Allopurinol Dosing in Renal Impairment: Walking the Tightrope Between Adequate Urate Lowering and Adverse Events

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ABSTRACT

Allopurinol is the mainstay of urate-lowering therapy for patients with gout and impaired renal function. Although rare, a life-threatening hypersensitivity syndrome may occur with this drug. The risk of this allopurinol hypersensitivity syndrome (AHS) is increased in renal impairment. The recognition that AHS may be because of delayed-type hypersensitivity to oxypurinol, the main metabolite of allopurinol, and that oxypurinol concentrations are frequently elevated in patients with renal impairment prescribed standard doses of allopurinol has led to the widespread adoption of allopurinol-dosing guidelines. These guidelines advocate allopurinol dose reduction according to creatinine clearance in patients with renal impairment. However, recent studies have challenged the role of these guidelines, suggesting that AHS may occur even at low doses of allopurinol, and that these guidelines lead to under-treatment of hyperuricemia, a key therapeutic target in gout. Based on current data, we advocate gradual introduction of allopurinol according to current treatment guidelines, with close monitoring of serum uric acid concentrations. In patients with severe disease and persistent hyperuricemia, allopurinol dose escalation above those recommended by the guidelines should be considered, with careful evaluation of the benefits and risks of therapy. Further work is needed to clarify the safety and efficacy of allopurinol dose escalation, particularly in patients with renal impairment.

Gout is the most common form of inflammatory arthritis affecting men, and prevalence rates are increasing worldwide (1). The principal manifestations of disease occur because of hyperuricemia leading to deposition of monosodium urate crystals within the joints. In early disease, patients present with recurrent episodes of self-limiting acute inflammatory arthritis. Over time, in the presence of prolonged hyperuricemia, tophaceous disease may develop, causing pain, mechanic joint disruption, severe articular and bone damage, and musculoskeletal disability. Urate-lowering therapy is a critical component of the long-term management of gout, and is indicated for patients with recurrent acute attacks (≥2 attacks per year), chronic gouty arthropathy, tophi, or radiographic changes of gout (2,3). In recent years, there has been growing recognition that intensive lowering of serum uric acid (SUA) to a target of ≤6 mg/dl (360 µmol/l) is required to achieve suppression of acute gout flares and regression of tophi (4,5).

There are emerging data that indicate that hyperuricemia may also play a causative role in other disorders such as hypertension, progressive nephropathy, and cardiovascular disease (6–8). Rat studies have shown that oxonic acid-induced hyperuricemia promotes hypertension in normal rats and progressive renal disease in the rat remnant kidney model, and that these effects can be inhibited by allopurinol (9,10). A small study of patients with hyperuricemia and chronic kidney disease has suggested that urate lowering with allopurinol might reduce the progression of renal disease (11). Furthermore, in patients with gout, effective urate-lowering therapy improves renal function; however, this effect may be due to reduced nonsteroidal anti-inflammatory drug use that is achieved when gout is adequately controlled (12). At present, treatment of asymptomatic hyperuricemia to prevent cardiovascular disease or progressive nephropathy is not recommended (3). Nevertheless, it is probable that intensive treatment of hyperuricemia with allopurinol has additional benefits for patients with renal impairment and gout.

Allopurinol is recommended as first-line urate-lowering therapy in patients with gout and renal impairment (2,3). This agent has the benefits of once daily dosing and has efficacy in patients with renal impairment. However, allopurinol dosing may be problematic in patients with renal impairment because of the risk of serious toxicity.

Allopurinol Pharmacokinetics

Following oral administration, allopurinol is absorbed within 2–3 hours and has an oral bioavailability of ~67 ± 23% (13). Allopurinol is rapidly metabolized to
Allopurinol Hypersensitivity Syndrome

In the majority of patients allopurinol is well tolerated. Approximately 2% of the patients develop a mild rash (22). However, allopurinol can be associated with a rare but potentially life-threatening allopurinol hypersensitivity syndrome (AHS), which is characterized by rash (e.g., toxic epidermal necrolysis and exfoliative dermatitis), cosinophilia, leukocytosis, fever, hepatitis, and progressive renal failure. The true incidence of AHS is unknown, although it is estimated to be ~0.1%. In the hospital-based Boston Collaborative Drug Surveillance Program, 7 out of 1835 (0.38%) patients treated with allopurinol had a life-threatening reaction, although not all of these were AHS (22). Whether the frequency of life-threatening adverse reactions is as high in nonhospitalized patients is unknown.

A number of studies have reported that renal impairment, diuretic use, and recent commencement of allopurinol therapy are risk factors for the development of severe AHS (Table 1). Many cases of AHS have occurred in patients treated for asymptomatic hyperuricemia, rather than proven allopurinol indications (15,23–25). It is unclear whether asymptomatic hyperuricemia is a specific risk factor, although a recent case-control study of AHS did report lower rates of gout in AHS cases than allopurinol-tolerant controls (26).

Some cases of AHS occur as a result of T-cell-mediated immune reactions to oxypurinol (27). More recently, a Taiwanese case-control study of AHS has identified HLA-B*5801 as a significant risk factor for toxicity; this allele was found in 100% of the AHS cases and 15% of the allopurinol-tolerant controls (odds ratio of 5.13 mg/l (33.75 μM) (21). However, this concentration of oxypurinol is considerably lower than those observed in clinical practice (17,20). It is also at the lower end of the reported therapeutic range of oxypurinol of 30–100 μmol/l at 6–9 hours post dose (15,16). Despite this, there are a group of patients with both normal and impaired renal function with high oxypurinol concentrations (even >100 μmol/l) who have inadequate lowering of SUA. In some cases, this may be because of concomitantly prescribed medications such as frusemide, which reduces both uric acid and oxypurinol excretion. The underlying cause of such resistance to allopurinol is unclear, although genetic variations in enzymes other than XO (e.g., aldehyde oxidase) in the metabolism of allopurinol may be one potential mechanism.

### TABLE 1. Risk factors for allopurinol hypersensitivity reactions

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<thead>
<tr>
<th>Risk factor</th>
<th>References</th>
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<tbody>
<tr>
<td>Recent onset of allopurinol</td>
<td>15,23,24,26</td>
</tr>
<tr>
<td>treatment</td>
<td></td>
</tr>
<tr>
<td>Renal impairment</td>
<td>15,23,25,26,28,43</td>
</tr>
<tr>
<td>Diuretic therapy</td>
<td>15,23,25,28,43</td>
</tr>
<tr>
<td>Presence of HLA-B*5801 allele</td>
<td>26</td>
</tr>
<tr>
<td>Allopurinol dose?</td>
<td>Positive association: 15,23,25,44</td>
</tr>
<tr>
<td></td>
<td>Negative association: 26,32,33</td>
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580.3; 95% CI: 34.4–9780.9) (26). If these results are confirmed in other populations, human leukocyte antigen (HLA) genotyping may allow for improved tailoring of urate-lowering therapies for patients with gout, assisting with both the choice of agent and dosing regimen. The mortality associated with AHS has been reported to be as high as 27% (25,28). There is no cure for AHS, and early recognition and drug withdrawal are important. Management consists of supportive care, and while corticosteroids have been used, their role is controversial (23,25). Whether increased excretion of oxypurinol through uricosuric drugs [such as probenecid (29)] or hemodialysis has a role in the management of AHS is unknown. Desensitization has been used successfully for patients with mild cutaneous hypersensitivity reactions, but is contraindicated for patients with life-threatening AHS (30).

Allopurinol Dosing Guidelines: Rationale and Limitations

The role of allopurinol dosing in AHS was highlighted by Hande et al., who reported that most of the patients in their institution and literature review with AHS had preexisting renal impairment and were treated with full doses of allopurinol (≥300 mg daily) (15). This observation, along with studies of oxypurinol clearance in patients with renal impairment, led to the development of dosing guidelines, indicating that allopurinol doses should be adjusted according to CrCL (Table 2). These guidelines are of great practical relevance in gout, as renal impairment is a frequent finding in patients with gout. For example, the UK General Practice Database study demonstrated that patients with gout were five times more likely to have renal impairment than osteoarthritis controls (31). In our recent study of 250 patients treated with gout in secondary care, 118 (47.2%) had a CrCL of ≤60 ml/minute (32). Thus, according to these guidelines, almost half of our patients with gout should have dose reduction of allopurinol in order to reduce the risk of AHS.

However, these guidelines have been challenged by a number of recent observations. First, the relationship between oxypurinol concentrations and AHS remains unproved. In addition, no study has systematically demonstrated that dose reduction in renal impairment, as recommended by these guidelines, reduces the risk of severe AHS. In a recent large case–control study of severe AHS, there was no difference in allopurinol doses between cases with AHS and allopurinol-tolerant controls (indeed, there was a trend to lower doses in the AHS group) (26). In this study, the median allopurinol dose in the AHS group was 100 mg/day, and only 7% of cases were taking allopurinol at ≥300 mg/day. Furthermore, in another case–control study of allopurinol dosing, AHS did not occur more frequently in those taking higher than recommended doses, compared with those on recommended doses (33). In our recent study of allopurinol dosing, minor hypersensitivity occurred in 4 of the 250 patients with gout, and none of these patients were taking higher than recommended doses of allopurinol (32).

The allopurinol dosing guidelines may also have a detrimental influence on control of hyperuricemia in patients with gout. We have recently studied the effect of these guidelines on target SUA concentrations in 250 patients attending rheumatology clinics in South Auckland, New Zealand (32). In our study, target SUA concentrations (≤6 mg/dl) were achieved in 28% of non-Polynesian patients on recommended allopurinol doses, compared with 60% of those on higher than recommended doses (p < 0.05). Furthermore, target SUA concentrations (≤6 mg/dl) were achieved in only 6% of Polynesian patients on recommended allopurinol doses, compared with 20% of those on higher than recommended doses (p < 0.05). The low rate of normouricemia in allopurinol-treated Polynesian patients reflects the severity of disease, which is well described in this population (34,35). Overall, these results indicate that adherence to the allopurinol dosing guidelines frequently results in suboptimal control of hyperuricemia.

Options for Therapy in Renal Impairment

The original purpose of the allopurinol dosing guidelines was to reduce the risk of serious adverse reactions related to allopurinol while not reducing the efficacy. These guidelines may be most suitable as the starting dose in an individual patient, as suggested by the recently published quality of care indicators for gout (2). The optimal allopurinol dosing regimen remains uncertain, and further work is required to clarify the safety and efficacy of allopurinol dose escalation, particularly in patients with renal impairment. At present, we recommend initiation of allopurinol at low dose (typically 50–100 mg daily) with gradual dose escalation to a maintenance dose that achieves a SUA ≤6 mg/dl, with care and consideration if increasing beyond the dose suggested by the guidelines. This approach requires close monitoring of SUA concentrations, and careful analysis of the risks and benefits of this approach. For example, given the very small risk of severe adverse drug reactions in patients taking allopurinol, the calculated risk of persistent hyperuricemia may be greater than the risk of allopurinol-related adverse events, especially for patients with severe gout. Gradual introduction of allopurinol is recommended for all patients with gout, as initiation of full-dose allopurinol may lead to a rapid decline in SUA concentrations, with precipitation of an acute gout flare.

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/minute)</th>
<th>Maintenance dose allopurinol</th>
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<tr>
<td>0</td>
<td>100 mg every 3 days</td>
</tr>
<tr>
<td>10</td>
<td>100 mg every 2 days</td>
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<tr>
<td>20</td>
<td>100 mg/day</td>
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<tr>
<td>40</td>
<td>150 mg/day</td>
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<tr>
<td>60</td>
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<tr>
<td>120</td>
<td>350 mg/day</td>
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<tr>
<td>140</td>
<td>400 mg/day</td>
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We also wish to emphasize the importance of prophylaxis therapy (particularly low-dose colchicine) while commencing allopurinol to prevent flares of disease related to sudden fluctuations in SUA concentrations (36). If target SUA concentrations are not achieved with this approach, compliance should be reviewed; measurement of oxipurinol concentrations may aid in this regard. Alternative or additional urate-lowering therapies should also be considered. For those patients with residual renal function, addition of uricosuric therapies are frequently beneficial, particularly benz bromarone if moderate renal impairment is present (5). Use of this agent does require close monitoring for hepatotoxicity. There are several new therapeutic agents in late-phase development for gout, including febuxostat, a potent nonpurine XO inhibitor that does not rely on renal clearance for its excretion (37). Although this agent appears to be well-tolerated in patients with renal impairment, long-term safety in severe renal impairment and end-stage renal disease is yet to be established (38).

**Allopurinol Therapy in Dialysis and Renal Transplant Recipients**

While hemodialysis reduces SUA concentrations, many patients will require additional urate-lowering therapy to achieve a sufficient reduction in SUA to prevent gout flares and promote resorption of tophi. In patients undergoing dialysis, the dose of allopurinol should be reduced. A usual starting dose is 100 mg alternate days given post dialysis, which may be cautiously increased to 300 mg according to response. If dialysis occurs on a daily basis an additional 50% of the dose may be required post dialysis (39). For dialysis-dependent patients, the phosphate binder sevelamer has a modest urate-lowering effect, and may be of benefit as an adjunct to allopurinol (40). Interestingly, the frequency of gout attacks often falls in patients with end-stage renal disease, despite persistent hyperuricemia. This observation has been attributed to altered monocyte cytokine responses to monosodium urate crystals in patients with chronic renal impairment (41).

Renal transplant recipients who experience gout prior to transplantation are likely to have had gout post transplant; thus allopurinol should be continued post transplant. The management of gout in transplant recipients has been recently reviewed (42). Minimizing diuretic use is of particular importance in renal transplant recipients.

**Conclusions**

Although allopurinol has been in use for over 30 years, optimal dosing remains unclear, particularly in patients with renal impairment. Whether increasing allopurinol doses above the recommended dose results in additional urate lowering without increased toxicity is the subject of ongoing investigation. The role of oxypurinol concentrations in guiding such dose adjustments also warrants investigation.

**References**