ABSTRACT

Gout is a prototypical crystal arthritis characterized by hyperuricemia and deposition of monosodium urate (MSU) crystals. Allopurinol is the time honored first-line treatment for chronic gout. Recent data reveals that restricting allopurinol dose to 300 mg/day sub-optimally controls gout in a substantial number of patients. Patients with renal impairment and gout pose special management challenges. Febuxostat is a novel non-purine xanthine oxidase inhibitor that offers an alternative to patients intolerant or unresponsive to allopurinol. Promising drugs on the anvil include pegloticase and interleukin 1 inhibitor- rilonacept.

INTRODUCTION

Gout is the commonest crystal arthropathy seen in clinical practice. It primarily afflicts the joints and kidneys. Articular gout is divided into four clinical stages: asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout and chronic tophaceous gout. It needs to be appreciated that hyperuricemia is a common biochemical problem. The vast majority of patients with hyperuricemia do not develop clinical problems like gout or renal disease. The development of gout depends on many factors including age of the patient and degree of hyperuricemia. Acute gouty arthritis generally follows longstanding hyperuricemia. While gout typically causes monoarticular or pauciarticular (2, 3 or 4 joints) involvement, polyarthitis (>5 joints) can also be seen occasionally. Polyarticular disease is seen in the elderly and in postmenopausal women on diuretics. Other less common manifestations include tenosynovitis and bursitis. Intercritical gout refers to the symptom free period in between attacks. The second attack may never occur or occur after a variable period of time. Chronic tophaceous gout is seen in individuals with uncontrolled, long standing hyperuricemia. Gout in the elderly is being increasingly seen. Risk factors include diuretic use and renal insufficiency. Unlike classical gout, gout in elderly does not exhibit male preponderance, articular involvement may be polyarticular and tophi come up relatively early. Renal disease in gout can assume 3 forms: urate nephropathy due to deposition of urate crystals in the renal interstitium; acute uric acid nephropathy due to precipitation of uric acid in the collecting tubules (usually in the setting of chemotherapy instituted for a lymphoproliferative disorder) and uric acid stones. It is interesting to note that not all patients with uric acid stones have hyperuricemia. Also, patients with gout have an increased tendency to develop stones other than uric acid. Other important contributory factors to renal dysfunction in gout include hypertension and non steroidal anti inflammatory (NSAID) use. The salient points about gout are summarized in Box 1. The challenges and complexities in the management are listed in Table 1. This chapter summarizes the current treatment principles for gout and outlines the recent advances.

CURRENT MANAGEMENT PRINCIPLES

Investigations

The gold standard of diagnosis of gout is the demonstration of MSU crystals in the synovial fluid or tophi. Though MSU crystals may be picked up on ordinary light microscopy, polarized light microscopy

Box 1: Key Points about Gout

- Crystal identification is the gold standard for diagnosis of gout. Serum uric acid (SUA) may be normal during acute attack of gout
- Hyperuricemia and gout are not synonymous. All patients with joint pains and high SUA do not have gout.
- Gout typically causes monoarthrits- red, hot joint
- The differential diagnosis of a red, hot joint includes gout and septic arthritis.
- Women account for ~5% cases of gout. 90% of affected women are postmenopausal. Gout is exceedingly rare in premenopausal women. Premenopausal women with gout should be screened for HT, renal insufficiency, diuretic use
- Gout is an unlikely diagnosis in premenopausal women with polyarticular disease
- Greatest utility of SUA is in monitoring treatment efficacy with xanthine oxidase inhibitors
- Detection of hyperuricemia mandates search for co-morbidities like metabolic syndrome, hyperlipidemia, diabetes etc
- Asymptomatic hyperuricemia does not warrant allopurinol
- Allopurinol should never be instituted or discontinued during acute attack of gout
- Acute attack: Treatment of choice NSAIDs. Where contraindicated, corticosteroids may be used
- Main role for colchicine is in prophylaxis of recurrent attacks (>2-3 attacks/year)
Table 1: Current Challenges and Complexities in the Management of Gout

- Increasing prevalence of disease
- Lack of availability of polarizing microscopy and over reliance on serum uric acid for diagnosis
- Atypical presentations
- Issues in the elderly: polyarticular disease, tophi come up early, male preponderance not seen, NSAIDs toxicity common
- Co-morbidities like chronic kidney disease, cardiovascular disease necessitate change in treatment
- Limitations of allopurinol: under dosing resulting in suboptimal control, hyperuricemia to drug, refractoriness

which permits detection of birefringence characteristics is ideal. Crystal identification relies on shape and birefringence. MSU crystals may be intracellular or extracellular, are needle shaped and exhibit strongly negative birefringence. ‘Strong’ birefringence means that crystal is bright and easily seen whereas ‘weakly’ birefringent crystal is subdued and difficult to see. ‘Positive’ and ‘negative’ birefringence refers to colors in reference to alignment of the red compensator. MSU crystals are yellow when parallel to the slow axis of the red compensator (negative birefringence). In contrast, CPPD crystals are blue when parallel to the slow axis of the red compensator (positive birefringence). A change in the orientation of the red compensator from parallel to perpendicular leads to change in the color of the crystals. MSU crystals can often be demonstrated during intercritical period from quiescent joints which have been the sites of previous attacks.

Serum uric acid (SUA) has limited utility in the diagnosis of gout and a diagnosis of gout should never be based only on SUA levels. The levels of uric acid may be normal during an acute attack since ACTH released in response to stress is uricosuric. Conversely, not all patients with joint pains and a raised SUA have gout. Therefore, save in classical attacks or typical situations, attempts should be made to obtain synovial fluid for crystal studies. The major utility of SUA is in monitoring response to treatment in patients on allopurinol. Estimation of 24 hour urinary uric acid (normally less than 800 mg) is sometimes required to differentiate overproducers from under excretors. Alcohol, radiographic contrast, and drugs like aspirin may interfere with urinary uric acid excretion.

Radiographs in early gout may be normal except for soft tissue swelling. Patients with chronic gout show punched out erosions with overhanging edges. The erosions may be in the joint or away from the joint. The joint space is preserved till late and periarticular osteopenia is absent or minimal.

TREATMENT

Diet and lifestyle changes are important adjuncts. Weight loss helps lower SUA. Purines in diet should be restricted to <200 mg/day. However, dietary purine restriction has only a modest effect on SUA lowering. A low purine diet is not the same as a low protein diet. Protein intake needs to be restricted only in those consuming very high amounts of proteins which is not common in Indians. Items rich in purine which should be avoided include red meat, liver, kidney, sardines, shell fish and some other varieties of sea food. The total amount of purine in the diet is more important than the item consumed. Spinach, pulses (lentils), peas, mushrooms, cauliflower, soya beans etc are rich in purines but cause much lower rise in SUA than meat. Tomatoes, while not being purine rich, can precipitate gout in some patients and are best avoided. Tophaceous gout, renal insufficiency, uric acid stones and patients on diuretics. Asymptomatic hyperuricemia does not warrant knee jerk treatment with allopurinol. On the contrary, this situation should provoke a search for other co-morbidities associated with metabolic syndrome like obesity, hypertriglyceridemia, insulin resistance etc. There is no cut off limit above which asymptomatic hyperuricemia should be treated.
The 5 year cumulative risk of developing gout is nearly 30% in those with SUA >10 mg/dL. Pharmacotherapy may be indicated in patients with a history of kidney stones and in asymptomatic patients with very high serum urate > 12 mg/dL in men or >10 mg/dL in women. All attempts should be made to identify risk factors and institute life style changes in such patients before instituting allopurinol. Prophylactic use of allopurinol is recommended in some situations like tumor lysis syndrome.

Aspirin doses in the range of 600–2400 mg/day cause uric acid retention while doses in excess of 4000 mg/day are uricosuric. A practical question often asked is regarding continuation or instituted if so warranted by the cardiac condition. thiazide diuretics also cause rise in SUA. in patients with hypertension, these may be substituted by other antihypertensives if possible, while in patients with gout and co-existent congestive cardiac failure it might be necessary to continue thiazides.

Drugs to treat hyperuricemia include xanthine oxidase inhibitors like allopurinol (uricosurics) or uricosuric agents like probenecid and sulfipyrazone. Uricosuric agents are seldom used. These are ineffective in renal insufficiency and carry a small risk of uric acid stone formation. Despite majority of the patients being under-excretors of uric acid, allopurinol is used as the first line drug for lowering urate in all patients because of its efficacy, safety and excellent benefit to risk ratio in both over producers and under-excretors of urate. The institution of allopurinol is deferred till 1-2 weeks after the acute attack. The dose varies from 100-900 mg p.o. given once daily. The dose is governed by the SUA levels. The ideal SUA to aim for is below 5-6 mg/dL. Dose reduction is required in renal insufficiency. Allopurinol is frequently under-dosed in clinical practice as there is a widely held, albeit erroneous, belief that the maximal dose is 300 mg/day. The figure of 300 mg/day stems from dosing guidelines for allopurinol in chronic kidney disease (CKD) dating from the 1980s. The intent of the older guidelines was to lessen the incidence of allopurinol hypersensitivity syndrome, particularly with CKD. It is now clear that these guidelines are not evidence based, fail to adequately treat hyperuricemia, and also fail to prevent allopurinol hypersensitivity syndrome in all patients, including those with CKD. The duration of antihyperuricemic therapy is indefinite.

Allopurinol is associated with side effects in quite a few patients. These include skin rash, dyspepsia, diarrhea, headache. Uncommon side effects include fever, bone marrow suppression, interstitial nephritis, hepatitis and toxic epidermal necrolysis. HLA-B58 is a recently identified risk factor for severe cutaneous adverse reactions to allopurinol. Notable drug interactions are with warfarin and azathioprine. The latter is important in renal transplant patients. Compliance is a major issue with gout treatment. Median length of treatment is only 3 months, 87.1% of patients in the gout cohort discontinue or interrupt allopurinol therapy, and few patients receive allopurinol doses of more than 400 mg/day. Other drugs used to treat gout include benz bromarone (50-200 mg daily), a potent uricosuric drug used in patients who do not tolerate allopurinol. A potentially serious side effect of benz bromarone is hepatotoxicity. Losartan and fenofibrate also lower SUA but are seldom used as stand alone agents.

NEW TREATMENTS

Febuxostat is a new non-purine xanthine oxidase inhibitor that is more potent than allopurinol 300 mg daily. Febuxostat is metabolized by the liver (glucuronidation 22%-24% and oxidation 2%-8% play major roles). The metabolites then undergo enterohepatic recirculation and are excreted in the feces, with renal function accounting for <10% of drug clearance. Data for the efficacy and safety of febuxostat have come from several clinical trials. CONFIRMS (Confirmation of Febuxostat in Reducing and Maintaining Serum Urate) was a 6-month, randomized, double-blind Phase III clinical trial, comparing febuxostat and allopurinol. The study enrolled 2269 patients who were randomized to febuxostat 40 or 80 mg/day or allopurinol 300 mg/day. At the final visit, 67% of patients met the primary endpoint of SUA levels <6.0 mg/dL in the febuxostat 80 mg/day group as compared to 45% and 42% in the febuxostat 40 mg/day and allopurinol 300 mg/day groups (p<0.001). The efficacy of febuxostat relative to allopurinol has also been assessed in the FACT (Febuxostat versus Allopurinol Controlled Trial) study. Febuxostat was approved by the US FDA in February 2009.

Febuxostat is indicated in cases of:
1. Allopurinol hypersensitivity or intolerance
2. Failure of allopurinol to normalize SUA
3. CKD where the reduced allopurinol dose sub optimally controls SUA levels

The European Medicines Agency (EMEA) recommends gout flare prophylaxis with colchicine or NSAIDs for a 6 month period when febuxostat is initiated. The dose of febuxostat approved for use in European countries is 80 and 120 mg daily while the dose approved in US is 40 mg daily. This may be increased to 80 mg daily if target SUA is not met after at least 2 weeks. Skin rash is seen in <2% of subjects. Other side effects include transaminitis, diarrhea and arthralgias. Like allopurinol, xanthine oxidase inhibition by febuxostat carries the potential for major drug interactions with azathioprine, 6-mercaptopurine and theophylline.

Another therapeutic target for urate lowering is the enzyme uricase, an enzyme which catalyzes the conversion of urate to the soluble allantoin. Uricase is present in mammals except apes and human beings. The recombinant fungal uricase, rasburicase, is approved only for short-term intravenous use to prevent tumor lysis syndrome in patients with hematological malignancy. It is unsuitable for use in gout owing to its short half-life and immunogenicity. Pegloticase is a pegylated, recombinant porcine-baboon uricase administered intravenously. Pegloticase lowers
Gout in 2010- Looking Beyond Allopurinol

serum urate and reduces tophus bulk in patients with treatment-failure gout.\textsuperscript{1,4,7} Intravenous infusions lower SUA levels to <3 mg/dl in the first 6 hours. The most effective and best tolerated dosing regimen has been 8 mg given intravenously every 2 weeks. The drug is unsuitable for subcutaneous use. Limitations include infusion reactions and attenuation of clinical response due to the development of inhibitory antibodies. Pegloticase is likely to find use as a short-term therapy to debulk incapacitating tophi.

Pro-inflammatory cytokines like interleukin-1 (IL-1) and tumor necrosis factor-a (TNF-a) are also being targeted in new drug development programmes. Agents include the IL-1 receptor antagonist anakinra and the TNF inhibitors infliximab and etanercept. Rilonacept (also called IL1 Trap) is a recombinant protein comprising the extracellular domains of both IL1RI and adaptor protein IL1RACP linked by the Fc region of the human IgG1 molecule. Rilonacept binds to IL1a, IL1b and IL1Ra thus preventing IL1 from binding to IL1RI.\textsuperscript{14} Inhibition of IL-1 inhibition with rilonacept has been shown to reduce pain and markers of inflammation in a small pilot study in patients with chronic active gouty arthritis.\textsuperscript{19}

CONCLUSIONS

Ageing of populations, life style changes, co-morbidities and drug interactions are some of the factors that have contributed to the increasing prevalence of gout and the current complexities in its management. Allopurinol, the cornerstone of present day urate lowering treatments, has several limitations. Febuxostat is an important addition to the therapeutic armamentarium. Pegloticase and IL-1 modulation represent potential new treatments that may address the unmet needs in gout management.

REFERENCES