Management of gout and hyperuricemia in elderly people

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ABSTRACT
Gout is a common inflammatory arthritis affecting many elderly people. The management of gout in the elderly is a real therapeutic challenge due to medical co-morbidities and drug interactions. The traditional drugs already in use are frequently associated with side effects. The current therapeutic strategies for gout and hyperuricemia in elderly people involve are distinct but linked, with attention to safety.

Keywords: gout, hyperuricemia, elderly, NSAIDs.

INTRODUCTION
Gout is a clinical entity characterized by dysregulation in metabolism and consequent deposition of monosodium urate crystals in joint tissues. Epidemiology suggests a male predominance in middle age, but after menopause, gout incidence in women shows an overwhelming increase. In elderly people, gout is a common medical condition predominantly attributed to comorbidities and concomitant medication interfering with urate metabolism. The complexity of diseases and corresponding medication in older patients makes effective gout treatment a real therapeutic challenge. This article reviews the current therapeutic strategies for gout and hyperuricemia in elderly people.

CLINICAL MANIFESTATIONS
The clinical presentation of gout in the elderly differs from that of the middle-aged in several ways; including fewer attacks of acute gout after medical illnesses and/or surgical procedures, more frequent symmetric or asymmetric polyarticular involvement, as well as tophi formation.® Prevalence is almost equally distributed between the two genders: multiple joints of the upper extremities are commonly affected, and the entire disease frequently follows a latent clinical course with few acute crises. On the contrary, tophaceous joints from chronic deposition of monosodium urate and joint erosion are ordinary findings in elderly patients. An additional issue regarding gout in the elderly is the scarcity of diagnoses based on crystal documentation. Not many physicians are prone to perform synovial fluid aspiration and polarizing microscopy in old patients, especially in a primary care setting.®

ACUTE GOUT TREATMENT
The aim of therapy is primarily to alleviate pain and shorten the duration of an acute attack. After resolution of a crisis, the patients are considered to have entered a symptom-free span, or as otherwise stated, an intercritical period lasting until the next relapse. Patients with frequent flares are candidates for urate-lowering therapy in order to prevent additional acute crises and chronic tophi deposition in soft tissues.® In the acute phase, current guidelines suggest that therapy can be initiated within 24 hours from symptom onset. In case the patient is already on urate-lowering treatment, such regimens should not be interrupted.® Possible choices include nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and colchicine. Interleukin-1 inhibitors such as anakinra and canakinumab represent novel treatment approaches which may result in better outcome. However, interleukin-1 (IL-1) inhibitors are probably associated with an increased risk of adverse events and definitely with a substantially higher cost compared to a more conventional approach.® NSAIDs (grade A evidence for Naproxen, Sulindac, Indomethacin) act through inhibition of cyclo-oxygenase (COX) and are commonly prescribed in an acute episode with minor adverse effects in young adults. Their toxicity profile in the elderly remains an important issue. Gastrointestinal side effects, such as peptic ulceration, bleeding, and even perforation, are not rare. Aged people taking oral anticoagulants due to atrial fibrillation or artificial heart valves are considered of high risk. The potential of cardiac impairment and blood pressure dysregulation in people suffering from cardiovascular disease is significant. Concurrent treatment with diuretics or renin angiotensin aldosterone system inhibitors renders the patients prone to acute kidney injury and thus close monitoring of renal function is required. Current data favor naproxen and indomethacin administered per os for the treatment of acute gout.® In case of gastrointestinal contradictions or intolerance to traditional NSAIDs, existing evidence support the efficacy of COX-2 selective NSAIDs (grade A for etoricoxib and celecoxib).® Aspirin is not considered part of the therapeutic approach because it results in increase of serum uric acid levels due to renal retention. Nevertheless, aspirin should not be discontinued in the acute phase of gout in patients with established coronary artery or other thrombotic disease.® Indomethacin may be a reliable choice in younger patients with acute arthritis, but adverse effects especially in regard to the central nervous system are more likely; thus, it should be avoided in the elderly.® Colchicine (grade A evidence for US FDA-approved regime) is an alternative - though not flawless - choice in patients with acute flares, provided that it is initiated as soon as possible, preferably within 36 hours from symptom onset. Although historically, colchicine has been for centuries the cornerstone of gout management, clinical trials are scarce, and the official approval of its use came only a few years ago. According to the American College of Rheumatology guidelines, low dose schemes are equivalent to high dose ones in terms of symptom resolution, but more favorable regarding side effects, namely muscle toxicity, diarrhea and abdominal cramping. It should be emphasized that in aged patients, doses smaller than 1mg per day are recommended, and in case of severe renal impairment (creatinine clearance <30ml/min), colchicine should not be instituted at all.® In the Greek market, colchicine is available only in tablets of 1mg, whereas the existing guidelines use formulations of 0.6mg.
Corticosteroids can be given either orally (grade A evidence) or by means of intravenous, intra-articular or intramuscular injection. When one or two joints are affected, an intra-articular injection (grade C evidence) can alleviate symptoms instantly on the condition that...
the provider is experienced in arthrocentesis and all precautions for iatrogenic infection are considered. When more joints are involved, then oral schemes seem more suitable with the drawbacks of diabetes mismanagement, susceptibility to infection and rebound phenomenon upon rapid steroid withdrawal. Apart from anti-inflammatory agents or steroids, adrenocorticotropic hormone (ACTH) (grade C evidence) consists an alternative treatment option in the acute phase, especially in aged people with multiple comorbidities. It is administered with a single subcutaneous dose and seems an attractive choice for patients who are instructed to fast and have not been on long-term steroid therapy. In the market, ACTH is available in the form of tetracosactide (commercial name Synacthen), its synthetic analogue.

In the era of biological therapy, IL-1 inhibitors have gained wide attention, and various studies are on the way. The notion is that monosodium urate crystals generate gout flares through IL-1β secretion. Data regarding elderly people are limited and mainly originate from trials of anakinra (grade C evidence) and canakinumab (grade A evidence). Interleukin-1 inhibition with anakinra (100mg subcutaneously daily for 3 days) shows instant clinical response and is emerging as an optimal choice in aged people with contraindication for anti-inflammatory agents, but is not approved by the FDA. The main side effects are minor injection-site reactions and less frequently serious bacterial infections. An important issue as well is the high cost compared to traditional treatment.

Complementary to the medication, additional measures that help to alleviate pain and ease patient symptoms are resting the affected joints and topical ice pack application, acetaminophen, and, in selected circumstances, opiates.

**URATE-LOWERING TREATMENT (ULT)**

There is substantial evidence that gout flares are significantly reduced or eliminated if uric acid blood levels are maintained in a serum level of <6.0mg/dl. Prescribing ULT is the mainstay of gout management in the long term. On the other hand, the traditional belief is that the introduction of urate-lowering drugs predisposes to a new flare due to manipulation of the uric acid pool. After many years of low interest in exploring novel treatment pathways, during which allopurinol and a few uricosuric agents were the only choices, novel therapies have emerged. The three basic mechanisms to lower blood levels are the inhibition of uric acid production through xanthine oxidase inhibitors, the increase of renal excretion with selective uric acid resorption inhibitors and the dissolution of urate through use of recombinant uricases. Allopurinol and febuxostat are the two xanthine oxidase inhibitors available today in the market. Allopurinol is a well established agent that works through conversion to its active metabolite oxypurinol which is largely excreted through the kidneys. In aged patients with renal impairment, oxypurinol levels are associated with higher incidence of hypersensitivity syndrome, a severe - although rare - side effect; thus, allopurinol should be introduced in a lower dose and gradually escalated. Doses not more than 300mg per day are considered safe and virtually preclude that severe side effect. Another issue to be addressed is the interaction of allopurinol with many drugs. Furosemide has been shown to diminish the effect of allopurinol therefore uric acid levels should be closely monitored followed by proper dose adjustment. In patients already on azathioprine, allopurinol is strictly contraindicated due to high probability of bone marrow suppression. Febuxostat is a novel agent that inhibits xanthine oxidase and has been introduced in the last decade. Apart from the significantly higher cost, the main differences compared to allopurinol are the absence of significant drug interactions and the fact that febuxostat is metabolized in the liver, indicating it as a favorable second choice in people with history of oxypurinol toxicity. In elderly people with estimated creatinine clearance, the >30ml/min dose adjustment is unnecessary. Even in a smaller dose of 40mg per day, febuxostat appears substantially effective. There are ongoing trials to define if an association between febuxostat and adverse cardiovascular thromboembolic events exists.

Another treatment approach regarding hyperuricemia and prevention of gout attacks is uricosuric agents. These drugs inhibit the urate transporters and thus reabsorption in the proximal tubule. The main concern associated with their use is the potential of deposition of urate crystal within the renal parenchyma or inside the tubules causing lithiasis. With the advent of novel agents, uricosuric drugs have fallen out of favour. Patients prescribed uricosuric agents should be guided to remain adequately hydrated. The lone representative of this category is actually probenecid, which has virtually no effect in patients with moderate renal impairment (creatinine clearance <60ml/min) and thus in the vast majority of elderly people. Benz bromarone is not available in Greece, and has been withdrawn from many markets due to reports of hepatotoxicity.

In resistant cases of hyperuricemia when standard medications are unable to lower the uric acid level, rasburicase has been introduced. It belongs to a novel class of recombinant urate lowering drugs called uricases that convert uric acid to allantoin. Its pegylated analogue, pegloticase, characterized by longer half-time, is already in use in other countries, though at a significantly higher cost. Patient education is very important in the management
of gout. Patients should be informed about the disease, dietary and other triggers of acute attacks, and the importance of compliance with long-term ULT.13

Last but not least, the physician is obliged to give clear and thorough dietary advice in order to manage hyperuricemia. It is common place that dietary interventions have a relatively low probability of adherence and completion: this probability is even lower in elderly patients with many comorbidities. A cross-sectional study has shown that the prevalence of hyperuricemia is lower in persons with long-term adherence to Mediterranean diet. It is a diet relatively poor in meat but rich in vegetables and legumes, and with an oddly high content of monounsaturated fatty acids compared to the typical Western diet. Although animal-derived purines are substantially reduced, plant purines and calories are not restricted. The effect of the Mediterranean diet on hyperuricemia is something that needs to be further clarified by large-scale trials.23

CONCLUSION

Gout is an inflammatory arthritis affecting many elderly people. The complexity of concomitant diseases and corresponding medication in such patients poses a therapeutic challenge for the physician. The traditional drugs already in use are associated with frequently severe side effects. With the advent of novel agents in the last years, more and larger scale trials are needed in order to optimize treatment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES