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Gout: a clinical syndrome illustrated and discussed

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ABSTRACT

Gout is an acute inflammatory arthritis with the potency to fully destroy the integrity of the joint leading to severe disability. Besides joint destruction, gout is often associated with an accelerated atherosclerosis culminating in an increased risk of cardiovascular disease. The current existing therapy modalities allow an efficient treatment that not only controls local inflammation but might also have an effect on the generalised features that surround this condition. Here we discuss the modes of clinical appearance, how we are nowadays supposed to treat gout and the current knowledge about the pathogenesis of this clinical syndrome.

KEYWORDS

Gout, cardiovascular risk, immunology

INTRODUCTION

Gout is an acute inflammatory arthritis caused by the deposition of monosodium urate (MSU) crystals intra-articularly. Patients experience acute severe pain that often forces them to seek medical care. Besides the acute presentation patients can present with tophi, which can even precede joint involvement.^{1,3} With an estimated prevalence of 1 to 2% in adults in developed countries, this therefore accounts for a substantial burden of work-related and medical costs. In the elderly (age >65 years) the incidence even increases to 8% for men and 3% for women.⁴ The male:female ratio ranges from 7:1 to 9:1.⁵ Most patients with gout (±90%) are diagnosed and treated by general practitioners in primary care.⁶ Besides the involvement of joints, gout is often accompanied by other symptoms of hyperuricaemia such as the

formation of tophi in numerous tissues. The prevalence of hyperuricaemia is 10 to 20% in the Western population and a substantial number of these patients stay asymptomatic during life.⁷ Only a minority of individuals with elevated serum urate levels develop gout (incidence rate less than 50/1000/year for ≥ 0.54 mmol/l; 5/1000/year for 0.42 to 0.54 mmol/l; 1/1000/year <0.42mmol/l).⁸ Compared with other mammals humans have high uric acid levels due to two deletions in the promotor site of uricase.⁹ This causes the uric acid plasma levels to be around 300 μ M, a level at which a small increment could cause supersaturation and crystal formation. There is a strong association between hyperuricaemia and the metabolic syndrome (the constellation of insulin resistance, hypertension, obesity and dyslipidaemia), potentially explained by dietary and lifestyle changes.¹⁰ This is profoundly demonstrated by the prototypic gouty patient being an obese, middle-aged man with a Burgundian lifestyle and a medical history of hypertension, kidney disease, diabetes mellitus and signs of vascular problems such as coronary artery disease, heart failure and stroke. But as previously reported gout can also present in elderly patients without known risk factors, even presenting only with tophi.¹¹ In gouty arthritis the formation of MSU crystals into the joint promotes acute inflammation. These crystals have the capacity to induce the release of various inflammatory mediators in inflammatory cells.¹²⁻¹⁶ In the past ten years research on the role of the innate immune system in the pathogenesis of gout has extended rapidly. As our knowledge on the inflammatory processes accompanying atherosclerosis also increases it is tempting to discuss the development of cardiovascular diseases in gout patients via immunological perturbations.

In daily clinical practice the diagnosis of gout can be made easily and with a high certainty using the gold standard. The gold standard is the presence of MSU crystals in the

synovial fluid or a tophus, and therefore a puncture of a joint or tophus should always be performed. Recently it was shown that the American College of Rheumatology (ACR) criteria from 1977 have a limited validity, at least in primary care.¹⁷ We describe two patients who visited the emergency department because of severe gouty arthritis. The aim of this study is to review the literature concerning cardiovascular risks and pathogenic aspects of gout. In addition, we provide an overview on the clinical assessment and therapeutic armamentarium.

CASES

PATIENT A

A 75-year-old male presented at the emergency unit with a five-day history of severe pain and swelling of digit IV of the left foot. The general practitioner had already started colchicine 0.5 mg ten times daily. This led to complaints of vomiting and diarrhoea and eventually to a visit to the emergency department. His medical history was characterised by major cardiovascular complications consisting of a myocardial infarction in 1986 followed by a large aneurysm of the left ventricle and mild mitral valve insufficiency (diagnosed in 1993). A second myocardial infarction followed in 1994. In 2002 an acute coronary syndrome led to dilation and placement of a stent in the right coronary artery. In 2008 diagnostic procedures were undertaken because of progressive dyspnoea and cardiac ultrasound revealed a markedly diminished function of the left ventricle (ejection fraction 25 to 30%), insufficiency of the mitral and aortic valves and suspicion of pulmonary arterial hypertension. Based on these observations, an intracardiac defibrillator was inserted. Besides his cardiac history, hypothyroidism, peptic ulcers and gout had been present for eight years. Physical examination revealed a swelling of digit IV of his left foot with a tophus that showed signs of infection and distinct tophi in the olecranal bursa bilaterally (*figures 1A and B*). Apart from the common signs of dehydration, no other signs of illness were present. Laboratory analysis was normal (no acute phase response present) except for the increased serum uric acid of 0.92 mmol/l (reference 0.20 to 0.40 mmol/l) and creatinine 306 µmol/l (reference 60 to 110 µmol/l) levels. Radiographic evaluation of the left foot revealed a complete resorption of the distal phalanx digit IV (*figure 1C*); no other abnormalities were present. Since the patient was dehydrated because of diarrhoea due to the high dose of colchicine, 120 mg, the arthritis was treated with triamcinolone acetonide intramuscularly and not with an NSAID, and the dosage of colchicine was lowered to 0.5 mg once daily. One week later the patient attended

our outpatient clinic. He was fully recovered and showed no signs of dehydration and pain in the toe. Although exceptional, since the gouty disease in this patient was very local and led to a high risk for an infectious complication, we discussed an amputation of digit IV with the patient. Not surprisingly, the toe had given many complaints over the past three years and the patient agreed to this approach. Two weeks after presentation at the emergency ward the toe was amputated. As expected, the histological analysis of the amputated digit showed clear MSU crystals and no evidence for infection. Two weeks after surgery the patient visited our outpatient clinic with complete healing of the site of amputation (*figure 1D*). Since the medical history of the patient included more than three gout attacks per year we started allopurinol 200 mg once daily under the cover of corticosteroids. This led to the normalisation of



the serum urate below the level of 0.36 mmol/l, which is the current target value of the European League against Rheumatism (EULAR), and absence of gout attacks after two years of follow-up.

PATIENT B

A 93-year-old female came to the rheumatology clinic with pain and swelling in both hands and a probable 12-year history of gout. She had not received any treatment for her gout so far. Her only relevant medical history was primary hypertension. Physical examination showed multiple swollen proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints in both hands with an extensive amount of tophi (figures 2A and B). Inspection of digit IV of the right hand revealed a fistulating tophus (figure 2C). Laboratory analysis showed a serum uric acid of 0.46 mmol/l (reference 0.20 to 0.40 mmol/l) and creatinine 69 µmol/l (reference 60 to 110 µmol/l) and an acute phase reaction: ESR 34 mm/h and CRP 45 mg/l. To analyse the extent of joint damage conventional radiological examination was performed which revealed extensive destruction of multiple PIP and DIP joints (known as 'punched out' lesions). As treatment, clindamycin 200 mg was given three times daily (for two weeks) and methylprednisolone (120 mg) was administered

once intramuscularly. Two weeks later all the signs of inflammation had completely resolved. At that moment allopurinol 200 mg once daily was added, which led to the normalisation of the serum urate level (<0.36 mmol/l). After two years of follow-up, the patient had twice suffered from a gout attack which quickly recovered (within two days) by the addition of colchicine three times daily 0.5 mg for one week.

GOUT AND CARDIOVASCULAR MORBIDITY AND MORTALITY: MORE THAN A LOCAL DISEASE?

While an association between gout and hypertension, other cardiovascular diseases and kidney diseases has been observed since the late 19th century, renewed interest started from the late 20th century through defining of new top priorities in medicine, such as reduction of cardiovascular morbidity and mortality.¹ To date, several studies underscore that gout is an independent risk factor for cardiovascular disease (table 1).^{10,18}

In the prospective Framingham study 'clinical' gout was associated with an increased risk of coronary heart disease. Abbott *et al.* found an excess risk of 60% for coronary heart disease (CHD) among subjects with gout compared with those who did not have clinical gout.¹⁹ The Meharry-Hopkins study showed contradictory results, the pooled risk-adjusted relative risk (RR) for cardiovascular disease was 0.59 (95% CI 0.24 to 1.46). However, this study was underpowered with just three events in the 31 subjects of the Meharry cohort and four events in 62 subjects of Johns Hopkins Precursors cohort.²⁰ A Dutch study based on data from general practitioners demonstrated that 270 patients with a first episode of gout had a statistically higher prevalence of one or more signs of cardiovascular disease (35 vs 26%) compared with 522 healthy counterparts. In follow-up of this study, 170 gout patients without cardiovascular disease were compared with 340 control patients from the general practitioners' database. Data revealed a statistically higher prevalence of hypertension (39 vs 14%), hypercholesterolaemia (8 vs 4%), diabetes mellitus (5 vs 1%) and obesity (52 vs 27%) among the 170 gout patients.²¹

The prospective Multiple Risk Factor Intervention Trial (MRFIT) was a randomised clinical trial designed to examine the efficacy of coronary risk reduction of adverse coronary events. During the six-year intervention phase gout was associated with an increased risk of nonfatal acute myocardial infarction, odds ratio 1.26 (95% CI 1.14 to 1.4).^{21,22} In 2008, Krishnan *et al.* reported a 17-year follow-up study of the men in the MRFIT cohort who did not have CHD during the six-year intervention phase. The hazard ratio (HR) for CHD mortality for gout vs non-gout was 1.35 (95% CI 1.06 to 1.72).²³

Figure 2. Patient B



A to C) Diffuse swelling of distal and proximal interphalangeal joints with multiple subcutaneous tophi and ulceration lateral side digit IV left, D) bone resorption and bone cysts due to chronic gouty inflammation. The patient provided consent to publish the photos.

Table 1. Gout and cardiovascular morbidity and mortality

Study	Population	Design	Follow-up (years)	Outcomes	Patients (total gout n)	Adjusted effect size (95% CI)
Abbott ¹⁹	Framingham cohort	Cohort	32	CHD	37 (94)	1.60 (1.10-2.50)
Gelber ²⁰	Meharry-Hopkins cohort	Cohort	30	CHD	7 (93)	0.59 (0.24-1.46)
Janssens ²¹	Continuous Morbidity Registration cohort	Case-control	11	CVD	44 (170)	(0.65-1.47)
Krishnan ²²	Multiple risk factor Intervention trial Cohort	Cohort	6.5	Fatal MIs All MIs	22 (1123) 118 (1123)	0.96 (0.66-1.44) 1.26 (1.14-1.40)
Krishnan ²³	Multiple risk factor Intervention trial Cohort	Cohort	17	Fatal MIs CHD mortality CVD mortality	36 (655) 78 (655) 110 (655)	1.35(0.94-1.93) 1.35(1.06-1.72) 1.21 (0.99-1.49)
Chen ²⁵	Ho-Ping Gout Cohort	Cross-sectional	NA	Q-wave MIs	393 (22,572)	1.18 (1.01-1.38)
Choi ²⁶	Health Professionals Follow-up cohort	Cohort	12	All-cause mortality CHD mortality CVD mortality	645 (2773) 238 (2773) 304 (2773)	1.28 (1.15-1.41) 1.55 (1.24-1.93) 1.38 (1.15-1.66)
Cohen ²⁷	US Renal Data System dialysis patients	Cohort	5	All-cause mortality CVD mortality	*(24,415) *(24,415)	1.49 (1.43-1.55) 1.47 (1.26-1.59)
Kuo ²⁸	Health Screening Program Chang Gung Memorial Hospital	Cohort	6	All-cause mortality CVD mortality	*(1311) *(1311)	1.46 (1.12-1.91) 1.97 (1.08-3.59)

*Numbers of outcome not reported.
CHD = coronary heart disease; CVD = cardiovascular disease; MIs = myocardial infarctions.

Recently, a large Taiwanese study reported about the relationship between clinical gout and electrocardiographic evidence Q-wave myocardial infarction using the Ho-Ping Gout database of 22,572 established gout patients according to the Wallace criteria.²⁴ In addition to this, Chen *et al.* demonstrated that gout was associated with Q-wave myocardial infarction.²⁵ The prospective Health Professional Follow-up Study investigated the relation between history of gout and the risk of death and myocardial infarction among 51,297 men. During the 12-year follow-up period, Choi *et al.* found RRs of 1.38 (95% CI 1.15 to 1.66) for cardiovascular-related death and 1.55 (95% CI 1.24 to 1.93) for cardiovascular-related death in males with gout.²⁶ Cohen *et al.* examined the association of gout and mortality among patients receiving dialysis therapy in the United States Renal Data System. In this study, gout was independently associated with CVD mortality with an HR of 1.47 (95% CI 1.26 to 1.59).²⁷ However, this national registry did not contain information on other potential risk factors for mortality such as malnutrition, infection and social circumstances. The most recent study to date by Kuo *et al.* further substantiates the relationship between cardiovascular disease and gout using a cohort of 61,527 individuals and a follow-up period of seven years.²⁸

Together, these prospective reports strongly suggest that men with gout, adjusted for various cardiovascular risk factors, are associated with increased cardiovascular disease risk, especially coronary heart disease mortality.

Therefore aggressive management of cardiovascular risk factors in men with gout is warranted.

GOUT AND PERTURBATIONS IN THE IMMUNE SYSTEM

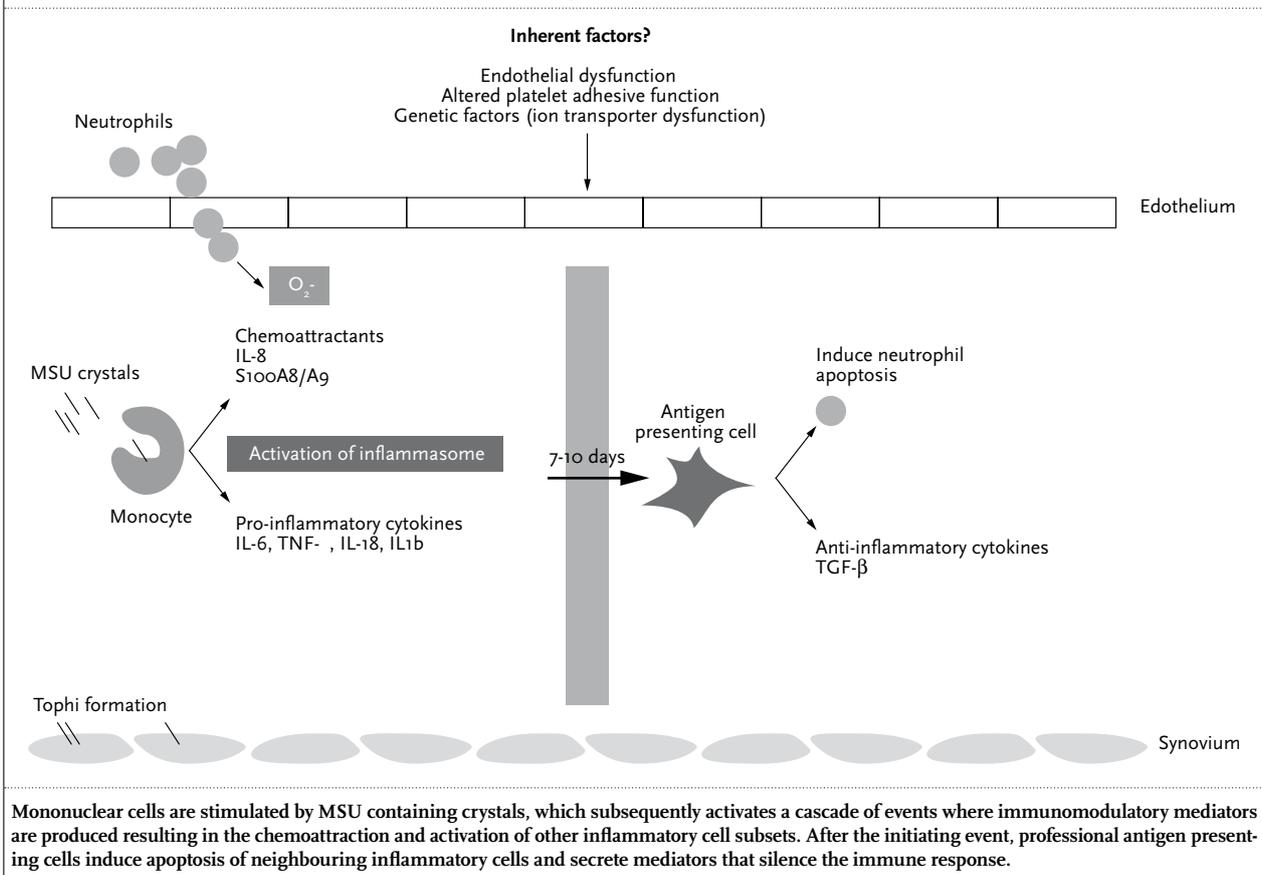
Whenever the level of uric acid in the synovial fluid fluctuates and the synovial fluid gets supersaturated with uric acid the risk for crystal formation increases. The solubility of urate in synovial fluid is influenced by more factors than solely the concentration, including temperature, level of dehydration and the presence of nucleating agents.²⁹ These factors in part explain the predilection of gout in the first metatarsal phalangeal joint (podagra, low temperature), in osteoarthritic joints (nucleating debris) and the nocturnal onset (dehydration).²⁹ An acute gouty attack causes a neutrophilic influx. The influx of neutrophils into the joint is caused by chemotactic factors.³⁰ Recent studies have shown that the most important phagocytic cells causing this gradient are the monocytes. Interaction between MSU and the lipid membrane and proteins in the cell membrane of a phagocyte cause activation of several signal transduction pathways resulting in IL-8 production, accounting for 90% of the neutrophilic chemotactic activity.³⁰ Other neutrophilic chemoattractant factors include S100A8 and S100A9.³¹ MSU released by injured cells act as a danger signal activating the innate immune system.³²

MSU crystals are potentially recognised by immune cells through Toll-like receptor 2 (and probably TLR4)^{33,34} and FcγRIIIB/CD16³⁵ subsequently leading to NF-kappaB activation and downstream signalling culminating in the production of proinflammatory cytokines such as interleukin-6, tumour necrosis factor α, interleukin-1β and interleukin-8 (IL-8). Actually, the stimulating capacity of MSU crystals to activate monocytes/macrophages to produce interleukin-1β (IL-1β) was already recognised 20 years ago but to date controversy remains about the precise mechanisms through which urate crystals drive inflammation.¹² Recent studies have led to significant advances in the understanding of the basic biology of crystal-mediated inflammation. Uric acid has been identified as a danger signal that triggers a cytosolic sensor, the inflammasome, a signalling platform that is required for the activation of interleukin-1, a cytokine that is critical to the initiation of acute inflammation in gout (reviewed in Martinon, 2010).³⁶ Interestingly, several studies have now suggested an effective treatment with IL1b inhibitors; however, these observations need confirmation in RCTs.^{37,38} Currently a study with canakinumab, an IL1b inhibitor, is underway. Another interesting finding recently published is the capacity of monocytes and/or the inflammatory environment in a

gout-prone individual to prime neutrophils to produce increased levels of superoxide in response to MSU stimulation.³⁹

Intriguingly, the natural course of a gout attack is to spontaneously resolve in seven to ten days. Clearance of MSU by differentiated macrophages results in a decrease of leucocyte and endothelial activation with the end result that the inflammatory response fades away.⁴⁰ Further *in vitro* research showed that *in vitro* generated macrophages failed to secrete cytokines in response to MSU.⁴⁰ It is therefore interesting to hypothesise that the time to resolve a gout attack is directly correlated with the time a monocyte needs to become a fully differentiated macrophage *in vitro*. Further research is needed though to confirm this hypothesis. On the other hand in chronic gout low-grade synovitis persists even during remissions of acute flares. The ongoing inflammation causes joint damage through chondrocyte activation and the following matrix metalloproteinase production.⁴¹ Furthermore, MSU is able to reduce the anabolic effects of osteoblasts, also contributing to irreversible joint damage. These series of events could possibly explain the inflammatory circuitry that leads to joint destruction when inflammation is not controlled (*figure 3*). Next to irreversible joint damage the increased cardiovascular risk in patients with gout is

Figure 3. Schematic overview of the pathogenesis of gout



still a medical conundrum. Two interesting hypotheses try to explain the pathophysiological mechanisms that lead to the accelerated atherosclerosis that underlies this phenomenon. First, activation of Toll-like receptors (TLRs) can block the induction of liver X receptor (LXR) target genes of the lipid metabolism.⁴² As activation of LXR and PPAR gamma can potentially prevent the development of atherosclerosis, an interaction between LXR and MSU induced TLR activation could explain the association with the uncontrolled rate of atherosclerosis in patients with gout. Second, two studies in rats, using dietary adjustments to induce hyperuricaemia, have shown that increased uric acid caused nephropathy resulting in increased renin levels and hypertension.^{43,44} Whether this mechanism can be translated to humans is a matter of debate and warrants further investigation. In addition, the contribution of chronic inflammation, oxidative stress and endothelial dysfunction to the development of cardiovascular disease in gout patients needs further attention as these processes intriguingly play a role in both diseases.

CURRENT INSIGHTS INTO THE MANAGEMENT OF GOUT

Following the clear evidence of the destructive effects of gout on the joints and the cardiovascular system a clinician facing a patient with gout should be triggered to start treatment for these aspects of this disease. The EULAR evidence-based recommendations for gout is a European combined effort to develop key recommendations concerning diagnosis and management of gout.^{4,45} A total of 22 key recommendations were generated through six Delphi rounds. *Table 2* presents a selection of the most important key recommendations for management of gout. In the short term, the treatment goal is to relieve symptoms as quickly as possible. For this purpose oral colchicine (dose needs to be corrected for renal function), NSAIDs or a low dose of oral prednisone can be used. The importance of using the correct dosage of colchicine is clearly illustrated in patient A who was nearly intoxicated. The efficacy of colchicine and its side effect is further discussed in Terkeltaub *et al.*⁴⁶ In a double-blinded randomised clinical trial oral prednisone and naproxen were found to be equally effective in the initial treatment of gout arthritis over four days.⁴⁷ In the longer term, urate-lowering therapy is indicated in patients with recurrent acute gout attacks, arthropathy, tophi or radiographic changes of gout. The first choice for urate-lowering therapy is a xanthine oxidase inhibitor (allopurinol). Allopurinol has a proven efficacy in all cases of gout. The most common dosage of allopurinol is 300 mg once-daily with which 56 to 65% of patients reach the recommended urate level of <0.36 mmol/l.^{48,49} If necessary, this dose can be increased to 600 mg daily. In 20% of the cases the use of allopurinol causes

Table 2. Modified recommendations for management of gout⁴⁵

1. Optimal treatment of gout requires both nonpharmacological and pharmacological modalities and should be tailored according to:
 - (a) Specific risk factors for gout such as elevated serum uric acid, previous attacks and radiographic signs
 - (b) Clinical phase (acute/recurrent, chronic tophaceous gout)
 - (c) General risk factors (age, sex, obesity, alcohol consumption, urate raising drugs, drug interactions and comorbidity)
2. NSAID and/or prednisolone are first-line agents for systemic treatment of acute attacks. Low-dose colchicine is an alternative.
3. Intra-articular aspiration and injection of a long-acting steroid is an effective and safe treatment for an acute attack.
4. Urate-lowering therapy is indicated in patients with recurrent acute attacks, arthropathy, tophi or radiographic changes of gout. The therapeutic goal of urate-lowering therapy is achieved by maintaining the serum uric below the saturation point of monosodium urate (< 360 μmol).
5. Allopurinol is an appropriate long-term urate-lowering drug; it should be started at a low dose (for example, 100 mg daily) and increased by 100 mg every 2-4 weeks if required; the dose must be adjusted in patients with renal impairment; if allopurinol toxicity occurs, options include other xanthine oxidase inhibitors, an uricosuric agent (benzbromarone) or allopurinol desensitisation (the latter only in cases of mild rash).
6. Prophylaxis against acute attacks during the first months of urate-lowering therapy can be achieved by colchicine (0.5-1 mg daily) and/or an NSAID.
7. When gout is associated with diuretic therapy, stop the diuretic if possible: for hypertension and hyperlipidaemia consider use of losartan and fenofibrate, respectively (both have modest uricosuric effects).
8. Associated comorbidity and cardiovascular risk factors such as hyperlipidaemia, hypertension, hyperglycaemia, obesity and smoking should be addressed as an important part of the management of gout.

side effects which are severe enough to stop treatment in 5% of the cases.⁵⁰ If there is intolerance against allopurinol an alternative approach is the use of an uricosuric drug; in the Netherlands benzbromarone as the only drug regularly available. In a recent randomised controlled trial the efficacy of benzbromarone 100 to 200 mg daily was equal to 300 to 600 mg allopurinol.⁵¹ Recently, a novel drug for the treatment of gout was introduced: febuxostat (Adenuric®). Febuxostat is a novel non-purine xanthine oxidase inhibitor. Urate levels of lower than 0.36 mmol/l were reached in 48 to 53% with daily use of 80 mg febuxostat and in 62 to 65% in the case of 120 mg febuxostat daily vs 56 to 62% and 85 to 93% with the use of 300 mg and 600 mg of allopurinol daily.³²⁻⁵⁴ However, the current position of febuxostat in the Netherlands is as a second choice after failure of allopurinol and/or benzbromarone (See Dutch Guidelines febuxostat www.nvr.nl) following the international recommendations.⁵⁵ Currently, there is a large debate about the effects that these treatments could have on cardiovascular risk. Aside from this urate-lowering therapy traditional cardiovascular risk factors such as hyperlipidaemia, hypertension, obesity and smoking should be addressed according to national cardiovascular risk management guidelines. Although clear trends are present

that suggest that gout/hyperuricaemia is associated with an increased risk for premature death due to cardiovascular diseases, the final answer needs to come from clinical intervention studies that still need to be performed.

CONCLUSION

The cases discussed in this report clearly illustrate the severity of gout and demonstrate that even today, gout is not always recognised and treated as it should be. Nowadays, gout can be treated very effectively with the currently available therapeutic armamentarium. So far, prospective studies supported by evidence from basal immunology studies clearly show that gout is an independent risk factor for CVD. In the coming years the precise interplay of inflammatory mediators mediating the arthritic symptoms and the potential connection with an increased cardiovascular disease profile is to be expected. For now, correct and proactive management of gout taking into account the present risk factors for the development of cardiovascular disease should have a place in the treatment of every patient with this clinical syndrome.

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