Therapeutic Challenges in the Management of Chronic Hyperuricemia and Gout in the Elderly

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Abstract

Gout is the most common inflammatory arthritis in the elderly population. The incidence and prevalence of gout in the elderly is increasing. Apart from its high frequency, gout is associated with disability, poor quality of life and increased mortality and therefore represents an ever increasing public health concern. Furthermore, substantial experimental and epidemiological evidence exists supporting the link between elevated levels of serum uric acid and several comorbidities including cardiovascular and kidney diseases. The cornerstone of effective gout management is the long-term lowering of serum urate below saturation concentrations (<6 mg/dL or <360 μmol/L) in order to promote crystal dissolution and prevent monosodium urate crystal formation. It is of great interest whether urate lowering strategies can also lower cardiovascular risk and some preliminary studies in both animal and human subjects suggest that they might. The management of gout includes not only pharmacological approaches, but also a number of non-pharmacological interventions aiming at lessening attack risk, lowering uric acid levels and promoting general health while preventing the development of comorbidities. The two xanthine oxidase inhibitors currently available are effective as long-term urate lowering therapy although the greater efficacy and high tolerability of febuxostat as a urate lowering agent has to be adequately considered especially when the reduction of serum uric acid levels to achieve the target is particularly ambitious and/or the presence of comorbidities increases the risk of adverse effects. Associated comorbidities and cardiovascular risk factors should also be addressed as an important part of the management of gout.

INTRODUCTION

The prevalence and incidence of chronic hyperuricemia and gout have risen in many countries over the last few decades, mainly because of the changes in dietary habits and an increased prevalence in comorbidities that promote hyperuricemia, including hypertension, obesity, metabolic syndrome, type 2 diabetes mellitus and chronic kidney disease [1,2]. Other factors responsible for the rising prevalence of chronic hyperuricemia and gout include the widespread prescription of drugs, including salicylate and diuretics, for cardiovascular diseases [3]. Gout is currently the most common inflammatory arthritis in developed countries, especially in elderly population with a prevalence between 0.9% in Italy and 3.9% in the USA and with an increasing incidence in Italy and other developed countries [1,2]. Apart from its high frequency, gout in the elderly is associated with disability, poor quality of life and increased mortality and therefore represents an ever increasing public health concern [4]. Furthermore, a growing body of evidence suggests a pathophysiological involvement of chronic hyperuricemia and gout in cardiovascular and renal diseases [5-9] supporting the intriguing hypothesis that these clinical conditions can potentially be prevented and/or treated by lowering high serum uric acid levels [10].

CLINICAL PRESENTATION

Elderly gout includes gout commencing at >65 years of age and those with chronic persistent gout that started before age 65. This differs from classical gout found in middle-aged subjects in several respects: poly-articular presentation with upper-extremity joint involvement, fewer acute gouty episodes, indolent clinical course and an increased incidence of tophi [11]. From an epidemiological standpoint, gout in the elderly tends to have a...
more equal gender distribution and there is a stronger association with comorbidities including hypertension, metabolic syndrome, diabetes, acute myocardial infarction and stroke [5,6,11-13]. A positive association between high circulating levels of uric acid and dementia syndrome has also recently been described which, at least in part, is independent of most cardiovascular, cerebrovascular and metabolic risk factors [12]. Gouty arthritis, when not adequately attended to, can be a functionally disabling disease that can lead to a substantial decrease in quality of life in the elderly population [4]. The diagnosis of gout can be more challenging in the elderly than in younger persons due to mimicking other types of arthritis including septic and rheumatoid arthritis [14-16]. In addition, gout can be mistaken for changes that are usually attributed to osteoarthritis. Indeed, tophi can supervene on Heberden's and Bouchard's nodes. Some of the distinguishing features of gouty arthritides are the asymmetrical distribution of the tophaceous joint swelling and the presence of typical radio-graphic findings of tophaceous gout [14,15]. The gold standard in establishing the diagnosis is the demonstration of the presence of monosodium urate crystals, typified as negatively birefringent needle-shaped crystals on light and polarizing microscopy of synovial fluid [17,18]. Interestingly, monosodium urate crystals were detected in asymptomatic joints of patients with gout [19]. Silent deposition of monosodium urate crystals as a result of hyperuricemia may lead to early destructive skeletal changes: a large percentage of patients with gout and normal radiographs have occult destructive arthropathy detectable by advanced imaging, such as MRI and/or ultrasound [20]. Ultrasound evaluation can identify a wide spectrum of sub-clinical morphostructural changes suggestive of gouty arthritis in both intra and extra-articular structures in asymptomatic individuals. These observations are of great clinical relevance, requiring careful reconsideration of the management of asymptomatic chronic hyperuricemia: although chronically elevated serum urate has not typically been considered to play a pathogenetic role in tissue damage, the ultrasound evidence reported above might warrant the use of urate lowering agents also in patients with persistent hyperuricemia without clinical signs of gout [12,21].

Therapeutic management

A fundamental prerequisite of gout is hyperuricemia which is defined as the presence of serum uric acid levels above 6 mg/dL which approximately mark the saturation point of monosodium urate at physiological temperature and pH [17,22]. The pathophysiologival model portrays, in the presence of hyperuricemia, the intra-articular deposition of monosodium urate crystals which is responsible for the onset of an acute attack and chronic arthropathy [17,22]. The current management of patients with gout is based on this simplified model and thus implies the control of risk factors related to hyperuricemia, the effective and rapid control of acute attacks and the persistent reduction of serum monosodium urate levels [23-26]. The goals of treatment are to end the pain of acute flares, prevent future attacks and slow or prevent formation of tophi and kidney stones. These effects can be achieved by maintaining the serum uric acid below the saturation point for monosodium urate [23-26]. However, managing gout in the elderly is clinically challenging as people in this demographic segment have lower creatinine clearance and a greater frequency of comorbidities which may impair handling of the uric acid load. This, combined with the associated concomitant medication use, which impacts both renal function and uric acid, may further increase serum uric acid levels [27]. In this regard, high rates of inappropriate prescribing patterns of gout medications related to contraindicated concomitant medications for other comorbidities has recently been documented [28]. Gout management can be further complicated by low therapeutic compliance; older gout patients have suboptimal adherence to urate lowering treatment compared with therapies for other chronic illnesses [29].

Management of acute flares

Therapeutic targets for the management of an acute gout flare up are suppressing the expression, secretion and signaling of inflammatory cytokines. The management of an acute attack of gout is based on the use of non-steroidal anti-inflammatory drugs (NSAIDs), oral colchicine or corticosteroids, preferably in the first 12-24 hours from the onset of symptoms [23,25,26]. The 2006 EULAR recommendations, which were based on RCT analysis, have concluded that colchicine and NSAIDs are of comparable efficacy [23]. In mild-to-moderate disease (≤6 of 10 on a 0-10 pain visual analogue scale), mono-therapy with NSAIDs, systemic corticosteroids or oral colchicine is recommended [25,30]. In order to effectively manage an acute gout attack, treatment should begin within 24 hours of symptom onset when the response to colchicine has a high clinical diagnostic value [31]. With respect to NSAIDs and corticosteroids, a randomized trial showed that oral prednisolone and naproxen are equally effective in the initial treatment of gout arthritus over 4 days [32]. In more severe disease, characterized by intense pain and often a polyarticular presentation, combination therapy is suggested (colchicine and NSAIDs, oral corticosteroids or colchicine, or intraarticular steroids with each of the other options) [23,25,26]. Low-dose colchicine is better tolerated and is as effective as a high dose, as suggested by the results of a randomized study [23,25,26].

Management of chronic hyperuricemia

The management of chronic hyperuricemia includes not only pharmacological approaches but also a number of non-pharmacological interventions aiming at lessening attack risk, lowering uric acid levels, and promoting general health while preventing the development of comorbidities [23,24,26]. Dietary recommendations suggest avoiding organ meats, high-fructose containing foods and excessive alcohol use, to limit large portions or concentrations of meat and seafood, naturally sweet fruit juices, sugar and salt and to encourage consumption of low-fat or nonfat dairy and vegetables [23,24,26]. Weight loss in those who are overweight, smoking cessation and exercise are also recommended as general lifestyle health considerations in patients with gout [24]. Cardiometabolic comorbidities, common in the gout population, are associated with a higher burden of disease, as reflected by an increased risk of flares [33]. Changing medications associated with hyperuricemia (e.g. diuretics) may also help to control serum uric acid levels, while other comorbidities should be carefully managed [30].

There is a dearth of evidence-based information on effective
management of urate lowering therapies in elderly patients. Available urate lowering long-term therapy options include xanthine oxidase inhibitors, allopurinol and febuxostat, as well as the uricosuric agent probenecid. Probenecid is ineffective in gout patients with renal impairment [34] since 30% to 60% of gout patients have some degree of renal dysfunction [35]. Thus, when urate lowering therapy is indicated, the xanthine oxidase inhibitors allopurinol and febuxostat are the options of choice [10,24,26,30] Although no data on the efficacy of sulphinpyrazone in patients with gout are available, its off-label administration is a treatment option as monotherapy for patients in which other urate lowering agents are contraindicated or as a combination drug with a xanthine oxidase inhibitor in treatment-resistant cases [26].

Allopurinol: Allopurinol has been widely used as urate lowering drug over the past 4 decades and it is the most commonly administered drug in the long-term management of gout. Results from non-controlled studies have shown a dose-responsive dependency to allopurinol of a lowering of 1 mg of serum uric acid levels for every 100 mg of allopurinol increase [36,37]. These results support the need for slow titration of the allopurinol dose till the attainment of target levels. The currently recommended starting dose of allopurinol is 100 mg daily and gradual increments at 2-4 weeks are recommended in light of efficacy and safety data [23,24,26,30]. Allopurinol is mainly excreted in urine and its metabolite, oxypurinol, can accumulate to toxic levels in patients with renal failure. Therefore, lower starting doses are indicated in this group of patients [38]. In the elderly, the usual starting dose of allopurinol is 50-100 mg on alternate days, increased cautiously by 50-100 mg daily every two weeks until serum uric acid levels <6 mg/dL at a minimum are achieved [11]. Previous guidelines have suggested starting doses of allopurinol based on creatinine clearance although it has been shown this may not provide adequate control of hyperuricemia [23,24]. When given at the usual dosage of 300 mg daily allopurinol allows the target uricemia of 6 mg/dL to be reached in only a minority of gouty patients [30,36,37]. On the other hand, raising the dose may lead to an increased risk of toxicities, although further evidence on this issue is required. Up to 20% of patients experience side effects with allopurinol with 5% discontinuing therapy [39]. Although rare, allopurinol can cause a life-threatening reaction consisting of a severe morbilliform or maculopapular rash with vasculitis, hepatitis and renal failure. This carries a 20% mortality risk [40].

Febuxostat: Febuxostat is a non-purine selective inhibitor of xanthine oxidase that exhibits antihyperuricemic activity by reducing the formation of uric acid [41,42]. Differing from allopurinol, febuxostat provides more selective and potent inhibition of both the oxidized and reduced forms of xanthine oxidase and provides more persistent enzyme inhibition and greater hypouricemic activity [42,43].

Primarily metabolized in the liver [41], its pharmacokinetic and pharmacodynamic profiles are not affected by age or by mild-to-moderate hepatic or renal dysfunction [44-46]. Data from a recent meta-analysis of five randomized controlled trials have shown a greater likelihood to reach the therapeutic target of <6.0 mg/dL (360 μmol/L) with febuxostat at 80 mg or more than with 300 mg of allopurinol [26]. Even more recently, another meta-analysis of five randomized controlled trials confirmed these findings showing that patients receiving febuxostat were more likely to achieve a serum uric acid of <6 mg/dL (<360 μmol/L) than allopurinol recipients (RR: 1.56, 95% CI: 1.22-2.00, I2:92%) [47]. The safety data analysis comparing febuxostat and allopurinol in both meta-analysis also indicated that the risk of any adverse event was slightly higher for febuxostat in comparison with allopurinol (RR: 0.94, 95% CI:0.90-0.99, I2: 13%, respectively) [26,47]. A comparison between efficacy and safety of febuxostat and allopurinol in elderly subjects has
recently been presented as post-hoc analysis of CONFIRMS study which enrolled hyperuricemic gout subjects (serum urate levels ≥ 8.0 mg/dL) randomized 1:1:1 to receive febuxostat, 40 mg or 80 mg or allopurinol [200 mg or 300 mg based on renal function once daily] for 6 months, according to a double-blind, randomized design [48]. In the cohort of 374 elderly included in the analysis urate lowering treatment with either dose of febuxostat (40 mg or 80 mg) was significantly more efficacious than fixed doses of allopurinol 200/300 mg in achieving the therapeutic serum urate goal <6.0 mg/dL [49]. In the total CONFIRMS study population, the efficacy of febuxostat 40 mg was comparable to that of allopurinol [48]. In this post-hoc analysis, the greater efficacy of febuxostat 40 mg over allopurinol 200/300 mg can be attributed to the very high proportion of elderly patients with mild or moderate renal impairment. Indeed mild or moderate renal impairment was determined in 139 (37.2%) and 229 (61.2%) subjects, respectively [49]. Interestingly, the study population had comorbidities that are commonly found in elderly subjects with gout. In addition to the predominance of renal impairment, the majority of subjects (87.2%) had some history of cardiovascular disease, inclusive of, but not limited to, hypertension (82.4%), coronary artery disease (24.3%), cardiac arrhythmia (21.1%), and myocardial infarction (10.7%) [49]. In addition, 59.6% of elderly subjects had a history of hyperlipidemia and 24.6% were diabetic [49]. Thus, the cohort seems to be quite representative of the real world elderly population. These results suggest that despite high rates of comorbidities, including renal impairment, the hyperuricemia of elderly gout patients may be more effectively managed with approved doses of febuxostat, with low risk of side effects.

Taken together the above findings indicate that febuxostat is an effective urate lowering agent in patients with gout and has shown greater efficacy at a dosage of 80 mg or more when compared to allopurinol at the maximum dose of 300 mg in the short-term control of hyperuricemia [26,47]. In addition, treatment with febuxostat seems to be more effective and safe in patients with mild or moderate renal insufficiency when compared to treatment with allopurinol [26,49]. The recommended dose of febuxostat is 80 mg once daily. If serum uric acid is >6.0 mg/dl after two to four weeks, febuxostat 120 mg once daily may be considered [20,25,30].

CONCLUSION

Despite the current in-depth knowledge of the pathophysiological role of hyperuricemia and gout in human diseases and the availability of valid therapeutic options, the management of patients with gout is still largely suboptimal [50]. As the prevalence of gout among the elderly continues to rise [51,52], optimal management of chronic gout and its underlying hyperuricemia is necessary to improve clinical outcomes and reduce healthcare utilization and associated costs. Achievement and long-term maintenance of serum uric acid levels <6.0 mg/dL leads to reduction of tophi and near-elimination of acute flares [53-57], and may stabilize or improve renal function in gout patients [58]. Both xanthine oxidase inhibitors currently available are effective as long-term urate lowering therapy although the greater efficacy and minor adverse effects of febuxostat as urate lowering agent has to be adequately considered, especially when the reduction of serum uric acid levels to achieve the target is particularly ambitious and/or the presence of comorbidities increase the risk of adverse effects [26,47]. Chronic hyperuricemia and gout have been also identified as independent risk factors for diabetes, cardiovascular disease, and all-cause and cardiovascular-related mortality [5-9]. Beyond their proven capacity to lower urate levels, it is of great interest whether urate lowering treatments, particularly xanthine oxidase inhibitors, can also lower the risk of cardiovascular events and some preliminary studies in both animal and human subjects suggest that they might [59]. If extra-articular benefits of hyperuricemia treatment will be confirmed, hypouricemic therapy would then decrease the cardiovascular risk of treated patients as well as obviously improve their quality of life via a direct decrement in uric acid-related clinical events and complications

REFERENCES


