29	–	0.747	200
7/11/2011‡	0.4	–	0.119	100

*First kidney transplant.
†Dialysis following failed kidney transplant.
‡New (second) kidney transplant.
POST, plasma concentrations and dose immediately after haemodialysis; PRE, plasma concentrations and dose immediately before haemodialysis.

DISCUSSION

Many patients become discouraged with taking allopurinol because of acute attacks of gout that can be triggered when the drug is commenced or the dosage is varied.[2] This feature is common to all drugs that lower the plasma urate concentrations. Slowly increasing the dose and covering for acute attacks with low-dose colchicine or non-steroidal anti-inflammatory drugs during the first few months of therapy can reduce the risk.[9 10] However, it is not surprising that especially patients, and even some prescribers, lose faith in allopurinol and consider that it has failed if, shortly after it is commenced, acute attacks of gout recur.[2] Variable compliance with allopurinol has also been shown to precipitate acute attacks of gout, a feature noticed in our patient.[11] Adherence to the dosing regimen is crucial for the successful and consistent reduction in plasma concentrations of urate and is essential for effective treatment of gout.

Renal impairment has long been linked to AHS, stemming from the hypothesis that the expected exposure to higher concentrations of oxypurinol leads to hypersensitivity reactions.[8] The symptoms, however, arise approximately 1–2 months after first commencing allopurinol therapy.[12] The development of AHS while oxypurinol concentrations are within the usual and putative therapeutic range suggests that high concentrations of oxypurinol are not the only trigger of AHS.[13] The strong association of AHS with the HLA-B*5801 allele in Han Chinese has shown that a genetic predisposition exists.[14 15] Gradually increasing the doses of allopurinol minimises the incidence of acute attacks of gout, and could reduce the risk of AHS, although this is speculative.

There are only two previous reports on the use of allopurinol in patients on haemodialysis, each showing the treatment method to be safe and effective.[16 17] Our case study confirms these findings, and demonstrates that plasma oxypurinol concentrations are reduced approximately 50% by haemodialysis (table 1). This should allay concerns regarding oxypurinol retention in similar patients.

Learning points

- Allopurinol therapy combined with haemodialysis sessions is a successful treatment method for severe, tophaceous gout and the combination can effectively lower the plasma concentration of urate and sufficiently clear the plasma concentrations of oxypurinol.
- It is important to encourage and educate the patient to adhere to the dosing regimen.
- Allopurinol is safe to use, even in patients on regular haemodialysis.

Competing interests None.

Patient consent Obtained.

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