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Update on gout 2012

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ABSTRACT

Significant scientific advances have been made over the last five years in the pathogenesis of hyperuricemia and understanding how monosodium urate (MSU) crystals provoke gout. New detection methods using ultrasound (US) have been evaluated and may become part of our routine diagnostic approach in a patient presenting with gout. This review will concentrate on the latest developments in the field, and discuss how these data may impact on clinical practice. Finally, a brief review of the therapeutic implications and new therapies that have become available will be presented.

1. Introduction

We are witnessing a golden era of clinical and scientific progress in the treatment of gout. Scientific advances, from molecular genetics to physiology and biochemistry, have increased our understanding of the mechanisms of hyperuricemia and inflammation triggered by monosodium urate (MSU) crystals. New and effective drugs to manage hyperuricemia and inflammation have been developed; yet in daily practice, our management of gout and hyperuricemia remains suboptimal [1]. Recent surveys have highlighted the gaps in our management of gout in daily practice (references): for example patients are frequently not treated with the optimal doses of urate-lowering therapy (ULT) to obtain the recommended serum level of 360 μmol/L of urate; prophylaxis against an acute atttack of gout is often not prescribed when initiating ULT. These are simple measures that can improve the effectiveness of and compliance with our current treatments, which require a renewed effort to educate and inform both doctors and patients.

2. Detection of gout

Making a correct diagnosis is the first and essential step to effective management. The gold standard of crystal identification by polarized light microscropy remains the reference to which all other criteria are compared. However, joint aspiraton and crystal identification is not always performed or are not feasible in a general practice setting. Therefore for many years, the ACR acute gout classification criteria have been used by clinicians, but its poor specificity has been criticized [2]. Janssens et al. in the Netherlands have performed a prospective study of acute monoarthritis and used crystal identification as the reference standard for gout diagnosis. Over 300 patients with suspected gout were evaluated, and a crystal-based diagnosis was established in over 200 subjects. Based on a detailed analysis of presenting clinical features, and contrasting their findings in patients who had crystal-proven gout or not, they proposed a model incorporating seven features that allows physicians to make a diagnosis of gout with greater reliability than the ACR criteria, even in the absence of joint fluid analysis (Table 1) [3]. However, it has to be emphasised that the study was performed in a general practice setting in a country with a well organized health network, and the validity of this diagnostic tool in other countries and other health system settings will need to be evaluated in the future.

Imaging of crystal deposits is another method to establish the diagnosis. Traditional radiology is not useful in assessing MSU deposits, as they are not radio-opaque, and can only be used to evaluate bony erosions due to long-standing deposits. Recent interest has centred on two different techniques, ultrasonography – a technology that is accesible and practised by many rheuamtologists or dual energy CT (DECT) – a much less widespread technology that is mainly hospital-based. This latter technique permits the detection of MSU deposits by their radioabsorption characteristics. These deposits may be subclinical, and DECT can provide a measure of the total mass of tophus in a patient [4]. In a prospective validation study involving 80 subjects (40 with gout), DECT was found to be highly specific for gout and when deposits were detected, there was high interobserver correlation. Five of six false negative patients were on ULT, which may have reduced the amount of detectable deposits. The overall sensitivity of the test was 0.78 [5]. It must be emphasised that all the gout patients in the study had a known diagnosis, and DECT has not been shown to be a diagnostic tool for gout when the diagnosis is suspected.

Ultrasonography is a much more widespread imaging technique that is available in most rheumatology centers. The characteristic US signs include the "double contour" sign (DC) that is attributed to

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Table 1
Diagnostic model for gout based on clinical characteristics proposed by Janssens et al. [3].

Variable	Clinical score if present
Male sex	2
Previous patient-reported arthritis attack	2
Onset within 1 day	0.5
Joint redness	1
Involvement of MTP1 joint	2.5
Hypertension or > 1 cardiovascular disease	1.5
Serum uric acid > 5.88 mg/dL or > 50 mmol/L	3.5
Maximum score	13

A total score of < 4 rules out gout in almost 100% of patients. Gout was confirmed in 80% of patients with a score of > 8. Score > 4 to < 8 leaves uncertainty about the diagnosis (gout was confirmed in 30% of cases).

cartilage surface deposition of MSU, a "snow storm" or hyperechoic appearance within the synovial space that is a sign of intra-articular tophus [6]. Other non-specific US signs include synovial thickening, a positive color Doppler signal or even joint erosions. A major question is whether US is specific enough to be used clinically as a diagnostic tool in clinical practice and how sensitive this technique is. A recent case-control study evaluated the utility of US in the diagnosis of gout. Ten joints were evaluated in each subject and the double contour sign and the presence of tophus were sought as signs of gout. Both signs were highly specific for gout, and had good sensitivity (67–74%). In this study, the mean disease duration of gout was over nine years [7]. In another study looking at patients with early gout, the same group found that the double contour sign was present in 60% of 15 patients evaluated, but the presence of tophus was only 26% [8]. Furthermore, the DC sign was found also in around 25% of asymptomatic hyperuricemic subjects investigated in different studies [9,10]. Overall, US appears to be a reliable and specific tool to visualise MSU deposits and may eventually become part of our routine list of investigations that all gout patients undergo on diagnosis. US detection of MSU deposits is likely to become a routine tool in clinical practice and may change our thinking on who to treat and how to treat.

3. Genetics of hyperuricemia

Gout is often a familial disease, but the genetic basis of primary gout has not been extensively investigated. In contrast, we have a wealth of information that has identified a number of genes that are important in hyperuricemia, the underlying metabolic condition. In a recent twin study involving over 500 sets of male twins from the US, the authors did not find a difference in the prevalence of gout between monozygotic or dizygotic twins. However, monozygotic twins were concordant for hyperuricemia twice as frequently as dizygotic twins (53% vs. 24%). These findings led that authors of the study to conclude that while hyperuricemia is genetically determined, the development of gout is due to environmental factors [11]. Using a more direct genetic approach, researchers from Iceland have studied if there are genes that predisposed to gout. Firstly, they sequenced the genomes of over 400 subjects from Iceland, and from this information, derived over 16 million SNPs that were then used to genotype a cohort of 41,000 subjects [12]. They found a mis-sense variant that was strongly associated with gout as well as serum urate levels. The gene *ALDH16A1* encodes a form of aldehyde dehydrogenase, but it is at present unclear how this enzyme may influence metabolism, hyperuricemia or the development of gout. In the same study, they confirmed the association of a number of recently discovered urate transport genes with hyperuricemia, as well as identifying a novel chromosome 1 genetic polymorphism that was strongly assoicated with hyperuricemia, but weakly with gout.

These data increase the list of genes that have been found to be associated with hyperuricemia based on results of genome wide association study (GWAS) involving many thousands of subjects (Table 2). Most of these genes are implicated in either the excretion or reasborption of urate in the renal tubule. The strongest association found is with the SLC2A9, a urate transporter that was previously thought to be important in glucose transport, hence its alternative name GLUT 9. Both genetic and functional studies showed that this gene plays a prominent role in urate transport in the kidney as well as the liver [13]. Other genes that have known urate transport function have also been identified by GWAS, such as *URAT1* (*SLC22A12*) and *SLC17A1*. However, other genes that are not known urate transporters have also been identified, such as *ALDH16A1* and *PDZK1*. These findings suggest that there are multiple levels where genetic mechanisms can act, some are on renal urate transport and excretion, others are likely to be involved in metabolic function, including glucose and fatty metabolism. Most of these studies were performed on populations that had not been specifically identified to study gout and hyperuricemia, therefore the phenotypic characterization of gout was very basic. Future studies will need to concentrate on patients who have better phenotypic characterization and will undoubtedly provide novel information on genes that have not yet been detected.

4. Gout and disease associations

Hyperuricemia is strongly associated with clinical features of the metabolic syndrome and was indeed considered to be a component of the syndrome by some [14] even though it does not appear among the recognized classification criteria. In clinical practice, patients with gout have a high prevalence of diabetes, cardiovascular disease (including hypertension) and renal impairment. For a long time, the debate has been over whether hyperuricemia is a consequence or a cause of these disease associations. Recent epidemiologic studies have shown that hyperuricemia to be an independent risk factor for the development of hypertension as well as the risk of developing coronary artery disease. In a meta-analysis that included 26 studies, the authors found that hyperuricemia was associated with an increased risk of incident

Table 2
Genetic loci associated with hyperuricemia or gout from studies.

Gene	Homonym	Function
SLC2A9	GLUT 9	Urate transport in proximal renal tubule
SLC22A12	URAT1	Urate transport in proximal renal tubule
ABCG2	Breast cancer resistant protein	Urate transport in the gut and renal tubule
SLC17A1	Sodium-dependent phosphate transporter 1	Urate and phosphate transport
GCKR	Glucokinase regulator	Glucose and triglyceride metabolism
PDZK1	PDZ domain containing protein	Scaffold protein for Na^+ dependent P transporter
LRRC16A	Leucine rich repeat containing sequence	Platelet development; actin filament organization
INHBC	Inhibin beta C chain	TGF-b superfamily, expressed in placenta and endometrium
SLC16A9	Monocarboxylic acid transporter 9	Carnitine transport
ALDH16A1		Aldehyde dehydrogenase

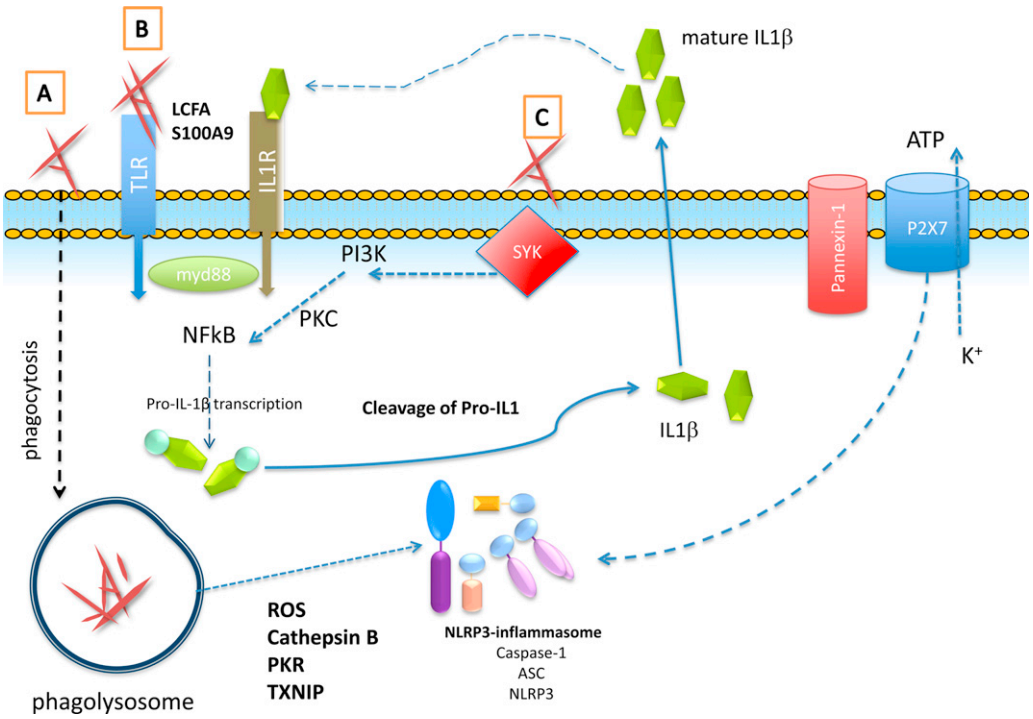

Fig. 1. Monosodium urate (MSU) crystals activate cellular responses in inflammasome-dependent and independent pathways. MSU can interact with cells by A) phagocytosis or B) binding to TLR2 & 4 or 3) interacting with cell membrane directly to activate Syk kinase. Activation of the NLRP3-inflammasome occurs through intermediates that either bind directly or indirectly to NLRP3. The P2X7 ATP receptor, in collaboration with pannexin-1, facilitates ionic currents across the cell membrane, and participates in activation of the inflammasome. TLRs are important for the priming signal, through binding of long chain fatty acids (LCFA) or the S100A9 protein.

cardiovascular disease (RR 1.34) as well as for cardiovascular mortality (RR 1.44) [15]. In another meta-analysis published by the same group, looking at the question of whether hyperuricemia predisposes to the development of hypertension, they found that there was an increased risk (RR 1.41) and for each 1 mg (60 μmol/L) increase in serum urate, they observed a 13% increase in risk of developping hypertension, even after adjustment for confounding factors [16]. These effects appear be greater in young female subjects and there may also be a larger effect in African Americans.

As mentioned already, gout patients frequently have co-morbid conditions. The question of whether gout predisposes to cardiovascular disease has also been addressed. Previous studies showed that gout acts as an independent risk factor for mortality and risk of coronary artery disease in men [17]. In a further study, they analyzed the cardiovascular risk of gout in a large cohort of elderly canadian women. They found the risk increase to be near 40% for acute myocardial infarction [18]. These epidemiological studies give further support to previous experimental data in rodents that showed that hyperuricemia led to endothelial dysfunction as well as inducing hypertension. In a cross-sectional cohort study of over 6000 subjects, serum urate levels correlated positively with circulating levels of IL6, TNFa and CRP, but a negative correlation with IL1β was observed [19]. Together these findings suggest that hyperuricemia has a pro-inflammatory effect that may be particularly relevant to cardiovascular health, but when the hyperuricemia becomes symptomatic and manifests as gout, there may be additional inflammatory mechanisms that excacerbate cardiovascular integrity.

5. Gouty inflammation and interleukin-1 (IL1)

It is now well established that one of the major mechanisms of gouty inflammation is through release of interleukin-1 (IL1) when MSU crystals are in contact with monocytes and neutrophils. MSU crystals are capable of activating the NLRP3-inflammasome in monocytes and dendritic cells to secrete large quantities of interleukin-1beta (IL1β) (???????1). The activation processes of the inflammasome is an active area of research, and a number of pathways have been elucidated that share as a common theme the generation of reactive oxygen species (ROS) [20]. Recently a number of novel molecules have been identified that could mediate inflammasome activation. One of them, PKR (a RNA dependent protein kinase) is implicated in MSU and ATP mediated IL1β release, as genetic deficiency in mice for this molecule blocked IL1b secretion. This molecule interacts physically with the NLRP3 component of the inflammasome to initiate caspase-1 activity [21]. Another molecule that interacts with NLRP3, but does not appear essential for MSU-mediated IL1β release, is a guanylate binding protein [22]. These results indicate that activation of the inflammasome is a complex process that involves many different molecular mediators, but we still lack a clear unifying model that could explain all the different findings.

MSU crystals have also been shown to elicit inflammation in an inflammasome-independent manner. At least two different pathways have been described – one through crystals interacting with the cell surface to initiate an intracellular signalling cascade that involves *Syk* kinase (Fig. 1). MSU in contact with the cell membrane triggers membrane cholesterol trafficking, actin polymerization and activation of the tyrosine kinase. *Syk* is expressed mainly in hematopoietic cells including neutrophils, and its activation leads in turn to PI-3 K (phosphatidylinositol 3-kinase) recruitment [23]. Another inflammatory pathway that is inflammasome-independent is the release of pro-IL1β into the extracellular space during cell activation or cell death, so that it is cleaved to its active form by serine proteases such as cathepsin G, elastase and proteinase 3 in the extracellular space [24]. These enzymes are found in neutrophils that accumulate at the site of inflammation, and when released by neutrophils, they can bypass the need for the inflammasome to process IL1. Finally, recent data showed that IL1α also participates in the inflammatory process in

Table 3
Studies evaluating Interleukin-1 (IL1) inhibitors in gout.

Agent	Study	References
Anakinra	Open-label study in acute gout – 10 patients	[35]
	Open-label study in 15 patients	[34]
Rilonacept	RCT in 10 patients with chronic gouty arthritis	[33]
	RCT in prevention of gout flares on initiating allopurinol – 241 patients	[32]
Canakinumab	RCT of canakinumab vs. triamcinolone acetate in acute gout – 200 patients	[30]
	RCT of canakinumab vs. colchicine in prevention of acute flares on initiating allopurinol – 432 patients	[31]

animal models of microcrystal-induced inflammation, indicating that not all gouty inflammation needs to be IL1β driven [25].

6. Accessory signals to trigger acute gout

From our clinical observations of patients with tophaceous gout, we know that the presence of MSU crystals does not neccesarily lead to clinical inflammation. How is this paradox explained – that crystals do not trigger inflammation even though they may be in contact with inflammatory cells? One hypothesis is that there are natural anti-inflammatory mechanisms that are activated upon an acute attack, which switches off the inflammatory response. The production of an anti-inflammtory cytokine such as TGFβ by macrophages has been demonstrated previously [26]. Another hypothesis is that immune cells need a supplementary trigger in addition to MSU crystals to develop a full-blown reaction. This phenomenom was already observed *in vitro*, as in all the assays of inflammasome activation, the cells require a priming step in order to stimulate the transcription and translation of pro-IL1. The nature of this priming molecule in the cliinical setting is the question. Data suggest that this priming signal may come from ingested food or from cell products that are released on injury. In an epidemiological study of food intake preceding a gout attack, increased intake of purines was associated with an acute flare and this was correlated with the amount of purine ingested, particularly if the purine source is of animal origin [27]. Another potential trigger could be ingested fats that release fatty acids into the circulation. In a new model of murine gouty arthritis, arthritis was only observed if MSU crystals in combination with long chain free fatty acids were injected into the joint, while injection of MSU crystals alone did not provoke arthritis. The long chain fatty acids were able to stimulate macrophages through the TLR pathway [28]. In the same context, other priming signals that stimulate cells through the TLR pathway could also be clinically relevant. These include molecules such as S100A8/9 (also known as MRP 8 and 14) proteins, released upon cell damage or cell death and that could synergize with the presence of MSU to trigger full inflammasome activation [29]. Finally, ATP can participate in triggering the inflammasome through its binding to the ATP receptor P2X7. There is experimental but no clinical data yet to show it participates in MSU-mediated inflammasome activation.

7. New drugs in the treatment of hyperuricemia and gout

Over the last ten years, we have witnessed a veritable explosion of new drug developments in the treatment of hyperuricemia and gout. Gout therapy is based on two principal strategies – the control of gouty inflammation to calm the acute attack and the control of hyperuricemia that predisposes to formation of crystals. The discovery of the IL1 axis of gouty inflammation has seen a number of clinical studies that have evaluated the effectiveness of IL1 inhibitors in acute gout or in the prevention of flares when initiating ULT. Gout patients frequently have co-morbidities that render treatment with standard drugs such as NSAIDs, colchicine or prednisone problematic, and there are many patients who do not tolerate these treatments. Therefore IL1 inhibition appears to be a promising alternative approach to block inflammation. In all the studies performed to date (Table 3), IL1 inhibitors have been found to be effective, either in the prevention of acute flare (on initiating ULT) or in the treatment of an acute flare. The frequency of flares was reduced by approximately 50% with canakinumab, a monoclonal antibody against IL1β, over the six months of the primary study, and a significant reduction in pain was observed compared to the comparator drug trimcinalone at 72 h after injection [30,31]. In studies investigating rilonacept, an inhibitor of both IL1a and b, when patients initiated ULT with allopurinol, the active drug significantly reduced gout flares by around 50% over the 16 weeks of the study [32,33]. In uncontrolled studies, anakinra has been found to be effective in the treatment of acute gout in difficult to treat patients who had either intolerance or contra-indications to standard therapy [34,35]. The safety profile of all three agents in published studies did not cause any concern. The overall result of these clinical trials is that IL1 inhibition is indeed effective in acute gout, but questions over its long term safety and the patient profile that would benefit most from this type of treatment has for the moment delayed its acceptance as an alternative therapy for acute gout.

Two new drugs have been approved by regulators over the last five years in the management of hyperuricemia. Febuxostat, a non-purine inhibitor of xanthine oxidase, has been investigated in a number of randomized controlled trials over the last seven years. In the largest trial (CONFIRMS) involving over 2000 subjects, the drug, at a dose of 80 mg daily, was more effective in achieving a target urate level of less than 360 μmol/L than allopurinol (67% vs. 42%). It was also effective in patients who have mild renal impairment and no dose adjustment was required for these subjects. The safety profile was similar to that of the comparator allopurinol [36]. Febuxostat has been approved both in the US and Europe. The other ULT drug that has been approved by the FDA is pegloticase, a drug that is currently not available in Europe. In a pivotal study, over 200 patients with severe gout were given pegloticase 8 mg i.v. either every two weeks or every month for six months. Compared to placebo, both dose regimens lowered serum urate effectively and there was a reduction in tophus size in the treated groups. Overall, 42% of patients treated every two weeks and 35% of patients treated monthly reached the target urate level (< 360 mmol/L). However, patients treated monthly had a higher rate of non-responsiveness to therapy that may be related to the development of anti-drug antibodies [37]. The long term efficacy and safety of the treatment will need to be evaluated, but in the short term, it has been demonstrated to be effective and has an acceptable safety profile.

8. Conclusions

The management of hyperuricemia and gout has undergone a transformation over the last decade. Newer drugs provide alternatives to existing therapies that are not always tolerated by patients, either in the control of hyperuricemia or in the control of

the acute attack. As our understanding of the mechanisms of hyperuricemia and gout improve, new therapies will certainly emerge as well. However, major improvements in patient and physician education are still needed in order to ensure effective management of this increasingly common disease.

Disclosure of interest

Alexander So has received honoraria and speaker fees from Novartis, Menarini and Ardea Biosciences for participation in scientific advisory boards and sponsored symposia.

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