REVIEW ARTICLE

Drugs 2005; 65 (18): 2593-2611
0012-6667/05/0018-2593/$39.95/0

Gout in Solid Organ Transplantation
A Challenging Clinical Problem

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Abstract

Hyperuricaemia occurs in 5–84% and gout in 1.7–28% of recipients of solid organ transplants. Gout may be severe and crippling, and may hinder the improved quality of life gained through organ transplantation. Risk factors for gout in the general population include hyperuricaemia, obesity, weight gain, hypertension and diuretic use. In transplant recipients, therapy with ciclosporin (cyclosporin) is an additional risk factor.

Hyperuricaemia is recognised as an independent risk factor for cardiovascular disease; however, whether anti-hyperuricaemic therapy reduces cardiovascular events remains to be determined.

Dietary advice is important in the management of gout and patients should be educated to partake in a low-calorie diet with moderate carbohydrate restriction

and increased proportional intake of protein and unsaturated fat. While gout is curable, its pharmacological management in transplant recipients is complicated by the risk of adverse effects and potentially severe interactions between immunosuppressive and hypouricaemic drugs. NSAIDs, colchicine and corticosteroids may be used to treat acute gouty attacks. NSAIDs have effects on renal haemodynamics, and must be used with caution and with close monitoring of renal function. Colchicine myotoxicty is of particular concern in transplant recipients with renal impairment or when used in combination with ciclosporin. Long-term urate-lowering therapy is required to promote dissolution of uric acid crystals, thereby preventing recurrent attacks of gout. Allopurinol should be used with caution because of its interaction with azathioprine, which results in bone marrow suppression. Substitution of mycophenylate mofetil for azathioprine avoids this interaction. Uricosuric agents, such as probenecid, are ineffective in patients with renal impairment. The exception is benzbromarone, which is effective in those with a creatinine clearance >25 mL/min. Benzbromarone is indicated in allopurinol-intolerant patients with renal failure, solid organ transplant or tophaceous/polyarticular gout. Monitoring for hepatotoxicty is essential for patients taking benzbromarone.

Physicians should carefully consider therapeutic options for the management of hypertension and hyperlipidaemia, which are common in transplant recipients. While loop and thiazide diuretics increase serum urate, amlodipine and losartan have the same antihypertensive effect with the additional benefit of lowering serum urate. Atorvastatin, but not simvastatin, may lower uric acid, and while fenofibrate may reduce serum urate it has been associated with a decline in renal function.

Gout in solid organ transplantation is an increasing and challenging clinical problem; it impacts adversely on patients' quality of life. Recognition and, if possible, alleviation of risk factors, prompt treatment of acute attacks and early introduction of hypouricaemic therapy with careful monitoring are the keys to successful management.

Gout has been recognised since the time of Hippocrates. Known as the 'disease of kings', gout is traditionally thought of as reflecting the excesses of society. In the modern world solid organ transplantation may be regarded as one of societies 'excesses' and is associated with an increased risk of gout. In the general population, gout is the most common form of arthritis in men >40 years of age[1] and it occurs in up to 28% of transplant recipients.[2]

A definitive diagnosis of gout requires demonstration of monosodium urate crystals in synovial fluid. There are four clinical stages: asymptomatic hyperuricaemia, acute gout, intercritical (or episodic) gout and chronic tophaceous gout. Gout can have a significant impact on quality of life, and chronic tophaceous gout is associated with bone and joint destruction. In transplant recipients, the quality of life gained for the patient at significant cost to the healthcare system can be lost with the onset of gout. A recent audit of transplant recipients in Canterbury, New Zealand revealed that 55% of patients who returned to work after receiving a solid organ transplant had to take time off work because of gout (unpublished data). Furthermore, once gout occurs in transplant recipients, attacks are likely to be recurrent. In our local transplant population in Canterbury, New Zealand, 79% have repeated episodes of gout and of these 75% have an attack at least every 3 months (unpublished data).

Unlike other forms of arthritis, gout can be 'cured' with appropriate therapy. However, the literature on the treatment of gout is sparse, with a paucity of randomised controlled trials compared with other rheumatic conditions.[3] An Ovid MED-

LINE search resulted in 72 136 hits for rheumatoid arthritis compared with only 6061 for gout. There are even fewer data on the management of gout in transplant recipients. As a result, the management of gout in both the general and transplant populations is often based on the availability of therapies and the experience and preferences of the physician rather than on evidence from clinical trials.

The recognition of hyperuricaemia as an independent risk factor for cardiovascular disease has renewed interest in hyperuricaemia and gout in both the general and transplant populations. New therapies undergoing clinical trials are providing therapeutic options for patients with gout. In the transplant population there are unique challenges in the management of gout that are related to drug interactions between hypouricaemic and immunosuppressive therapies and a higher risk of adverse effects.

We have reviewed the current literature on gout in solid organ transplantation. This review is based on a MEDLINE literature search from 1966 to July 2005. The keywords 'gout', 'transplantation', 'renal transplant', 'liver transplant', 'cardiac transplant', and individual drug names were used. Articles obtained from this search were reviewed for additional references.

1. Risk Factors for the Development of Hyperuricaemia and Gout in Transplant Recipients

1.1 Shared Risk Factors with the General Population

Obesity, weight gain, hypertension and diuretic use are important risk factors for gout in the general population.[4,5] In a prospective study of 223 men with asymptomatic hyperuricaemia the key risk factor for the development of gout was hyperuricaemia.[6] Gout and hyperuricaemia are also recognised as important features of the insulin resistance syndrome, which is characterised by obesity, hyperlipidaemia, impaired glucose tolerance, hypertension and increased cardiovascular risk.[7] In a recent study of 64 patients presenting with primary gout the prevalence of the metabolic syndrome was 82%.[8]

1.1.1 Diuretics

Loop and thiazide diuretics are commonly used in the management of hypertension. In the general population these drugs can decrease renal excretion of uric acid and deplete extracellular volume, resulting in hyperuricaemia and, in some patients, gout. The increase in serum uric acid occurs within a few days of commencing diuretics and persists for the duration of therapy.[9] In a retrospective study of 9249 patients with no history of therapy for gout, the relative risk for initiation of anti-gout therapy within 2 years of commencement of antihypertensive therapy was examined. In patients receiving non-thiazide antihypertensive therapy this relative risk was 1.0 (95% CI 0.65, 1.53) compared with 1.99 (95% CI 1.21, 3.26) for patients taking thiazide diuretics and 2.29 (95% CI 1.55, 3.37) for patients receiving both. Furthermore, the risk significantly increased when the thiazide dosages exceeded 25 mg/day (hydrochlorothiazide-equivalent milligrams).[10] In a more recent study, the odds ratio for use of a thiazide diuretic in the 24 hours prior to an acute attack of gout was 7.3 ($p = 0.02$).[11] These changes presumably also apply to transplant recipients.

However, in renal transplant patients treated with either ciclosporin (cyclosporin) or azathioprine, plasma uric acid levels have been reported to be both higher[2,12-14] and unchanged by concomitant diuretic use.[15,16] The magnitude of the effect of diuretics on hyperuricaemia and the development of gout is difficult to quantify. Even if the effect is small, it may be clinically important in patients whose gout is difficult to control and in whom therapeutic options for gout may be limited. The majority of renal transplant recipients receive loop diuretics to aid diuresis in the immediate post-transplant period. However, the reasons for continuation of diuretic therapy are less well defined. In this group of patients who are at high risk of gout, the reasons for long-term diuretic use should be carefully considered and alternative agents used if possible.

1.1.2 Renal Impairment

The relationship between plasma uric acid and renal function is complex. Renal impairment is associated with hyperuricaemia, which may lead to renal impairment, albeit rarely. In the general population, renal impairment associated with gout is especially apparent in postmenopausal women.[17] Several

studies in renal transplant recipients have shown a correlation between serum creatinine and uric acid,[1,4,13,18] although this is not a universal finding.[15] However, gout is rare in patients with end-stage renal failure (ESRF), whereas hyperuricaemia is common.[19] Similarly, in transplant recipients treated with azathioprine, hyperuricaemia but not gout is common.[16] These findings suggest that factors other than renal impairment contribute to the development of gout.

1.2 Risk Factors for Hyperuricaemia/Gout Specific to Transplant Recipients

1.2.1 Immunosuppressive Therapy

Ciclosporin, tacrolimus, azathioprine, mycophenylate mofetil and corticosteroids are commonly used immunosuppressive agents in transplant recipients. The majority of studies examining gout in transplant recipients are from a time when immunosuppression was provided by corticosteroids plus either azathioprine or ciclosporin, rather than the combination. In all of these studies there is an increased risk of hyperuricaemia and gout in patients receiving ciclosporin compared with those taking azathioprine (table I). Thus, ciclosporin is considered the most important risk factor for the development of gout in the transplant population. There are fewer data on the newer agents tacrolimus and mycophenylate mofetil. Some reports suggest that plasma uric acid decreases upon changing from ciclosporin to tacrolimus,[20,21] and this may be useful in the management of gout in transplant recipients.[22] However, an increase in plasma uric acid in liver transplant recipients treated with tacrolimus has also been reported.[23]

In patients receiving ciclosporin post-renal transplant it has been observed that the best predictor for the development of gout is plasma uric acid.[14] However, the mechanisms by which ciclosporin contributes to hyperuricaemia and gout are complex and not understood. Studies of the relationship between blood concentrations of ciclosporin and serum uric acid are inconsistent.[12,13,15,18,35] Ciclosporin appears to affect renal handling of uric acid, resulting in decreased uric acid clearance. Both reduction in glomerular filtration rate[27,36-38] and alterations in tubular handling of uric acid[14,18,39] have been suggested to be important in the impairment of uric acid clearance observed with ciclosporin. However, there are other conflicting studies.[15,36,40,41]

2. Pathogenesis of Gout

The primary biochemical abnormality in gout is an elevation in plasma uric acid. Hyperuricaemia is generally defined as serum uric acid >7.0 mg/dL (0.42 mmol/L) in men and >6 mg/dL (0.36 mmol/L) in women. Hyperuricaemia can result from either overproduction or underexcretion of uric acid. Approximately 95% of circulating uric acid is filtered at the glomerulus, with most being resorbed in the proximal tubule and then secreted. This is followed by further post-secretory absorption of uric acid. Renal clearance of uric acid is only about 7–10% of the filtered load. When supersaturation levels are reached, monosodium urate crystals are formed and can deposit in joints and periarticular tissues. The deposition of monosodium urate crystals is also influenced by other factors, including temperature, pH and concentrations of other ions such as sodium and calcium.[42] Urate crystals will remain within joints until serum uric acid has been adequately lowered.[43,44] Once deposited in tissues, monosodium urate crystals cause damage through local mechanical pressure and acute/chronic inflammation.

Painful acute attacks of gout are due to the acute inflammatory response incited by monosodium urate crystals. Monocytes release the proinflammatory cytokines interleukin (IL)-1 and tumour necrosis factor (TNF)-α,[45] and both monocytes and synoviocytes release IL-6[46] in response to monosodium urate crystals. Within the synovial membrane and synovial fluid there is a marked accumulation of neutrophils, which are attracted to the joint by chemokines such as monocyte-derived IL-8[47] and SA100A8/A9[48] as well as complement components.[49] Neutrophils within the joint have a central role in the inflammatory response. Monosodium urate crystals induce neutrophils to release a variety of inflammatory mediators, including IL-1, IL-8, proteases and superoxide (reviewed by Terkeltaub[42]).

Acute attacks of gout can be self-limiting or respond rapidly to short-term therapy. In addition, not all patients with hyperuricaemia develop gout.

Table I. Incidence of hyperuricaemia and gout in transplant recipients

Study (year)	Transplant type	Number of patients	Patients with asymptomatic hyperuricaemia	Patients with gout
Najarian et al.[24] (1985)	Renal	230 total 121 CsA 109 AZA-ATG	52% CsA 11% AZA	Not stated
Tiller et al.[25] (1985)	Renal	37 CsA 23 AZA	Not stated	11% CsA 0% AZA
West et al.[15] (1987)	Renal	243 total 211 CsA 32 AZA	55.5% CsA 25% AZA	10% total group 11.8% CsA 0% AZA
Kahan et al.[26] (1987)	Renal	402 CsA	30–45% 2 years post-transplant 7% 5 years post-transplant	4.7% CsA
Gores et al.[16] (1988)	Renal	246 total 131 CsA 115 AZA	80% CsA 55% AZA	4.5% CsA 0% AZA
Lin et al.[12] (1989)	Renal	297 total 129 CsA 168 AZA	84% CsA 30% AZA	7% CsA 0% AZA
Noordzij et al.[14] (1991)	Renal	78 total 55 CsA 23 AZA	Not stated	24% CsA 0% AZA
Ahn et al.[13] (1992)	Renal	187 total 140 CsA 47 AZA	51% CsA 19% AZA	3.5% CsA 0% AZA
Delaney et al.[2] (1992)	Renal	293 total 203 CsA 90 AZA	82% CsA 28% AZA	28% CsA 8% AZA
Marcen et al.[27] (1992)	Renal	169	59% CsA 23% AZA	Not stated
Marcen et al.[18] (1995)	Renal	214 133 CsA ± AZA 81 AZA	66.9% CsA ± AZA 19.7% AZA	9.9% CsA ± AZA
Ben Hmida et al.[28] (1995)	Renal	Not stated	Not stated	13% CsA 0% AZA
Braun et al.[29] (1999)	Renal	Not stated	Not stated	23% AZA
Farge et al.[30] (1990)	Heart/heart-lung	117 CsA + AZA	Not stated	1.7%
Burack et al.[31] (1992)	Heart/heart-lung	196	81% women on CsA 72% men on CsA	10% male *de novo* post-transplant 13% *de novo* and gout pre-transplant in CsA treated
Wluka et al.[32] (2000)	Heart	225	Not stated	10% *de novo* gout 44% patients with gout pre-transplant had recurrence
Robinson et al.[33] (1990)	Liver	31	Not stated	13% patient diagnosis
Taillandier et al.[34] (1995)	Liver	59	5% transient hyperuricaemia	Nil

ATG = antilymphocyte globulin; **AZA** = azathioprine; **CsA** = ciclosporin (cyclosporin).

The reasons for this remain unclear. A number of factors act to limit the proinflammatory response to the monosodium urate crystals in these situations. These include protective proteins coating monosodium urate crystals,[50,51] differentiation of monocyte/macrophages to a non-inflammatory phenotype,[52] induction of peroxisome proliferator-activated receptor-γ,[53] neutrophil apoptosis and inactivation of inflammatory mediators. Transforming growth factor-β has recently been shown to have a key role in suppression of inflammation induced by monosodium urate crystals.[54]

Over time the presence of monosodium urate crystals leads to damage to cartilage, bone and soft tissues. Gouty tophi, which only occur in some patients, are often associated with tissue damage. Tophi are extra-articular collections of uric acid crystals. Microscopically they are granulomas with a central core of amorphous debris and monosodium urate crystals surrounded by macrophages and multinucleated cells.[55] Both matrix metalloproteinases (MMPs) and nitric oxide (NO) may have a role in monosodium urate-induced tissue damage. The MMPs are a family of enzymes produced by macrophages/monocytes, chondrocytes and synoviocytes, which are involved in degradation of extracellular matrix. NO may be involved in cartilage damage through inhibition of proteoglycan synthesis,[56] activation of MMPs[57] and inhibition of type II collagen production[58] (for review see Clancy and Abramson[59]). MMP-9 and MMP-2 are both produced by monocytes/macrophages in response to uric acid crystals.[60] In an experimental model, chondrocytes produce NO and MMP-3 in response to monosodium urate crystals.[61] In a murine macrophage cell line and in bone marrow-derived macrophages, monosodium urate crystals have been shown to enhance inducible NO synthase and NO production in response to interferon-γ.[62]

3. Asymptomatic Hyperuricaemia

It is unclear why only some patients with hyperuricaemia develop gout, although the risk of gout increases with the degree of hyperuricaemia.[12,31,63] In the Normative Aging study, which prospectively followed 2046 men, the annual incidence of gout was 4.9% for those with a serum urate >9 mg/dL (0.5 mmol/L) compared with 0.1% for those with serum urate <7 mg/dL (0.42 mmol/L).[64] By multivariate analysis of risk factors in renal transplant recipients, plasma uric acid levels outweighed other risk factors including male gender, serum creatinine, hypertension, diuretic use and presence of ciclosporin for gout.[2] Asymptomatic hyperuricaemia usually remains untreated,[65] in part, because of concerns over the potential for allopurinol hypersensitivity syndrome[66] but also because of the requirement for more robust evidence detailing the potential risks and benefits of treating asymptomatic hyperuricaemia.

The association of hyperuricaemia with obesity, insulin resistance, hypertension and dyslipidaemia has led to debate as to whether uric acid is an independent risk factor for the development of cardiovascular disease. The mechanisms by which uric acid may contribute to hypertension and cardiovascular disease include endothelial dysfunction and vascular smooth muscle cell proliferation and inflammation (reviewed in Johnson et al.[67]). A recent review by Baker et al.[68] concluded that hyperuricaemia is an independent cardiovascular risk factor in high-risk patients, while the risk attributable to hyperuricaemia is small in healthy individuals. In a retrospective audit of patients with chronic heart failure, long-term high-dose (≥300 mg/day) allopurinol (for the management of gout) was associated with lower cardiovascular mortality than low-dose allopurinol.[69] Whether reduction in cardiovascular events outweighs potential adverse events associated with treatment of 'asymptomatic hyperuricaemia' in patients with high cardiovascular risk warrants further investigation.

Cardiovascular events are a leading cause of morbidity and mortality in the transplant population. In renal transplant recipients cardiovascular events are responsible for approximately 50% of deaths.[70-72] In cardiac transplant recipients cardiac allograft vasculopathy affects 50–60% of patients within 5 years of transplantation,[73] and approximately 10% of liver transplantation recipients have cardiovascular complications within a mean of 5 years post-transplant.[74] Thus, in the transplant population, where hyperuricaemia and cardiovascular disease are more common, there may be a role for treatment of asymptomatic hyperuricaemia. In the renal transplant population, it is unclear whether hyperuricaemia *per se* adversely affects renal graft survival.[16,75] In the general population, treatment of asymptomatic hyperuricaemia with allopurinol has been shown to result in a nonsignificant increase in serum creatinine. This rise was particularly evident in patients with pre-existing renal disease and impaired function (creatinine clearance 40–80 mL/min).[76] There are only limited data in the transplant population. In a small study of ten liver transplant recipients, treatment of asymptomatic hyperuricaemia with allopurinol resulted in improvement in renal function, without significant complications.[77]

In renal transplant recipients, treatment with either allopurinol or benzdiorone (a uricosuric) has been shown to be effective in reducing plasma uric acid in both those with gout and those with asymptomatic hyperuricaemia. While there were few serious adverse effects, it is not stated which group these adverse effects occurred in or whether there was any effect on graft or patient survival.[78] There are no studies examining whether reduction of serum uric acid leads to a reduction in cardiovascular deaths in the transplant population. Given the potential risks of treatment, which are discussed in section 6, further investigation is required before treatment of asymptomatic hyperuricaemia becomes routine clinical practice in the transplant setting.

4. Clinical Features of Gout in Transplant Recipients Compared with the General Population

In the general population the prevalence of hyperuricaemia ranges from 5% to 30%.[79] Gout is the most common form of arthritis in men >40 years of age[1] and in women gout tends to occur after the menopause.[17] In the UK the prevalence of gout in a general practice population was 1.4%, with higher rates (~7%) in men aged >65 years.[80] Both hyperuricaemia and gout are more common in certain ethnic groups such as New Zealand Māori[81] and Taiwanese.[82] Hyperuricaemia and gout are also more common in renal, cardiac and, to a lesser extent, liver transplant recipients, with a prevalence ranging from 5% to 84% for hyperuricaemia and 1.7% to 28% for gout (table I). Gout can recur post-transplant or it can occur *de novo*. While many patients with ESRF are hyperuricaemic, few develop gout.[19] However, the mechanisms preventing gouty attacks in patients with ESRF remain unclear. Impaired immune responses to monosodium urate crystals have been demonstrated with reduced skin reactivity to intradermal or subcutaneous injection of monosodium urate crystals in patients with ESRF.[83] More recently, monocytes from patients with ESRF stimulated with either monosodium urate crystals or lipopolysaccharide *ex vivo* have been shown to produce significantly lower amounts of IL-1β, IL-6 and TNFα compared with monocytes from healthy individuals.[84] Increased body lead stores have also been associated with reduced urate excretion and gout in patients with chronic renal insufficiency.[85]

In both the transplant and general populations gout is more common in men than women and the first metatarsophalangeal joint is commonly involved.[31] However, in transplant patients unusual sites such as the sacroiliac joints may be affected.[86,87] Hyperuricaemia precedes the first attack of gout by several years in the general population. However, post-transplant, the mean length of time before the first attack of gout is reported to be between 17 and 24 months.[12,31,77]

In the general population, tophi usually occur in patients who have had longstanding hyperuricaemia. It has been reported in the European population that up to 30% of patients develop tophi in the first 5 years after the initial episode of gout without anti-hyperuricaemic therapy.[88] In a recent clinical trial in the US, approximately 20% of participants had tophaceous disease, although the authors do not state the duration of disease or whether there had been any previous anti-hyperuricaemic therapy.[89] Tophi occur more frequently in the transplant population and follow a much shorter duration of hyperuricaemia. Baethge et al.[90] reported four renal transplant recipients who developed tophi within 5 years of the initial attack of gout. In another study of heart/heart-lung transplant recipients, 43% of those with gout post-transplant developed severe polyarticular gout and/or tophi after a mean of only 31 months.[31] Tophi may also develop in more uncommon sites in transplant recipients, such as the lumbar spine, with potentially severe complications.[91,92]

5. Liver versus Other Solid Organ Transplants

In liver transplant recipients there appear to be fewer instances of gout and hyperuricaemia than in renal and cardiac transplant recipients. While plasma uric acid increases after liver transplantation, hyperuricaemia is uncommon. In one study only 3 of 59 patients treated with ciclosporin developed transient hyperuricaemia during the first year post-liver transplant.[34]

Several factors may explain the apparently lower incidence of gout in liver transplant recipients. In comparison with patients with ESRD and cardiac

disease who have hyperuricaemia prior to transplantation, patients with liver failure tend to have normal plasma uric acid levels prior to transplantation.[34] In the liver transplant population the relatively lower need for diuretics may also be important.[77] Variations in immunosuppressive regimens and dosage of ciclosporin may also alter the likelihood of hyperuricaemia.[34] Finally, other risk factors for hyperuricaemia, such as hypertension and renal impairment, may be less frequent.

6. Management of Gout in Transplant Recipients

The management of gout poses unique difficulties in transplant recipients. Renal impairment, drug interactions and drug toxicity are challenging issues that need to be considered prior to implementation of therapy.

6.1 Education and Lifestyle Factors

Education and lifestyle issues are of key importance in the management of gout. Compliance with urate-lowering therapy is often poor.[93,94] The long-term nature of anti-hyperuricaemic therapy needs to be carefully explained to patients. In addition, the importance of continuing allopurinol during an acute attack of gout must be highlighted. Compliance is critical to the successful management of gout and education plays a key role in this regard.[95]

Alcohol, in particular beer, is associated with hyperuricaemia and increased risk of gout.[96,97] Consumption of seafood and meat is also associated with hyperuricaemia and increased risk of gout, whereas consumption of dairy products is associated with a reduced risk of hyperuricaemia and gout.[98,99] Interestingly, moderate intake of purine-rich vegetables or protein confers no increased risk of gout.[99]

Traditional dietary advice for hyperuricaemia/gout involved a low purine, low protein and low alcohol diet. Such a diet may reduce serum uric acid by about 0.06–0.12 mmol/L.[7] Long-term adherence to such a restricted diet often proves difficult; however, patients should be counselled to avoid ingestion of large quantities of food and drink that they know precipitates a gouty attack.

More recently, dietary advice has centred on weight reduction rather than restricted purine intake. This is at least in part because of the strong association between hyperuricaemia/gout and the insulin resistance syndrome.[100] In a 16-week study of 13 men with gout, a low calorie diet with moderate carbohydrate restriction and increased proportional intake of protein and unsaturated fat resulted in significant weight loss and reduction in serum lipids, frequency of gouty attacks and serum uric acid concentration.[101] While these findings need to be confirmed in larger, long-term studies they suggest this type of diet may be more beneficial than the traditional low purine diet, which is often high in carbohydrate and saturated fat. This is particularly true for patients with gout and the insulin resistance syndrome. In transplant recipients, where cardiovascular risk is high and other features of the insulin resistance syndrome may be present, such a diet should be encouraged, at least in those with good and stable renal function.

6.2 Management of Acute Attacks of Gout

The American College of Rheumatology recently published quality of care indicators for gout management.[65] These guidelines suggest the use of NSAIDs, colchicine or corticosteroids in patients with acute gout without significant renal impairment or peptic ulcer disease. In the post-transplant setting these same agents are used; however, special care is required in order to avoid complications.

6.2.1 NSAIDs and Cyclo-oxygenase-2 Inhibitors

NSAIDs are effective in the treatment of acute gout but, as discussed in this section, should be used with caution in transplant recipients. In the general population NSAIDs are usually given in a relatively high dose as soon as the symptoms of gout commence. NSAIDs exert their anti-inflammatory effect by inhibiting cyclo-oxygenase (COX), thereby decreasing production of proinflammatory eicosanoids (prostaglandin E_2, prostacyclin and thromboxane A_2) [figure 1]. However, because these eicosanoids also have effects on renal haemodynamics, inhibition of their production can lead to renal vasoconstriction, reduced renal blood flow, salt and water retention, hyperkalaemia and hypertension. NSAIDs can thus precipitate acute renal failure in susceptible individuals. This may be a particular risk in hyperreninaemic situations (e.g. diuretic use, cardiac fail-

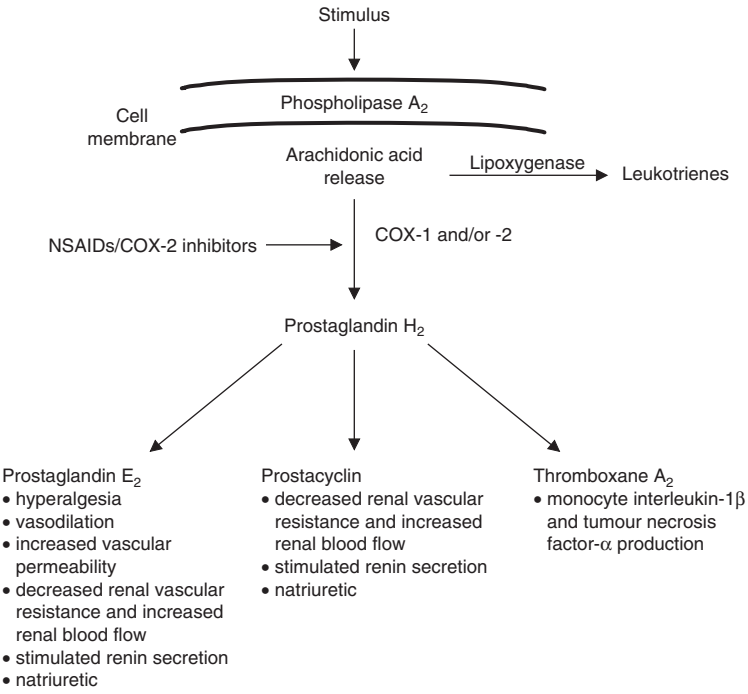

Fig. 1. Cyclo-oxygenase (COX) pathway: NSAIDs/COX-2 inhibitors exert their anti-inflammatory effect by inhibiting COX-1 and/or -2; hence, decreasing production of the proinflammatory eicosanoids prostaglandin E_2, prostacyclin and thromboxane A_2. However, renal haemodynamics and blood flow are also affected.

ure) when renal prostaglandins are critical for the maintenance of renal blood flow. NSAIDs may also cause an acute interstitial nephritis in some patients. This may be mediated by inhibition of COX, leading to increased leukotriene production.

In comparison with other NSAIDs, sulindac has less effect on renal prostaglandin synthesis and renal function.[102] However, whether it is as effective in acute gout as other NSAIDs has not been examined.

COX exists in two forms: COX-1 and COX-2. It is now well recognised that the original concept that COX-1 is responsible for physiological functions (e.g. maintenance of gastric mucosa, renal homeostasis) and COX-2 for 'normal' functions associated with inflammation (e.g. vasodilatation, hyperalgesia) is an oversimplification. Both COX-1 and COX-2 have important and overlapping physiological functions within the kidney. It is generally thought that COX-2 inhibitors do not offer any significant advantage over traditional NSAIDs with regard to renal adverse effects.[103,104] There are two clinical trials comparing the COX-2 inhibitor etoricoxib with the traditional NSAID indomethacin in acute gout.[105,106] In both studies, etoricoxib was comparable with indomethacin in efficacy. In the larger of the two studies, which examined 189 patients, there was only one serious adverse event, namely renal failure in a patient receiving etoricoxib. While the patient was presumed to have been dehydrated on entry into the study, the investigator assigned the adverse event to etoricoxib.[106] Rofecoxib has also been reported to be more effective than diclofenac in the management of acute gout.[107]

There is increasing evidence that COX-2 inhibitors are associated with cardiovascular risk.[108,109] In September 2004 rofecoxib was withdrawn worldwide by Merck when the interim safety analysis of the APPROVe (Adenomatous Polyp Prevention on Vioxx) study showed an increased relative risk of cardiovascular events after 18 months of therapy with rofecoxib compared with placebo.[108] Interest-

ingly, even after a shorter duration, thrombotic events have been reported with COX-2 inhibitors.[110-112] Until the situation is clearer these agents should be used with caution in patients with cardiovascular and/or renal disease, and those who are at increased risk for cardiovascular events. This clearly applies to many transplant recipients.

Another concern with the use of NSAIDs in transplant recipients is the potential interaction with ciclosporin.[113] Among the mechanisms involved in ciclosporin nephrotoxicity is renal vasoconstriction, which is exacerbated in a rat model by the administration of COX inhibitors.[114]

In summary, NSAIDs should be used with caution in transplant recipients and renal function should be closely monitored. Use of specific COX-2 inhibitors does not confer any renal protective advantage and may increase the risk of cardiovascular events in patients who are already at increased risk.

6.2.2 Colchicine

Colchicine is another commonly used agent for the management of acute gout. It appears to work rapidly (within 48 hours) but can be associated with gastrointestinal toxicity prior to the onset of pain relief.[115]

Colchicine is a highly lipophilic drug and is rapidly distributed throughout all tissues in the body. Thus, colchicine has a large apparent volume of distribution (4.87 ± 2.05 L/kg[116]). Peak plasma concentrations are achieved 1–2 hours after oral administration of colchicine.[117] However, although colchicine has a short plasma half-life it has a long-terminal half-life and can be detected in leukocytes 10 days after intravenous administration.[118] Colchicine undergoes extensive enterohepatic recirculation, which may account for the gastrointestinal manifestations associated with colchicine toxicity.

Colchicine myotoxicity is an important adverse effect. It typically affects males aged 50–70 years of age who have renal impairment and are taking relatively low-dose colchicine (1.2 mg/day).[119] While it generally occurs after prolonged exposure, colchicine myotoxicity has been reported after only 2 weeks of therapy.[120] Renal impairment is an important risk factor for the development of colchicine myopathy. In one series of 17 patients with demonstrated colchicine myotoxicity, all had renal impairment and a calculated creatinine clearance of around ≤50 mL/min.[121] Thus, the dose of colchicine should be adjusted for renal impairment and significant renal impairment (creatinine clearance <50 mL/min) should be considered a relative contraindication to the use of colchicine.

Colchicine myotoxicity has been recognised as a particular problem in both renal[122-124] and cardiac transplant recipients.[32,125] In a recent audit of 225 cardiac transplant patients, 32 received colchicine post-transplantation for gout. Of those, 16.5% developed colchicine myotoxicity. Importantly, renal function was similar in those who developed myotoxicity and those who did not (1.06 vs 0.96 mL/s, respectively). The colchicine dosage was 1–2 mg/day and symptoms developed 1.5–4 weeks after commencing colchicine. The authors suggest that even small doses of colchicine for a short period may not be safe in cardiac transplant patients with only mild renal impairment.[32]

Patients with colchicine myotoxicity generally present with subacute proximal muscle weakness and reduced deep tendon reflexes. Serum creatine kinase is usually, but not always, elevated. Electromyography (EMG) demonstrates a myopathic pattern with prominent fibrillations, positive sharp waves and polyphasic small amplitude motor unit potentials. Nerve conduction studies are generally consistent with axonal neuropathy. Muscle biopsy demonstrates a distinctive lysosomal vacuolar myopathy.[119] Although symptoms improve and serum creatine kinase falls on cessation of colchicine, this condition is painful and disabling.

It is important to consider other potential causes of muscle weakness in transplant recipients. Ciclosporin, HMG-CoA reductase inhibitors (statins) and prednisone may all cause myopathy.[126,127] However, in these cases EMG is usually normal or nonspecific and muscle biopsy reveals nonspecific type IIb muscle fibre atrophy.

The combination of colchicine and ciclosporin appears to predispose patients to colchicine myotoxicity.[128] In one study of renal transplant recipients taking colchicine and ciclosporin, colchicine myopathy developed in 50%.[129] The mechanism of drug interaction between colchicine and ciclosporin is thought to involve the multi-drug resistance (MDR-1) transport system, with colchicine being an

MDR-1 substrate and ciclosporin an inhibitor of MDR-1 transport.[128] Colchicine is excreted via both renal and hepatic mechanisms involving MDR-1.[130,131] Ciclosporin has been reported to have no effect on the renal excretion of colchicine in dogs[63] and to profoundly inhibit renal elimination of colchicine in rats.[131] Ciclosporin has also been shown to inhibit hepatic elimination of colchicine in a rodent model.[130] It has also been suggested that ciclosporin inhibits colchicine efflux from nerve and muscle cells, and this combined with reduced renal and hepatic elimination results in myotoxicity.[128] Interestingly, it has also been suggested that colchicine can precipitate ciclosporin toxicity.[123,132]

In summary, colchicine should be used with caution in transplant recipients with gout. Dose reduction is required and a protocol for the use of colchicine in renal transplant recipients has recently been published.[133] However, as indicated, patients with only mild renal impairment may have adverse effects even with reduced doses of colchicine.

6.2.3 Corticosteroids

Corticosteroids are the third main option for the treatment of acute gout. Oral, intra-articular, intravenous and intramuscular corticosteroids can all be effective. In the general population, oral prednisone 20–50 mg/day is effective in improving symptoms of acute gout within 12–24 hours and results in complete resolution in most patients by 7 days.[134] Most transplant recipients receive maintenance prednisone and the acute gouty episode can be treated with an increased dose. Higher doses should be continued until the attack has resolved and then reduced gradually to avoid rebound attacks of gout. In a small study of 13 patients with acute gout, oral or intravenous corticosteroids were used for the treatment of gout. The mean duration of therapy was 11 days (range 2–20 days) and in only one patient was there are rebound attack of gout.[134] Renal impairment and long-term self prescription of oral corticosteroids for gout are associated with the development of intradermal tophi[135] in addition to the other complications of long-term corticosteroid use. Thus, oral corticosteroids are best limited to short courses for acute attacks rather than being used for long-term management of chronic gout.

If only one or two joints are involved and they are easily accessible, an intra-articular corticosteroid is a useful option in the management of acute gout.[136] Relief from symptoms usually occurs within 12–24 hours.[136] Intra-articular triamcinolone (triamcinolone acetonide) has been shown to be as safe and as effective as indomethacin in the treatment of acute gout.[137] Because septic arthritis can mimic gout, it is important that joint fluid be aspirated, cultured and examined for crystals at the time of injection.

Corticotropin (adrenocorticotropic hormone [ACTH]) has also been shown to be useful for the management of gout in patients with a variety of other medical problems, including cardiac failure and renal insufficiency.[138,139] In the general population, patients presenting within 24 hours of onset of acute gout a single intramuscular dose of corticotropin 40IU results in very rapid relief of symptoms (3 ± 1 hours).[140] It has been suggested that the beneficial effect of corticotropin is due to the resulting adrenocorticosteroid hormone release.[140] However, a recent rodent model of gouty arthritis showed that intra-articular corticotropin inhibited the inflammatory process by a corticosteroid-independent process. The anti-inflammatory effect of corticotropin was inhibited by a selective melanocortin-3 receptor antagonist, while the anti-inflammatory activity of corticotropin was retained with a selective melanocortin-3 receptor agonist.[141] Thus, corticotropin may be a useful adjunct in the management of acute gout for patients receiving corticosteroids, such as transplant recipients. Long-acting preparations of corticotropin, such as depot tetracosactide (tetracosactrin), are available and may be preferable to shorter-acting preparations.

6.3 Preventative Treatment – Urate-Lowering Therapy

Gout is the only chronic form of arthritis that can be cured. With long-term reduction of plasma uric acid concentrations, crystals present in joints, soft tissues and tophi dissolve and acute attacks of gout abate. In the general population, sustained reduction of plasma uric acid to <0.36 mmol/L is generally required, although concentrations may need to be lower for resorption of tophi.[142-145]

In the general population, urate-lowering therapy should be commenced in patients who have hyperuricaemia and gouty arthritis with tophi, gouty erosive change on radiograph or two or more attacks per year.[65] Urate-lowering therapy may be considered after one attack in the transplant population since the majority of patients will experience repeated attacks once gout occurs (unpublished data). Reduction in plasma uric acid can be achieved by either increasing the excretion of uric acid through the use of uricosuric agents or by reducing the formation of uric acid production by the use of xanthine oxidase inhibitors.

6.3.1 Allopurinol

Allopurinol, through inhibition of xanthine oxidase, reduces the production of uric acid from purines (figure 2). It is the most frequently used hypouricaemic agent. However, of particular relevance in the transplant setting is the important interaction with azathioprine. Mercaptopurine, the active metabolite of azathioprine, is partly inactivated by xanthine oxidase (figure 2). Inhibition of xanthine oxidase by allopurinol may, therefore, lead to increased levels of mercaptopurine and myelosuppression.[146] It is recommended that the dose of azathioprine should be reduced by 50–75% before commencing allopurinol and that the starting dose of allopurinol be lower than normal. However, despite dose adjustment, patients can become pancytopenic with this combination after months or even years of therapy.[32,147] Thus, the azathioprine-allopurinol combination must be used with great caution and with careful blood monitoring for the duration of combination therapy. While there may be a reluctance to reduce immunosuppression for fear of transplant rejection, there are case reports of successful management of gout by this means.[148]

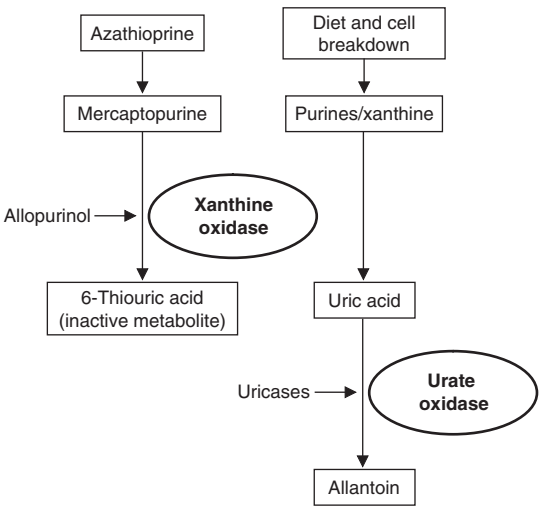

Fig. 2. Metabolism of azathioprine and purines: uric acid is formed from purines via xanthine oxidase, which is also involved in the metabolism of azathioprine. Uric acid is broken down by urate oxidase, which is absent in humans allowing the development of hyperuricaemia.

6.3.2 Uricosuric Agents

Uricosuric agents, such as probenecid, lower plasma uric acid by increasing renal excretion of uric acid. Deposition of uric acid crystals within the kidney may occur as a consequence of increased uric acid excretion through the kidney. Ultimately, this can lead to urate nephropathy and/or formation of uric acid stones. To minimise the risk of these complications, uricosuric agents should be commenced at a low dose and gradually increased. Urine volume should be at least 1500 mL/day and the urine should be alkalinised (target pH 6.4–6.8). A history of renal calculi and/or poor urine volume are contraindications for the use of uricosuric agents.

Traditional uricosurics, such as probenecid, are ineffective in renal impairment. However, the benzofuran derivative, benzbromarone may be a useful alternative. Benzbromarone, a potent uricosuric agent, lowers plasma uric acid by inhibiting postsecretory tubular resorption of uric acid.[149] Benzbromarone at low dosage (75–100 mg/day) has been reported to be more potent than allopurinol 300 mg/day[150] and equipotent to probenecid 1–1.5 g/day in the general population.[151] Benzbromarone appears to have only slightly impaired efficacy in patients with impaired renal function, resulting in a clinically useful reduction of plasma uric acid.[150] Benzbromarone has also been shown to be beneficial in renal transplant recipients with a creatinine clearance >25 mL/min.[152]

Benzbromarone is available in New Zealand (with special application) and in Europe, although in Spain its use is restricted to specialists treating allopurinol-intolerant patients with renal failure, renal transplant or tophaceous or polyarticular gout.[153] Benzbromarone is not available in the US, largely

because of concerns over the potential for hepatotoxicity. Hepatic toxicity, rarely leading to death, has been reported in patients taking high doses of benzarone (an analogue of benzbromarone)[154] and benzbromarone.[155-157] However, in the largest series published, albeit retrospective data, there was no significant liver toxicity in 200 patients treated for a mean of 5 years with benzbromarone 75–125 mg/day.[158]

In summary, benzbromarone is a useful agent in patients with renal impairment both in the general and transplant populations. It appears to be safe when used in low dosages (≤100 mg/day); however, liver function should be monitored closely and benzbromarone therapy should be ceased if liver function abnormalities occur.

6.3.3 Newer Agents

Urate oxidase catalyses the conversion of uric acid to allantoin (figure 2), which is more water soluble and, thus, more readily excreted via the kidneys. This enzyme is absent in humans. Urate oxidase has been extracted from *Aspergillus flavus*, and used in the treatment and prevention of hyperuricaemia and tumour lysis syndrome.[159] Successful treatment of severe gout in a patient post-cardiac transplantation with short-term urate oxidase has been reported.[160] Ippoliti et al.[161] reported the use of uricozyme (urate oxidase) in six heart transplant recipients receiving ciclosporin, azathioprine and prednisone who developed acute gout. Plasma uric acid levels rapidly normalised and symptoms of gout resolved with no change in serum creatinine, creatinine clearance or blood count. The authors suggest that urate oxidase is a therapeutic option that enables transplant recipients to overcome hyperuricaemia without compromising immunosuppressive therapy.[161] More recently, a recombinant *A. flavus* uricase, rasburicase, has been approved by the US FDA for single use in prevention of tumour lysis syndrome. Rasburicase has been shown to rapidly and profoundly lower plasma uric acid and resorb tophi. However, repeated use of recombinant uricase has been reported to result in the development of antibodies,[159] allergic reactions and anaphylaxis.[162] The potential for immunogenicity needs to be resolved before considering the use of rasburicase in the transplant setting. In this regard, a pegylated uricase that has reduced antigenicity and an increased half-life has been developed.[163] A pilot study of subcutaneous pegylated uricase has shown rapid and sustained reduction in plasma uric acid levels.[164] While antibodies to uricase did not develop, low-titre antibodies to the polyethylene glycol did occur in five patients and in three of the five antibody-positive patients there were delayed injection-site reactions.[165] These agents have potential for use in patients in the general and transplant populations with gout who have not responded to standard therapy. Further clinical trials are awaited.

Febuxostat is a new non-purine selective inhibitor of xanthine oxidase. In hyperuricaemic patients with gout it results in significant reductions in serum uric acid compared with placebo.[89] In patients with normal, mild or moderate impairment in renal function a single dose of febuxostat has no significant effect on renal function.[166] Further study is required, but this agent may provide an alternative to allopurinol in both the general and the transplant populations.

6.4 Alteration of Immunosuppressive Therapy

An alternative approach to urate lowering is to alter immunosuppressive therapy. This needs careful consideration by both patient and physician. In a case report, changing from ciclosporin to tacrolimus resulted in resolution of previously difficult to control gout and normalisation of plasma uric acid without a change in renal function.[22] Sirolimus, another potent immunosuppressive agent, is structurally homologous to tacrolimus but has a different mechanism of action. Sirolimus has been shown to be an alternative to ciclosporin in the prevention of graft rejection in renal transplantation when combined with either azathioprine[167] or mycophenolate mofetil.[168] Furthermore, in renal transplant recipients treated with sirolimus, serum uric acid concentrations are significantly lower than in patients treated with ciclosporin, with hyperuricaemia evident in 18.9% of sirolimus- versus 52.4% of ciclosporin-treated patients after 3 months of therapy.[169] Mycophenolate mofetil has also been used as an alternative immunosuppressive to azathioprine in renal transplant recipients with gout. This allows the 'safe' introduction of allopurinol with no adverse

drug reaction or loss of graft function.[170] Thus, in patients with troublesome gout, replacement of ciclosporin with an alternative immunosuppressive agent may help reduce serum uric acid and cessation of azathioprine may allow 'safe' introduction of allopurinol.

6.5 Management of Associated Conditions

Hypertension and hyperlipideamia are common problems that are associated with both gout and transplantation. Some agents used in the management of these conditions can help reduce plasma uric acid levels, while others can increase plasma uric acid. Therefore, consideration should be given to the most appropriate therapeutic option.

In comparison with the loop and thiazide diuretics, which increase plasma uric acid, the angiotensin II receptor antagonist losartan has been reported to have uricosuric effects.[171] In the general population, losartan may be useful to help prevent the thiazide-induced increase in plasma uric acid.[172] While its role in the transplant setting is yet to be established,[173-176] it could be considered an additional treatment option in transplant patients with troublesome gout. The calcium channel antagonist amlodipine has also been shown to be an effective antihypertensive agent in renal transplant recipients.[177,178] Furthermore, amlodipine significantly increased uric acid clearance and reduced plasma uric acid in comparison with tertatolol or perindopril in renal transplant recipients.[179,180] Some calcium channel antagonists, such as verapamil and diltiazem, increase serum ciclosporin concentrations;[181] however, amlodipine has no effect on ciclosporin concentrations.[179,182] Thus, clinicians need to consider the underlying reasons for use of loop or thiazide diuretics and whether alternative agents, which do not result in retention of uric acid, could be used.

Hyperlipidaemia is also common in patients with gout in both transplant recipients and the general population. In transplant recipients there is an increase in total cholesterol, predominantly in the form of low-density lipoprotein (LDL), as well as an increase in triglycerides and cholesterol in the form of very low-density lipoproteins. Statins are the most commonly prescribed lipid-lowering drugs, and they lead to a reduction in LDL cholesterol and a slight decrease in triglycerides. In patients with primary hyperlipidaemia, atorvastatin, but not simvastatin, results in a reduction of serum uric acid.[183] However, the same uric acid-lowering effect of atorvastatin was not observed in patients with combined hyperlipidaemia.[184] Both ciclosporin and statins are metabolised by cytochrome P450 3A4 and, thus, there is potential for interaction between these two agents. Of particular concern is the potential for myositis and rhabdomyolysis.[185,186] However, despite the risk of myositis, patients have been successfully treated with the statin-ciclosporin combination.[187] The risk of such combination therapy must be weighed against the potential cardiovascular benefit in a group of patients at high risk of cardiovascular death. Further clinical studies in transplant recipients are needed to determine whether any individual statin confers an advantage with respect to uric acid reduction.

Fenofibrate is used to reduce plasma lipid levels, in particular triglycerides. Fenofibrate, but not other fibric acid derivatives (fibrates), has been shown to reduce plasma uric acid through enhanced uric acid clearance.[188-190] Like losartan, fenofibrate also increases oxypurinol clearance.[189] Furthermore, in patients with gout receiving established treatment with allopurinol or benzbromarone, the addition of fenofibrate results in further plasma uric acid reduction.[191-193] However, the fibrates (both fenofibrate and gemfibrozil) have been associated with an increase in serum urea and creatinine in both the general and the transplant populations.[194-196] The mechanism of fibrate-induced renal impairment is not fully elucidated. While there are reports that plasma ciclosporin concentrations are reduced when ciclosporin is combined with fibrates,[197] the decline in renal function does not appear to be due to rejection in renal transplant recipients.[196] It has been hypothesised that fibrates activate peroxisome proliferator-activated receptors, resulting in inhibition of COX-2 and, thus, impaired production of vasodilatory prostaglandins.[195] Therefore, while fenofibrate may be useful in terms of its effects on uric acid in transplant patients with gout, its effects on renal function are of concern. This is particularly so in renal transplant recipients as a decline in renal function may lead to concern about rejection and renal biopsy.

In summary, careful choice of treatments for the management of associated conditions such as hypertension and hyperlipidaemia may help reduce plasma uric acid levels.

7. Conclusions

Gout is a common and challenging problem in the transplant population. The development of gout can have a significant impact on quality of life post-transplantation. The risks and benefits of therapeutic options for both gout and associated conditions such as hypertension and hyperlipidaemia must be considered. In particular, the rationale for long-term use of diuretics should be questioned and consideration given to the use of alternative agents if required for hypertension. Ideally, most patients should receive hypouricaemic therapy, although this may require adjustment to their immunosuppressive therapy and careful monitoring. Newer hypouricaemic agents, such as febuxostat or uricase, may prove to be useful alternative agents in the transplant setting and clinical studies are awaited with interest.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest to declare.

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