ejpmr, 2023, 10(10), 203-208

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

ADVANCES IN GOUT MANAGEMENT: FOCUS ON PREVALENCE, IMAGING, AND TARGETED TREATMENT APPROACHES

Danyalakshmi P.G. S.[1]*, Velmani C.[1], Thaila R.[2] and Dr. Senthil Raja M.[3]

[1]Assistant Professor, Department of Pharmacognosy, Kasthooribha Gandhi Pharmacy College, Rasipuram (tk) 637401, Namakkal, Tamilnadu, India.

[2]Associate Professor, Department of Pharmacology, Kasthooribha Gandhi Pharmacy College, Rasipuram (tk) 637401, Namakkal, Tamilnadu, India.

[3]Principal, Department of Pharmaceutical Chemistry, Kasthooribha Gandhi Pharmacy College, Rasipuram (tk) 637401, Namakkal, Tamilnadu, India.

***Corresponding Author: Danyalakshmi P.G. S.**
Assistant Professor, Department of Pharmacognosy, Kasthooribha Gandhi Pharmacy College, Rasipuram (tk) 637401, Namakkal, Tamilnadu, India.

Article Received on 08/08/2023 **Article Revised on 29/08/2023** **Article Accepted on 19/09/2023**

ABSTRACT

Academic and clinical settings have become increasingly interested in gout. This may be due to a number of factors. Gout prevalence and hyperuricemia have increased in developed countries, increasing its burden. According to recent literature, hyperuricemia is associated with gout and could also benefit cardiovascular health. Imaging techniques can be used to assess the extent of crystal depletion and urate deposition before clinical symptoms appear. As a treatment approach for various diseases, treating to target has become increasingly popular. Different targets have been recommended depending on disease burden and treatment stage. Efforts should be directed towards dissolving urate crystals in the tissues to prevent further symptoms and structural damage. It is recommended that gout and its associated comorbidities be treated as early as possible. A new imaging technique can also be used to assess the burden of urate deposition and the response to urate-lowering treatments. Urate crystal deposits are the final strategic goal of healthcare for patients with taste disorders.

KEYWORDS: Gout, Uric acid, Urate crystals, Crystal deposition disease.

INTRODUCTION

Over the past few decades, hyperuricemia and gout have become more prevalent in developed countries. The potential benefits of early intervention for hyperuricemia have been demonstrated in recent studies, particularly in the case of gout. Before clinical manifestations of gout occur, crystal deposition and subclinical inflammation could be detected and treated more effectively. An excess of serum uric acid (sUA) in joints leads to gout, which is caused by long-term hyperuricemia.

Several stages of hyperuricemia have been identified by recent research. Hyperuricemia increases the risk of MSU crystal deposits, which can be detected using ultrasound or dual-energy computed tomography (DECT).[1] Inflammatory flares are triggered by MSU crystals that form on the cartilage surface and shed into the joint space. It is possible for these crystals to interact with cells within joint spaces once they have been formed. The presence of MSU crystal deposits or tophi may indicate chronic inflammatory responses caused by hyperuricemia in chronic gouty arthritis or chronic gout. In addition to the growth of deposits and comorbidities, gout becomes even more difficult to treat, leading to the term "refractory gout."

As sUA levels remain high, gout develops into a chronic, progressive disease. In order to manage gout, it is crucial to treat MSU crystal deposits. The clinical symptoms of gout can be alleviated by lowering sUA levels to 6 mg/dl (360 lml/L) to dissolve pathogenic MSU crystals.[2,3] In addition to damaging joints, kidneys, and the cardiovascular system, chronic diseases should also be taken seriously.

The prevalence of hyperuricemia and gout has increased worldwide in recent years.[4] Cardiovascular mortality increases during such epidemics due to adverse effects on joint function, the utilization of health resources, and the quality of life. Studies have shown that gout is an independent cardiovascular risk factor[5–7], especially if it is severe.[8] Gout patients are more likely to die from cardiovascular diseases as a result. There is no doubt that gout contributes significantly to the risk of cardiovascular mortality despite the presence of numerous associated comorbidities. Although NSAID use may contribute to flares, inflammation and hyperuricemia are deemed significant factors.

It was long believed that well-known cardiovascular risk factors contributed to the association between

asymptomatic hyperuricemia and cardiovascular morbidity and mortality. As a result of adjusting for associated traditional risk factors, hyperuricemia no longer correlated with cardiovascular events in the Framingham heart study.[9] The prevalence of cardiovascular diseases associated with hyperuricemia correlates with the frequency of asymptomatic hyperuricemia. The increase in death rates was thought to be due to comorbidities, not hyperuricemia itself. Hyperuricemia and cardiovascular events have been linked independently for the past few decades, although the association is less pronounced than the one between hyperuricemia and gout. Aside from hyperuricemia, hypertension, heart disease, type 2 diabetes, kidney disease, and chronic renal failure have also been linked to hyperuricemia.[10,11] Thus, traditional statistical adjustments for confounding variables will not be accurate. The adjustment for hypertension makes no sense if hyperuricemia directly contributes to hypertension in hyperuricemia-related outcomes.

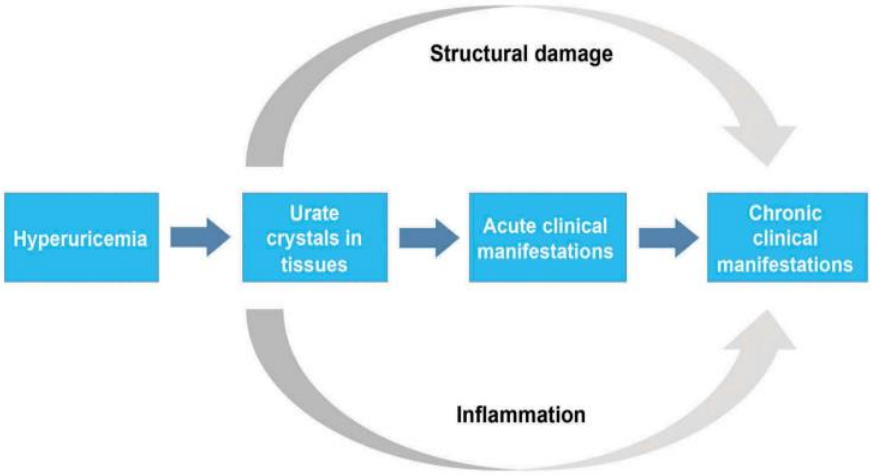

Figure 1: Hyperuricemia pathway.

Hyperuricemia often precedes hypertension in prospectively followed human cohorts,[12] There have been several studies demonstrating that urate-lowering drugs reduce blood pressure in rats induced by hyperuricemia, using different methods of causing hyperuricemia.[13-15] Furthermore, hyperuricemic adolescents with prehypertension or incipient hypertension showed beneficial effects from urate-lowering medications (ULMs).[16,17] Human hyperuricemia has been linked to metabolic syndrome and type 2 diabetes, and prospective studies have indicated that hyperuricemia precedes the development of diabetes.[4] Fructose-enriched diet rats who were treated with urea-lowering interventions were corrected from hyperuricemia and hyperinsulinemia.[14] Hyperuricemia negatively impacts kidney function in animal studies.[13] Chronic kidney disease (CKD) is associated with high levels of hyperuricemia in humans[18], and some renal conditions are associated with poor outcomes.[4]

Several randomized controlled trials have also suggested that lowering sUA may improve renal outcomes in CKD patients.[4] In randomized controlled trials (RCTs), lowering sUA did not reduce cardiovascular mortality. Allopurinol consumption has been linked to lower rates of myocardial infarction and mortality in retrospective studies[4,19], especially if sUA is reduced below 6 mg/dL with adequate doses.

Despite some ongoing controversies, hyperuricemia remains an independent cardiovascular risk factor. The treatment of asymptomatic hyperuricemia hasn't been approved by any country, other than Japan, despite large RCTs showing that urate lowering improves cardiovascular mortality.

GOUT AND THE ROLE OF IMAGING IN CLINICAL MANAGEMENT: A NEW LOOK

The pathophysiological relationship between hyperuricemia and the formation of urate crystals in tissues can now be demonstrated through imaging techniques, even before first clinical symptoms of gout appear.[20] When urate levels fall during treatment, studies have shown they can be used to measure crystal depletion by measuring crystal concentrations, but also by measuring crystal depletion when percentages decrease.

We are learning more about gout and developing new treatments thanks to a variety of imaging modalities. In the above description, MSU crystals are the main component of gout, and the body's reaction to them causes clinical symptoms. In order to assess MSU crystal deposition, a wide range of imaging methods have been studied, including ultrasonography and DECT. A 'double contour' sign indicates the presence of MSU crystals when they are found overlying the articular cartilage on sonography.[21,22] An MSU tophi consists of MSU crystals enclosed by fibrovascular tissues.[23,24] Tophi can

also be detected by ultrasonography.[21] With a dual-source DECT, a computerized tomography (CT) technique, different attenuation patterns are analyzed to determine if there are urate crystals in a material. Taste urate can be visualized and measured using color-coding and automatic volume measurement software

A few people with hyperuricemia who don't have clinical symptoms of gout have been found to have MSU crystals on ultrasonography, giving insight into the pathogenesis of the disease. Hyperuricemia is frequently associated with gout, but not everyone develops clinically apparent gout.[25] It is therefore necessary to consider other factors in influencing clinically apparent diseases as well. Recent studies report that 17–42% of individuals with mean serum urate concentrations of 8 mg/dL have ultrasonographic features of MSU crystal deposition. In most cases of crystal deposition on ultrasound, MSU crystals are present.[26] The deposition of MSU crystals probably occurs before clinical signs of the disease become evident. In hyperuricemic patients with MSU crystals on ultrasonography, it is not known whether this can predict the presence of clinically obvious gout.[27-29] There are no interventions known to reduce image features of MSU crystal deposits in individuals with hyperuricemia and joint damage from gout, in addition to reducing serum urate levels.

During intercritical periods, most gout patients are completely asymptomatic, suffering from recurrent flares of severe joint inflammation. MSU crystals have been found in previously inflamed joints in people with gout and persistent hyperuricemia.[30] When joints do not appear acutely inflamed or during the intercritical period, MSU crystal deposition is frequently demonstrated on imaging.[31] These findings have led to increased recognition of gout as a chronic disease caused by accumulated MSU crystals, regardless of the presence or absence of inflammation in the joints.

Additionally, advanced imaging methods, including DECT, have shown MSU crystal deposition in gout patients. Physical examination can detect only a fraction of urate deposits using this technique.[24] Similarly, ultrasonography and DECT have been used to clarify crystal deposit patterns, particularly in the periarticular area. The first metatarsal dorsal cartilage, the patellar tendon, the first metatarsophalangeal recess, the triceps tendon, femoral condyle cartilage, quadriceps tendon, and radiocarpal dorsal recess (35%) have been shown to be highly depleted in MSU crystals by ultrasound.[32] As well as the 5th metacarpophalangeal metacarpophalangeal, it rarely affects the dorsal or palmar cartilage, as well as the elbow's posterior recess, the deep infrapatellar bursa, the gastrocnemius-semimembranosus bursa, and the palmar recesses of the first and fifth metacarpophalangeals. People with tophaceous gout commonly develop urate crystal deposition in tendons as well as in bones.[33] During a physical examination, such tendon involvement can be hard to detect.

Image studies have also linked MSU crystal deposition with joint damage. A radiograph of a person with advanced gout often shows erosion of the bones. Furthermore, bone spurs and sclerosis are frequently observed as well as narrowing of joint spaces.[34] In conventional CT and DECT studies, MSU crystals are usually observed around areas of bone erosion caused by structural joint damage due to urate deposition. In the event of structural changes, urea-lowering therapy may be indicated.[35,36] According to recent studies, MSU crystal deposition contributes to joint damage, emphasizing the importance of reducing crystal burden before structural damage occurs.

As we gain a better understanding of the various methods for treating gout, imaging is playing an increasingly important role in clinical management. Based on a recent meta-analysis comparing advanced imaging with microscopic diagnosis, ultrasonography and DECT are both useful for diagnosing gout; however, their diagnostic accuracy is not perfect. A pooled sensitivity and specificity of 0.83 and 0.76 were reported for the US double contour sign, 0.65 and 0.80 for the US tophus, and 0.87 and 0.84 for the DECT.[37] Despite advanced imaging, microscopic diagnosis remains the gold standard for gout diagnosis.[38] A scan can also help detect diseases complications such as nerve damage, spinal problems, or structural joint dysfunction that mimic the symptoms of acute flare-ups of gout. Consider MRI bone marrow edema when considering possible infection via magnetic resonance imaging (MRI) rather than gout.[39] DECT may not be widely used in most clinical settings due to its high costs and ionizing radiation associated with serial disease monitoring, but it may be useful in certain clinical scenarios. Clinic ultrasonography may benefit patients who do not adhere to urate-lowering therapy and who have target serum urate concentrations and ongoing symptoms.[40,41] It is also possible to improve patient understanding of disease by using ultrasonography and DECT during diagnostics and follow-up. Gout is a chronic disease caused by the deposition of MSU crystals, which may be visualized by imaging methods, helping the patient to better understand that serum urate must be reduced over the long term, and crystals should be dissolved.

IMPORTANCE OF TARGET TO TREATING HYPERURICEMIA IN GOUT

A number of diseases, including diabetes, hypertension, hyperlipidemia, and rheumatoid arthritis, have become increasingly popular with T2T strategies in recent years. Hyperuricemia in gout can also be treated based on the actual clinical stage of the disease, as well as for long-term management. Gout 'cure' requires dissolving MSU crystals completely[42] and preventing new crystals from forming once the crystal burden has been removed.[43] In

order to achieve strategic objectives, tactical movements or interventions are made.

The importance of educating gout patients and providing them with appropriate information is crucial when dealing with gout patients.[44] In this way, adherence is improved, withdrawal of treatment is prevented, and lost follow-up is reduced. Clinics may encounter problems if they invest time in diagnosis, education, and information.[44]

It is highly recommended that anti-inflammatory prophylaxis be used prior to or at the start of urate-lowering therapy (ULT), generally lasting 6–12 months, to prevent acute flares of inflammation, although the doses and medications vary greatly from country to country.[2,45] It is also important to provide instructions on how to handle acute episodes of inflammation despite adequate prophylaxis in urate-lowering therapy.

Gout can be cured by reducing sUA levels to target levels.[46] Through this approach, the crystallization mechanism of MSU is inverted, which is pathophysiologically sound. In addition to the targets that have been identified, there are also stages of treatment[43], beginning with dissolving pre-formed crystals and stopping the formation of new crystals. These targets can vary depending on the amount of deposition[47] or the progression of the disease.[46]

The concept of treating to target sUA, which means that for all patients with taste, the level of sUA in plasma should be at least 6 mg/dl (360 lmol/L) for the long term.[2,3] Achieving this minimal target has been shown to reduce flare-ups and tissue deposits.[48] However, based on the recommendations of the European League Against Rheumatism (EULAR) in 2006[2], the American College of Rheumatology (ACR) recommends that patients with extensive MSU crystal deposition on either clinical examination or imaging studies should target a level of sUA lower than 5 mg/dl (300 lmol/L)[3], since lower sUA levels result in quicker tissue reduction.[40,49]

Throughout life, sUA levels should remain subsaturated. Nevertheless, the guidelines and recommendations previously cited do not address the question of whether these targets should be maintained after the last MSU crystal disintegrates since the ULT has been adequate for a very long time, since long before the last MSU crystal disintegrates. After long-term treatment, some patients may not require ULMs because they may show subsaturating levels of Sua.[50] Hence, the urate-lowering process consists of two phases: the first is a concentrated urate-lowering phase to dissolve the MSU crystals completely. It is followed by a lifelong lowering of sUA below saturation over the remainder of the patient's life. Cleanliness is more important than maintaining it.[43]

It is recommended that ULMs be prescribed to gout patients with a definite diagnosis of gout. Using these guidelines, prescribing ULMs starts from a different clinical point. It is recommended to begin treatment with xanthine-oxidase inhibitors as a monotherapy. If the desired initial sUA is not achieved, uricosuric medications can be added or considered as monotherapy. Additionally, allopurinol and probenecid[51] and allopurinol and benzbromarone[49] reduced sUA further, and these compounds are especially useful for dissolving tophi. Lesinurad has also been shown to work well when combined with allopurinol and febuxostat.[52,53]

CONCLUSION

In addition to increasing hyperuricemia and gout, MSU crystal deposition and subclinical inflammation are increasingly detected before gout shows clinical symptoms. Several studies have found that gout and hyperuricemia lead to adverse cardiovascular outcomes, although the reason for this association is unclear. The use of ultrasonography and DECT to evaluate the presence and extent of MSU crystal deposition and the effectiveness of urate-lowering therapy is particularly useful. It is important to remember that targeted urate-lowering therapy can effectively and rapidly dissolve MSU crystal deposits, therefore, it would be a mistake to ignore a treatable condition. A growing number of medications have been developed in recent years to achieve such a goal.

REFERENCES

1. Bardin T, Richette P. Definition of hyperuricemia and gouty conditions. Curr Opin Rheumatol, 2014; 26: 186–91.
2. Zhang W, Doherty M, Pascual E, Bardin T, Barskova V, Conagham P, Gerster J, et al. EULAR evidence based recommendations for gout Part II. Management. Report of a Task Force of the EULAR Standing Committee for international clinical studies including therapeutics (ESCISIT). Ann Rheum Dis., 2006; 65: 1312–24.
3. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken), 2012; 64: 1431–46.
4. Richette P, Perez-Ruiz F, Doherty M, Jansen TL, Nuki G, Pascual E, et al. Improving cardiovascular and renal outcomes in gout: what should we target? Nat Rev Rheumatol, 2014. doi:10.1038/nrrheum. 2014.124.
5. Smith EU, Diaz-Torne C, Perez-Ruiz F, March LM. Epidemiology of gout: an update. Best Pract Res Clin Rheumatol, 2010; 24: 811–27.
6. Perez-Ruiz F, Martinez-Indart L, Carmona L, Herrero-Beites AM, Pijoan JI, Krishnan E. Tophaceous gout and high level of hyperuricaemia are both associated with increased risk of mortality in patients with gout. Ann Rheum Dis., 2014; 73: 177–82.

7. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. Circulation, 2007; 116: 894–900.
8. Krishnan E, Svendsen K, Neaton JD, Grandits G, Kuller LH. Long-term cardiovascular mortality among middle-aged men with gout. Arch Intern Med., 2008; 168: 1104–10.
9. Stack AG, Hanley A, Casserly LF, Cronin CJ, Abdalla AA, Kiernan TJ, et al. Independent and conjoint associations of gout and hyperuricemia with total and cardiovascular mortality. QJM., 2013; 106: 647–58.
10. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med., 1999; 131: 7–13.
11. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007–2008. Am J Med., 2012; 125: 679–87.
12. Grayson PC, Kim SY, LaValley M, Choi HK. Hyperuricemia and incident hypertension: a systematic review and meta-analysis. Arthritis Care Res (Hoboken), 2011; 63: 102–10.
13. Johnson RJ, Kang DH, Feig DI, Kivlighn S, Kanellis J, Watanabe S, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension, 2003; 41: 1183–90.
14. Sanchez-Lozada LG, Tapia E, Bautista-Garcia P, Soto V, Vila-Casado C, Vega-Campos IP, et al. Effects of febuxostat on metabolic and renal alterations in rats with fructose-induced metabolic syndrome. Am J Physiol Renal Physiol., 2008; 294: F710–8.
15. DeBosch BJ, Kluth O, Schu¨ rmann A, Moley K. Early-onset metabolic syndrome in mice lacking the intestinal uric acid transporter SLC2A9. Nat Commun, 2014; 5: 4642. doi:10.1038/ncomms 5642.
16. Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension. A randomized trial. JAMA., 2008; 300: 925–32.
17. Soletsky B, Feig DI. Uric acid reduction rectifies prehypertension in obese adolecents. Hypertension, 2012; 60: 1148–56.
18. Kawashima M, Wada K, Ohta H, Terawaki H, Aizawa Y. Association between asymptomatic hyperuricemia and new-onset chronic kidney disease in Japanese male workers: a long-term retrospective cohort study. BMC Nephrol, 2011; 12: 31. doi:10.1186/1471-2369-12-31.
19. Grimaldi-Bensouda L, Alperovitch A, Aubrun E, Danchin N, Rossignol M, Abenhaim L, et al. Impact of allopurinol on risk of myocardial infarction. Ann Rheum Dis., 2012. doi:10.1136/annrheumdis-2012-202972 (Epub ahead of print).
20. Wei L, Mackenzie IS, Chen Y, Struthers AD, MacDonald TM. Impact of allopurinol use on urate concentration and cardiovascular outcome. Br J Clin Pharmacol, 2011; 71: 600–7.
21. Grassi W, Meenagh G, Pascual E, Filippucci E. ‘‘Crystal Clear’’-sonographic assessment of gout and calcium pyrophosphate deposition disease. Semin Arthritis Rheum, 2006; 36: 197–202.
22. Thiele RG, Schlesinger N. Ultrasonography is a reliable, non-invasive method for diagnosing gout. Rheumatology, 2007; 46: 1116–21.
23. Palmer DG, Highton J, Hessian PA. Development of the gout tophus. An hypothesis. Am J Clin Pathol., 1989; 91: 190–5.
24. Choi HK, Al-Arfaj A, Eftekhari A, Munk PL, Shojania K, Reid G, et al. Dual energy computed tomography in tophaceous gout. Ann Rheum Dis., 2009. doi:10. 1136/ard.2008.099713.
25. Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the normative aging study. Am J Med., 1987; 82: 421–6.
26. De Miguel E, Puig JG, CastilloC, Peiteado D, Torres RJ, Martin-Mola E. Diagnosis of gout in patients with asymptomatic hyperuricaemia: a pilot ultrasound study. Ann Rheum Dis., 2011; 71: 157–8.
27. Howard RG, Pillinger MH, Gyftopoulos S, Thiele RG, Swearingen CJ, Samuels J. Reproducibility of musculoskeletal ultrasound for determining monosodium urate deposition: concordance between readers. Arthritis Care Res (Hoboken), 2011. doi:10.1002/acr.20527.
28. Pineda C, Amezcua-Guerra LM, Solano C, Rodriguez-Henriquez P, Hernandez-Diaz C, Vargas A, et al. Joint and tendon subclinical involvement suggestive of gouty arthritis in asymptomatic hyperuricemia: an ultrasound controlled study. Arthritis Res Ther., 2011; 13: R4.
29. Puig JG, de Miguel E, Castillo MC, Rocha AL, Martinez MA, Torres RJ. Asymptomatic hyperuricemia: impact of ultrasonography. Nucleosides Nucleotides Nucleic Acids., 2008; 27: 592–5.
30. Pascual E, Batlle-Gualda E, Martinez A, Rosas J, Vela P. Synovial fluid analysis for diagnosis of intercritical gout. Ann Intern Med., 1999; 131: 756–9.
31. Schauer C, Janko C, Munoz LE, Zhao Y, Kienho¨fer D, et al. Aggregated neutrophil extracellular traps limit imflammation by degrading cytokines and chemokines. Nat Med., 2014; 20: 511–7.
32. Naredo E, Uson J, Jimenez-Palop M, Martinez A, Vicente E, Brito E, et al. Ultrasound-detected musculoskeletal urate crystal deposition: which joints and what findings should be assessed for diagnosing gout? Ann Rheum Dis., 2013. doi:10. 1136/annrheumdis-2013-203487 (Epub ahead of print).
33. Dalbeth N, Kalluru R, Aati O, Horne A, Doyle AJ, McQueen FM. Tendon involvement in the feet of

patients with gout: a dual-energy CT study. Ann Rheum Dis., 2013; 72: 1545–8.
34. Dalbeth N, Milligan A, Doyle AJ, Clark B, McQueen FM. Characterization of new bone formation in gout: a quantitative site-by-site analysis using plain radiography and computed tomography. Arthritis Res Ther., 2012; 14: R165.
35. Dalbeth N, Clark B, Gregory K, Gamble G, Sheehan T, Doyle A, et al. Mechanisms of bone erosions in gout: a quantitative analysis using plain radiography and computed tomography. Ann Rheum Dis. 2008;. doi:10.1136/ard.2008.094201.
36. Dalbeth N, Aati O, Kalluru R, Gamble GD, Horne A, Doyle AJ, et al. Relationship between structural joint damage and urate deposition in gout: a plain radiography and dual-energy CT study. Ann Rheum Dis. 2014;. doi:10.1136/annrheumdis-2013-204273 (Epub ahead of print).
37. Ogdie A, Taylor WJ, Weatherall M, Fransen J, Jansen TL, Neogi T, et al. Imaging modalities for the classification of gout: systematic literature review and meta-analysis. Ann Rheum Dis. 2014;. doi:10.1136/annrheumdis-2014-205431 (Epub ahead of print).
38. Konatalapalli RM, Lumezanu E, Jelinek JS, Murphey MD, Wang H, Weinstein A. Correlates of axial gout: a cross-sectional study. J Rheumatol, 2012; 39: 1445–9.
39. Poh YJ, Dalbeth N, Doyle A, McQueen FM. Magnetic resonance imaging bone edema is not a major feature of gout unless there is concomitant osteomyelitis: 10-year findings from a high-prevalence population. J Rheumatol, 2011; 38: 2475–81.
40. Perez-Ruiz F, Martin I, Canteli B. Ultrasonographic measurement of tophi as an outcome measure for chronic gout. J Rheumatol, 2007; 34: 1888–93.
41. Thiele RG, Schlesinger N. Ultrasonography shows disappearance of monosodium urate crystal deposition on hyaline cartilage after sustained normouricemia is achieved. Rheumatol Int., 2009. doi:10.1007/s00296-009-1002-8.
42. Doherty M, Jansen TL, Nuki G, Pascual E, Perez-Ruiz F, Punzi L, et al. Gout: why is this curable disease so seldom cured? Ann Rheum Dis., 2012; 71: 1765–70.
43. Perez-Ruiz F, Herrero-Beites AM, Carmona L. A two- stage approach to the treatment of hyperuricemia in gout: the ‘‘Dirty Dish’’ hypothesis. Arthritis Rheum, 2011; 63: 4002–6.
44. Rees F, Jenkins W, Doherty M. Patients with gout adhere to curative treatment if informed appropriately: proof-of-concept observational study. Ann Rheum Dis., 2013; 72: 826–30.
45. Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: Therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken), 2012; 64: 1447–61.
46. Perez-Ruiz F. Treating to target: an strategy to cure gout. Rheumatology, 2009; 49: ii9–12.
47. Perez-Ruiz F, Castillo E, Chinchilla SP, Herrero-Beites AM. Clinical manifestations and diagnosis of gout. Rheum Dis Clin North Am., 2014; 40: 193–206.
48. Perez-Ruiz F, Liote´ F. Lowering serum uric acid levels: what is the optimal target for improving clinical outcomes in gout? Arthritis Rheum, 2007; 57: 1324–8.
49. Perez-Ruiz F, Calabozo M, Pijoan JI, Herrero-Beites AM, Ruibal A. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. Arthritis Rheum, 2002; 47: 356–60.
50. Perez-Ruiz F, Atxotegi J, Hernando I, Calabozo M, Nolla JM. Using serum urate levels to determine the period free of gouty symptoms after withdrawal of long-term urate-lowering therapy: a prospective study. Arthritis Rheum, 2006; 55: 786–90.
51. Reinders MK, Van Roon EN, Houtman PM, Brouwers JR, Jansen TL. Biochemical effectiveness of allopurinol and allopurinol-probenecid in previously benzbromarone-treated gout patients. Clin Rheumatol, 2007; 26: 1459–65.
52. Perez Ruiz F, Sundy J, Krishnan E, Hingorani V, Welp J, Rodgers T, et al. Efficacy and safety of lesinurad (RDEA594), a novel URAT1 inhibitor, in combination with allopurinol-refractory gout patients: results from a randomized, blinded, placebo controlled, phase 2B extension study. Ann Rheum Dis., 2012; 71: 439.
53. Fleischmann R, Kerr B, Yeh LT, Suster M, Shen Z, Polvent E, et al. Pharmacodynamic, pharmacokinetic and tolerability evaluation of concomitant administration of lesinurad and febuxostat in gout patients with hyperuricaemia. Rheumatology (Oxford), 2014. doi:10.1093/ rheumatology/ket487.