Review

Gout: one year in review 2023

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ABSTRACT

Gout is a chronic joint disease caused by the deposition of monosodium urate crystals into and around the articular tissues. In the last two years, new insights regarding diagnosis, genetic involvement, pathogenesis, comorbidities, and clinical data, have allowed the identification of new strategies to improve the control of the disease and its flares. In keeping, the discover of new mechanisms concerning crystal-induced inflammation have suggested new ways for the management not only of gout, but also other systemic diseases, mainly including renal and cardiovascular disorders. In this context it is very representative the case of colchicine which, given the surprising results obtained both in laboratory and clinical experiments, has recently received by FDA the approval for the prevention of cardiovascular disorders.

Introduction

The drafting of this 2023 One year in review on Gout proved more complex that the previous ones (1, 2), due to the explosion of interest toward hyperuricaemia and gout, as demonstrated by the number of papers present in Pubmed in 2023, about 800, most of which published in good quality Journals. What is surprising in these papers is the impressive enlargement of the fields of interest toward new previously unexplored area, ranging from laboratory to clinical research, including the therapy. The new mechanisms concerning gout inflammation, in particular those induced by crystals, have suggested new ways for the management not only of rheumatological diseases, but also of other systemic diseases, including mainly cardiovascular disorders (CVD). In this context it is very representative the case of colchicine, which is now proposed for number of conditions, due to surprising results obtained both in laboratory and clinical experiments. June 21 may be considered historic due to it being the date of approval of colchicine for the prevention of CVD by FDA (3).

Epidemiology and diagnosis

The prevalence of gout and its incidence is clearly increasing all around the world. Data collected from different studies, despite variation due to the population and the methods employed, indicate a prevalence ranging from <1% to 6.8% and an incidence of 0.58-2.89 per 1,000 person-years (4) with New Zealand, Australia, and the US having the highest age-standardised point prevalence estimates of gout (5).
A recent study reporting the burden of gout and its attributable risk factors in the Middle East and North Africa region between 1990 and 2019 has shown an 11.1% increase on annual incidence rates of gout with a positive association with the sociodemographic index (6).
An increased burden of gout has also been encountered in Asia-Pacific countries and prompted the Asia Pacific League of Associations for Rheumatology (APLAR) to create a longitudinal, multinational physician-reported registry of people with gout living in these countries (7). The aim of this registry is to increase the knowledge about gout and how to manage it in the Asia-Pacific regions.
The gold standard for the diagnosis of gout is arthrocentesis with identification of monosodium urate (MSU) crystals in synovial fluid. However, imaging is increasingly being used to confirm the diagnosis due to its non-invasiveness. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have collaboratively approved classification criteria for gout that include clinical, laboratory, and imaging findings (8). Among traditional imaging techniques, ultrasound (US) is the

most commonly used to detect urate crystals stones. Musculoskeletal US findings of tophaceous deposits include the double contour sign, "snowstorm" sign of periarticular, heterogeneous collection in soft tissue, and occasionally intra-tendinous tophi (9). However, the results of musculoskeletal US may depend on the specifics of the scanner and operator experience. To overcome this poor reliability, a recent study applied an artificial intelligence learning system to train a convolutional neural network for the identification of tophi in US images (10).

Over the last few years, omics technologies have been applied to different biological fluids to discover potential diagnostic biomarkers. Although this approach has significantly contributed to provide aetiological insights into the mechanisms of hyperuricaemia and gout development, no specific diagnostic markers for the diagnosis of gout have emerged yet (11).

Take-home messages

- The prevalence of gout and its incidence is steadily increasing all around the world with an important rise on annual incidence rates in the Middle East and North Africa region (6).
- Although synovial fluid analysis is the gold standard for the diagnosis of gout, musculoskeletal ultrasound is commonly used to detect urate crystals stones (9-10).

Genetics

Gout is a condition influenced by both lifestyle and genetic factors. Previous research has identified mutations in several genes encoding renal transporters as a significant underlying cause. Over the past two years, novel genetic studies have further expanded this list. Recently, Bardin *et al*. have identified specific genetic mutations linked to gout in the lactate dehydrogenase D (LDHD) gene. High D-lactate levels in the blood and/or urine due to these mutations may lead to gouty arthropathy (12). Another study has found associations between gene expression of inflammatory regulators including free fatty acid receptor 2 (FFAR2) and suppressor of cytokine signalling 3 (SOCS3), and gout flares, suggesting a role in the initiation and resolution of flare, respectively (13). Additionally, certain genetic variations near the major histocompatibility complex class 1 (MHC-1) region and copy number variants (CNVs) in specific regions were linked to increased serum urate levels and gout risk in different populations (14, 15).

Some researchers explored the genetic relationship between gout, uric acid levels, and five common psychiatric disorders, identifying common candidate genes between gout and attention-deficit/hyperactivity disorder (16). Lifestyle factors, including diet, were also investigated. Genetic analyses revealed shared genetic bases for body mass index and gout, and adherence to a healthy diet was associated with a lower risk of gout in genetically susceptible female individuals (17, 18).

Epigenetic studies highlighted microRNAs that could influence gout development by regulating gene expression (19). An epigenome-wide association study identified specific CpG DNA sequences associated with SUA levels, providing insights into co-regulation and genetic effects on SUA levels, particularly in genes related to small molecule transport and cardiometabolic traits (20).

Genetic applications including machine learning modelling

Several studies have recently explored the applications of post-genome-wide association studies (GWAS) in gout. For instance, researchers suggested to consider genetic variations in ABCG2 gene, coding for the transporter ATP Binding Cassette Subfamily G Member 2, during diagnostic procedures for pediatric-onset hyperuricaemia and when prescribing allopurinol (21). Another study investigated the impact of ABCG2 genotype on the response to allopurinol treatment, observing any alteration in the drug pharmacokinetics (22).

The polygenic risk score (PRS) derived from combining multiple genetic variants obtained in GWAS is being explored as predictive tools. For example, a PRS consisting of 19 European gout genetic risk variants was associated with earlier age at gout onset and tophaceous disease. Stratifying studies by sex is also emphasised (23, 24).

GWAS contribute also to drug discovery. *In silico* screening identified potential drug candidates for gout targeting genes involved in the IL-4 and IL-13 pathway (25). Multiomics approaches on serum and urine samples from hyperuricaemia patients reveal differential metabolites and related genes as potential therapeutic targets, *i.e*. caffeine metabolism pathway (26).

Artificial intelligence and machine learning (ML) techniques assist in interpreting complex data and identifying clinically relevant patterns, supporting biomarker discovery (27). ML models have been developed to predict the risk of renal underexcretion phenotype in gout patients using genetic and clinical variables (28). Another ML model differentiates infrequent from frequent gout flares based on metabolomics data (29). AI is also applied to automated image recognition for diagnosing and monitoring rheumatic diseases. For instance, an AI learning system accurately identifies MSU deposition in ultrasound images of gouty patients with a high degree of accuracy (30).

Take-home messages

- Some genetic factors, like those related to obesity and ADHD, may overlap with gout susceptibility, suggesting an intricate interplay between genetics and lifestyle and highlighting the importance of a holistic approach to managing gout (16, 17).
- Epigenetic influences on urate regulation and potentially contribute to the risk of developing gout or related cardiometabolic traits (20).

Pathogenetic mechanisms

The regulation of NLRP3 inflammasome activation, which plays a key role in the development of MSU crystal-induced inflammation, has remained a question of interest throughout the 2023. An *in vitro* study suggested that MSU crystals alters cell circadian clock reducing the levels of its components, such as BMAL1 and REV-ERBα, and thus leading to loss of NLRP3 inflammasome repression (30). Inflammasome response can be regulated also by en-

dogenous molecules. For instance, the stress-induced protein cold-inducible RNA-binding protein (CIRP) can prime neutrophils to produce pro-interleukin (IL)-1β, which later is transformed into IL-1β through NLRP3 inflammasome activation (31). A synergistic effect of ATP and MSU crystals in NLRP3 activation, mediated by purinergic receptor P2X7, was observed in macrophages from gout patients and in a rat model of spontaneous gout (32). Interestingly, the mechanosensitive TRPV4 channel expressed in macrophage has shown critical involvement in MSU crystal-induced NLRP3 inflammasome activation and requires the presence of the TRPV1-expressing nociceptors. This observation provides evidence of a neuroimmune axis in these processes (33). A more recent study demonstrated that mitochondrial pyruvate carrier (MPC) regulates the NLRP3 inflammasome via metabolic reprogramming (34). In contrast, PYD only protein 1 (POP1), Lipoxin A4 (LXA4) and C4b-binding protein (C4BP) suppress MSU crystal-induced inflammasome activation by blocking NLRP3 assembly in *in vivo* and *in vitro* models. The first shows 64% sequence identity to the ASC pyrin domain (PYD) (35), while LXA4 and C4BP are a lipoxygenase-derived eicosanoid mediator and a complement inhibitor, respectively (36, 37).

Inflammasome activation is not the only mechanism involved in gout. A genome-wide transcriptomic analysis using non-primed human and murine macrophages demonstrated that MSU crystal alone induce inflammatory-metabolic changes through JNK signalling in an inflammasome independent way (38). Furthermore, inhibition of NLRP3 pathway did not suppress MSU crystal-induced necrosis in murine macrophages (39). $Na_v1.8$ and TRPV1 channels, sensory neuron-specific channels preferentially expressed in small and medium size DRG neurons, and angiotensin type 2 receptor (AT2R) plays an important role in gout pain (40-42). In contrast, Clec12a receptor limits MSU-induced acute inflammation through lipid raft expulsion, neutrophil activation and cytokine release inhibition *in vitro* and *in vivo* (43).

In recent years, macrophages have largely been studied in crystal-induced inflammation. Macrophages stimulated by MSU crystals have demonstrated to secrete factors that promote a proinflammatory state in osteoblasts and thus indirectly induce bone erosion (44). Conversely, SF macrophages may play a key role in resolution of MSU crystal-induced inflammation by clearing neutrophil extracellular traps (NETs) without causing any significant immunological response (45). Interestingly, dysregulated immune cell subsets in gout at different stages were identified also by single-cell analysis, highlighting that the length of the clinical course may play important roles in the variation and distribution of immune cell subpopulations (46, 47).

Pathological progression of gout seems to be influenced also by the physicochemical properties of MSU crystals. Experiments conducted in experimental models of inflammation induced by engineered MSU crystals demonstrated that the highest degree of inflammatory parameters were obtained using medium-sized long aspect ratio (23±8 μm) crystals (48). Observations in SF reveal that NET levels were not correlated with PMN recruitment, as previously hypothesised, but with the number of crystals present (49).

Several additional factors have been shown to be involved in the mechanisms underlying MSU crystal-induced inflammation. For instance, TGF-β in plasma of individuals with hyperuricaemia, phospholipase A2, intracellular STING (stimulator of interferon genes) and Type II collagen in SF, and myeloid Src-family kinases and Soluble mediators secreted by synoviocytes in experimental models of gout have shown to facilitates MSU crystal-induced acute inflammatory reactions (50-54). Conversely, protein phosphatase 2, and Sirtuin 3 may play a part in the resolution phase (55).

Take-home messages

- Several factors have shown significant involvement in MSU crystal-induced NLRP3 inflammasome activation, such as CIRP, ATP and TRPV4 (31-33).
- MSU crystal-induced inflammation can be regulated by NLRP3-independent pathways, including Nav1.8 and TRPV1 channels and Clec12a receptor (40, 41, 43).
- Type II collagen and myeloid Src-family kinases can facilitate MSU crystal-induced acute inflammatory reactions (52, 53).

Animal models

The use of animal models represents an irreplaceable system for in-depth investigation of the pathogenesis of the disease and for testing preclinical efficacy of new treatments in gout. In addition to the classical methods, which consist in inducing a potent NRLP3-dependent self-limiting inflammation by intra-articular or intra-peritoneal inoculation of MSU crystals, new models emphasise different aspects such as the accumulation of urate in muscles of the limbs and the recurrent attacks of gout. Recently, the SMASH (Standardised Microscopic Arthritis Scoring of Histologic Sections) recommendations have been published. These guidelines are aimed at defining standard procedures in the collection, fixation and staining of samples and contributes to the definition of observable histopathological hallmarks to evaluate the tissue damage of the joint specimens collected from experimental arthropathies (56).

In vivo models of spontaneous deposition of MSU crystals in the joint and the formation of tophi have never been described. To bypass the uricase enzyme which degrades urate into allantoin, since 1994 new laboratory rodents' strain have been produced knocking out uricase or ablating pivotal UA transporter genes such as URAT1, SLC2A9, SLC22A12 and ABCG2. However, these knock out mice presented either a high mortality due to severe multi-organ failures or a relatively normal phenotype characterised by variable levels of SUA, various grade of nephropathies, or an increased urinary excretion of urate to compensate for the high SUA levels hence preventing the onset of observable clinical signs.

Recently, a zebrafish (Danio Rerio) knock out for uricase was produced using CRISPR/Cas 9 gene editing, show

high levels of urate in the tissues. By injecting urate into the hindbrain, zebrafish Uox---/-- exhibited a limited inflammatory response but observable formation of tophi with a prevalent macrophage component (57).

Ma and colleagues demonstrated that KO mouse conditioned for glucose transporter 9 (GLUT9) and fed a purine-rich diet for 22 days became hyperuricemic with SUA levels between 9 and 12 mg/dl, but if stimulated with MSU injected into the air pouch dorsal and in the cremasteric muscle, showed only mild inflammation (58). This model could be useful in investigating the reason why hyperuricaemia in itself is not sufficient to cause the acute inflammation associated with MSU crystal deposition. Other knock out strains that have demonstrated resistance to inflammation are knockout mice for transient receptor potential vanilloid 4 (TRPV4), Lamtor1, Glucagon-Like Peptide-1 Receptor and Pyrin domain (PYD), PYD-only proteins (POPs) lacking an effector domain- POP1 (33, 35, 59, 60).

On the contrary, starting from observations on human patients, some experimental strategies have been aimed at exacerbating experimental inflammation as in miR-223 KO mice or in animals treated with an agonist of TRPV4 (33, 61). The repeated contraction of the Triceps Surae muscle induced by electrical stimulation leads to accumulations of UA in the muscles with formation of NETs and hyperalgesia reversible by uricosuric drugs (62).

A mouse model that reproduces a link between gout and osteoarthritis is described by Accart and colleagues using repeated intra-articular injections of LPS and MSU for 10 weeks. This procedure reproduces recurrent attacks of gout and has highlighted, through MRI and MicroCT imaging, erosive damage at the joint level and significant fibrosis of the lower limb muscles comparable to a human patient with osteoarthritis (63).

A recent study shows the first application of lentiviral vector mediated gene transfer using transplanted autologous haematopoietic stem/progenitor cells (HSPCs) to deliver steady high levels of IL-1 Ra in order to neutralise overexpression of IL-1β induced by MSU intraperitoneal injection (64).

Take-home messages

- The experimental inflammation induced by MSU injection in knee, ankle, paw joints or in peritoneum and dorsal air-pouch maintains a significant translational value for preclinical study aimed at investigating new therapies for gout (56).
- The main limit of *in vivo* models remains the impossibility to realise experimental model where measurable hyperuricaemia is associated to spontaneous deposition of MSU crystals and tophi formation in joint tissues (63).

Comorbidities

Novel associations with gout

Hyperuricaemia and gout are known to be associated with a variety of severe comorbidities, such as CVD and renal disorders. High SUA levels have shown to contribute to inflammation, oxidative stress and endothelial dysfunction, which in turn may result in atherosclerotic vascular changes, cardiovascular and chronic kidney diseases (2, 65). A study investigated this hypothesis by measuring blood oxidative stress markers and various cytokines levels in an attempt to stratify patients and their comorbidities using a cluster analysis (66). Interestingly, the clusters identified by clinical variables were very similar to those identified by blood markers, meaning that the systemic inflammatory fingerprint reflects the type of comorbidities the patient develops.

These comorbidities greatly impact the mortality rate, as confirmed by a recent population-based study on the US Department of Veterans Affairs (VA) cohort and a Swedish population-based study on acute coronary syndrome (4, 5, 67, 68). It bears noting that even though cardiovascular causes were numerically relevant, in the VA cohort the most overrepresented cause of mortality in gout patients *versus* controls was not CVD but genitourinary conditions including nephritis (HR 1.91 [95% CI 1.69–2.15]), chronic kidney disease (HR 1.71 [95% CI 1.65–1.76]), acute renal failure (HR 1.54 [95% CI 1.49–1.60]), and kidney stones (HR 1.10 [95% CI 0.79–1.53]) (67).

In addition, it has recently emerged that gout is not only linked to hypertension, ischaemic heart disease and renal disease but also cardiac arrhythmias. According to another large population study in the United States, one fourth of hospitalised patients with gout develops cardiac arrhythmias. Although atrial fibrillation accounts for 88% of arrhythmias, also other types of dysfunctions such as atrial flutter, conduction disorders, ventricular tachycardia, paroxysmal supraventricular tachycardia, sinoatrial node dysfunction and ventricular fibrillation can arise. As in other cohorts, patients with gout display higher baseline comorbidity burden. However, hazard ratios for in-hospital mortality risk, overall mortality rate, in-hospital time, and hospitalisation costs were higher in gouty patients with arrhythmias after correction for other comorbidities (69).

The cardiovascular burden of patients with gout did not fail to influence the outcome of the SARS-CoV2 infection. Indeed, higher rates of hospitalisation and deaths were reported also among lower risk groups such as vaccinated and female patients (70).

During the latest years, some interesting publications focused on the association between gout and neurological or neuropsychiatric well-being. Whereas three studies agree on the decreased risk of neurodegenerative disorders such as dementia, Parkinson's disease and motor neuron diseases in patients with gout (67, 71, 72), the relationship between depression, anxiety and gout is debated. A Canadian population-based study reported an increased incidence of anxiety and depression in new onset gout (73), but the US Veterans Administration cohort did not report a cause-specific mortality related to these conditions (67). Adding to the puzzle, Watson *et al*. highlighted that, although gout specific variables are important, the main factor impacting HRQoL is comorbid depression and anxiety (74). Therefore, we suggest that whatever the incidence of depression and anxiety, and whatever their specific impact on mortality, they remarkably influence

Table I. Gout-related comorbidities.

Author	Study design	Participants	Comorbidity	Key results
Helget L (67)	Matched retrospective cohort (US Veteran Administration)	Gout (n=559,243) and matched non-gout controls (n=5,428,760)	Genitourinary conditions, digestive system, blood, musculoskeletal, skin, infection, cardiovascular, external causes, metabolic, malignancy, respiratory, mental health, nervous system)	Adjustment for age, sex, race, BMI, smoking, comorbidities - lower risk of death related to neurologic (HR 0.63 [95% CI 0.62–0.65]) and mental health (HR 0.66 [95% CI 0.65–0.68]) conditions. Overrepresented causes of death: - genitourinary disease (HR 1.50 [95% CI 1.47–1.54]) - digestive disease (HR 1.26 [95% CI 1.23–1.29]) - blood disorders (HR 1.20 [95% CI 1.12–1.29]) - musculoskeletal disease (HR 1.19 [95% CI 1.11–1.27]) - skin disease (HR 1.14 [95% CI 1.03–1.26]), - infection (HR 1.10 [95% CI 1.07–1.13] - CVD (HR 1.07 [95% CI 1.06–1.08]).
Mhanna M (69)	Retrospective cohort	60,360 hospitalisations Arrhytmia 45200 pts; non-arrhytmia 15160 pts	Cardiac arrhytmias	¼ gout patients have arrhytmia; atrial fibrillation was the most common type (88%) In gout & arrhytmia: higher inhospital cardiac arrest and mortality 693 *vs*. 77/100,000 hospitalisations, $p<0.001$ longer median hospital stay 4.3 *vs*. 3.7 days, $p<0.001$
Xie D (70)	Retrospective cohort	54576 gout 1333377 non-gout	SARS-CoV2 severe outcome in vaccinated pts	In vaccinated gout pts higher risk of breakthrough infection, hospitalisation (HR 1.30, 95% CI: 1.10–1.53) and death (HR 1.74 95% CI 1.14–2.67) increased risk of death in women with gout
Howren A (73)	Matched retrospective cohort (1:1)	157,426 incident cases of gout and 157,426 non-gout controls	Anxiety and depression	Incidence rate of depression and anxiety was higher in gout *vs*. non-gout In gout adjusted HR for depression 1.08 [95% CI 1.05–1.11]; for anxiety 1.10 [95% CI 1.05–1.14]
Watson L (74)	Prospective cohort	1186 participants	Depression and HRQoL	Gout flares were the major factor associated with worse HRQOL. Comorbidities associated with worse outcome were CKD ≥3, more severe depression and anxiety
Choi HG (75)	Matched retrospective cohort (1:4)	23817 gout pts 95268 controls	Benign paroxysmal positional vertigo (BPPV), Meniere's disease, and vestibular neuronitis	1.13-fold higher risk of BPPV [95% CI, 1.06–1.21, $p<0.001$] and a 1.15-fold higher risk of Meniere's disease [95% CI, 1.15–1.37, $p<0.001$] than the matched control group
Chen JW (76)	Matched retrospective cohort (1:4)	3255 thalassaemia pts 13020 non thalassaemia pts	Thalassaemia	In thalassaemia aHR was 1.00 [95% CI 0.80 to 1.25]
Schlesinger N (77)	Retrospective cohort	47 pts with gout	Fatty liver disease and liver fibrosis	Steatosis in 85.1% of pts, fibrosis in 19.1% and cirrhosis in 17%
Galozzi P (78)	Retrospective cohort	213 synovial fluid (SF) samples from PsA pts	Psoriatic arthritis and gout	5 (2.3%) SFs displayed MSU crystals and 8 (3.8%) SFs displayed calcium pyrophosphate crystals
Hong CC (79)	Retrospective cohort	13 patients with septic arthritis and gout	Septic arthritis outcome	Gout and septic arthritis have a considerable risk of long inhospital stay, need for complex care, and limb amputation

the HRQoL of gouty patients, imposing a careful evaluation of this dimension in clinical practice. Remaining in neurological surroundings, a study from Korea investigated whether benign paroxysmal positional vertigo (BPPV), Ménière's disease, and vestibular neuronitis were associated with gout, finding an increased risk of BPPV and Ménière's disease but not vestibular neuronitis (12, 75). The mechanisms underlying this link are still to be elucidated.

Other interesting associations have emerged from smaller studies, that are reported in Table I. A Taiwanese study investigated whether a cohort of more than 3000 patients with thalassaemia have an increased risk of gout compared to controls, finding a non-significant association between the two diseases (76). Schlesinger *et al*. selected 47 consecutive patients with gout and performed a FibroScan, finding a surprisingly high incidence of hepatic steatosis, fibrosis, and overt cirrhosis of the liver – 85%, 19% and 17%, respectively. Nevertheless, given the likely selection bias it is difficult to support the author's claim that all gout patients should be screened for hepatic

disease (77). Galozzi *et al*. investigated concomitant gout in 213 patients with psoriatic arthritis ("psout") undergoing arthrocentesis for suspected flare: as little as 2.3% of synovial fluids showed MSU crystals and as little as 3.8% showed calcium pyrophosphate crystals (78). Finally in Singapore, Hong *et al*. described the outcome of 13 patients with gout and septic arthritis, observing a considerable risk of long in-hospital stay, need for complex care, and limb amputation (79).

Take-home messages

- It has been shown that high SUA levels contribute to inflammation, oxidative stress and endothelial dysfunction, which in turn may result in atherosclerotic vascular changes, cardiovascular and chronic kidney diseases (2, 65).
- New evidence shows an association between gout and cardiac arrhythmias (69), neurological and neuropsychiatric well-being (73, 74).

Therapy

In the last two years, no international recommendations and/or guidelines have been published, probably reflecting the absence of new drug approvals for the management of gout and/or hyperuricaemia. Paradoxically in the meantime, the interest on the recommended drugs raised, mainly oriented toward studies clarifying their best use, especially in the presence of comorbidities, in particular renal and CVD. Among drugs for acute flares, NSAIDs is contraindicated in most cases, and should be avoided in subjects with advanced chronic kidney disease (CKD) (80). Furthermore, NSAIDs should be cautionally prescribed in older people, especially when taking anticoagulant or antiaggregants (2). As regards colchicine, the increasing number of studies demonstrating its effectiveness are showing that its tolerability is higher than previously believed (81). Despite this, in clinical practice colchicine remains still underutilised. A possible interpretation for this attitude may be because the dosage in older studies was largely higher than the current one, which rarely exceed 1 mg/day (80). Main concerns derive from the mechanism of colchicine which is partially cleared by the kidney and so, the interaction with various drugs, such as statins, cyclosporin and macrolide antibiotics, may be worsened when drug half-life is increased. However, as regard patients with gout and CKD, no studies have investigated these effects (80). Thus, when scientific evidence is lacking, in clinical practice we must look for the best solution for our patients, which in most cases derives from the personal experience. Accordingly, no side effects we have observed by associating low doses of colchicine (0.5 mg/day) to steroids (25 mg prednisone for 4–5 days) in the acute attack and colchicine 0.5 mg every other day for the prophylaxis, as also reported by other authors (80). The compliance toward colchicine is strengthened by the increasing demonstration of pleiotropic effects of this old drug in various diseases, as demonstrated by recent approval by FDA for the prevention of CVD (3).

In keeping with international recommendations, in patients who do not respond to standard therapies, interleukin-1 (IL-1) inhibitors represent a good option, since they have demonstrated to be effective and safe, for both gout flares and prophylaxis. Among available drugs, only anakinra and canakinumab received indication for gout by international agencies. Although trials excluded subjects with advanced CKD (eGFR < 30 ml/min per 1.73 m^2), in real life anti-IL-1 inhibitors seem don't affect renal function (80). Typical example of appropriateness of these drugs is in the transplanted patients, especially renal, when the very high levels of SUA despite urate lowering treatment (ULT), allow to the formation of diffuse deposits and subsequent frequent acute attacks, for which NSAIDs are contraindicated, and colchicine and/or hypouricaemic agents must be prudently taken and in addition, at low doses (82).

Since the obligatory prerequisite of gout is hyperuricaemia, it is obvious that main goal of the management is to lower the SUA levels in order to progressively reduce the deposits and mainly, the frequency and severity of flares. According to the international recommendations, the gold standard is the SUA levels <6 mg/dl which however should be titrated <5 mg/dl in the presence of severe tophaceous gout. To this aim, the available ULTs are the xanthine-oxidase inhibitors (XOI) allopurinol and febuxostat, the uricosurics and the uricase. Allopurinol may be considered effective and safe, for both hypersensitivity syndrome and acute flares, especially when started at low doses (<100 mg) and escalating progressively until the objective obtained (2). Since the active metabolite of allopurinol, oxypurinol is renally excreted, there are frequent concerns in the presence of CKD, thus leading to an undertreatment. However, recent studies shown that allopurinol may be considered safe to reduce SUA in patients with CKD, even in patients with creatinine clearance (CrCl)<30 ml/mn (4,7) (80, 83).

The other XOI febuxostat is effective and safe in patients with CKD, especially when starting at low dose (40 mg/day). Some concerns derived for the potential CV risks observed in CARES trial, in comparison with allopurinol (84). However, the more recent FAST (85) study showed that patients treated with febuxostat did not have an increased risk of CV death compared to patients with allopurinol and that patients with gout treated with febuxostat had fewer deaths when compared with the patients taking allopurinol (86).

Another class of ULT are uricosurics, drugs that prevent reabsorption of urate in the proximal tubule and promote renal clearance of urate. These medications include probenecid, benzbromazone, and lesinurad. This latter is now withdrawn from both America and European markets after a business decision of the manufacturer. However, the availability of uricosurics may varies in different countries. For example, in Italy no uricosurics are available (2). However, when available, the association XOI with uricosurics seem more effective that XOI alone, and with less side effects, especially in patients needing high doses of XOI (87).

In difficult cases, such as severe gout refractory or intolerant to first line ULT, pegloticase, a mammalian recombinant uricase, is a useful drug. The main

concern regarding this drug is its tolerability, since it may induce at times severe immunoreaction. However, last studies demonstrated that the concurrent utilisation of immunomodulating drugs, such as mycophenolate mofetil or methotrexate, reduce remarkably these reactions (88). Interestingly, pegloticase improved hepatic fibrosis in chronic refractory gout patients (89).

Take-home messages

- In recent years, the increased number of new indications for colchicine, have shown that its tolerability is higher than previously believed (81).
- The recent approval by the FDA of colchicine for cardiovascular risk is an important step for the approach to inflammatory diseases, especially when induced by crystals (3).
- For ULT, new studies demonstrated their general safety, especially in patients with decreased renal function (80, 83).

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