View Point

When to Start Urate Lowering Therapy?

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Gout is one of the most common inflammatory arthritis, affecting up to 1–2% of adult men in western countries.[1] Persistently high serum uric acid (SUA) levels result in monosodium urate (MSU) crystal deposition not only in joints but also in periarticular structures such as tendons and ligaments.[2] MSU crystals are known to cause inflammation[3], and clinically gout commonly presents as recurrent episodes of acute inflammation, frequently at the joints, but which can also involve the tendons[4] or the bursa.[5] In time, joints can become chronically inflamed and deposits can accumulate in the form of tophi.

Although in most patients gout is an episodic disease that can be taken as benign, gout is far from innocuous. MSU deposits produce persistent low-grade inflammation as evidenced by an increased synovial fluid leukocyte count in asymptomatic knees with MSU crystals compared with knees without crystals[6], increased edema surrounding tophi and other MSU deposits and higher vascularization at asymptomatic joints; the inflammatory cellular components surrounding tophi have been well characterized.[7] Consequences of this continuous low-grade inflammation is harmful for gout patients.

Also, patients with gout are well known to have an increased risk of developing cardiovascular (CV) diseases for decades.[8] Hyperuricemia and gout are common features of metabolic syndrome, alongside hypertension, diabetes mellitus, dyslipidemia and obesity (the traditional CV risk factors). In gout, the presence of these comorbidities is significantly increased when compared with the general population[9], at a rate even higher than other rheumatic diseases.[10] The coexistence of traditional CV risk factors in patients with gout has commonly been considered the main reason for the increased CV risk.

However, in the last years several population-based studies have noted that gout is an independent CV risk factor in itself[11–15], leading to an increased mortality.[16] This circumstance seems especially relevant in younger patients without CV risk factors (a subgroup with a low baseline incidence of coronary heart disease) in which the presence of gout may enhance the CV risk by more than 80%.[17] The CV risk is particularly high in tophaceous patients[18], suggesting an association with the crystal deposit burden (and probably the total amount of inflammation associated to the crystals that likely rises as the deposits do). The risk of stroke seems to be increased as well in gouty patients.[19] Subclinical indicators of CV involvement, such as the carotid intima–media complex thickness and the presence of atherosclerotic plaques, also seem to be more prevalent in gouty patients than in control non-gouty patients.[20] All these data quite strongly suggest that in gouty patients CV complications of atherosclerosis are heightened, explaining the resulting higher mortality.

Moreover, as Sustained inflammation seems to promote an accelerated form of atherosclerosis[21,22], the same mechanism proposed for other chronic inflammatory conditions, such as rheumatoid arthritis[23], and systemic lupus erythematosus[24], could apply to gout.

In line with other chronic inflammatory conditions[25,26], the anti-inflammatory therapy could decrease the CV risk in gouty patients. Colchicine reduces crystal-induced inflammation[27] and is a standard agent used for both flares and prevention of further episodes.[28,29,30] A population-based study pointed out a lower prevalence of myocardial infarction in gouty patients that were on colchicine[31,32]; this could be explained through its anti-inflammatory properties. Whether urate-lowering therapy could revert the inflammation-related pro-atherogenic state remains to be demonstrated; however, as persistent low-grade inflammation in gout intensely relates to MSU crystal presence in synovial fluid and the joint surface, it appears logical to surmise that crystal clearance will resolve it. In view of current evidence, at least in those gouty patients at a high risk for atherosclerotic vascular disease or having already suffered from its complications, to aim for a rapid elimination of MSU crystal deposits appears more than sensible.

Furthermore, patients with gout frequently show an abnormal renal function[33], ranging from mild increases in serum creatinine to an end-stage renal disease. In some cases gout develops as a consequence of the hyperuricemia resulting from the impaired urate excretion due to poor kidney function.

Some studies have noted a mild improvement in the renal function of patients with severe gout after successful SUA lowering therapy.[34-36] These results support the involvement of MSU crystals deposition in at least a subset of gouty patients with renal impairment. Their elimination would explain improvements in the renal function, and it might even prevent further evolution to end stage disease.

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Despite all of that, both European League Against Rheumatism recommendations[28] and American guidelines[29] recommend starting urate-lowering therapy only after gout has reached a certain severity. This approach implies that the deposited MSU crystals are considered harmless for the patients, other than for the obvious clinical inflammation during acute gouty episodes or with the later appearance of tophi and joint damage.

So, it seems that early and a more intensive pharmacologic urate-lowering therapy strategy might be advantageous for patients with gout and hyperuricemia. Besides improving the 'classical' clinical picture of recurrent acute arthritis episodes, it is worth considering collateral but serious complications related with sustained inflammation, such as atherosclerosis, and renal impairment.

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