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Recent Developments in Imaging and Biological Treatments for the Management of Refractory Gout

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Abstract

Background.

The deposition of monosodium urate crystals in the joints leads to gouty arthritis, characterised by chronic inflammation. Patients with tophaceous or treatment-resistant gout may encounter difficulties in achieving sustained disease control, although many individuals experience symptom relief with standard medication. Recent advancements in imaging, including dual-energy computed tomography (DECT) and ultrasound, have significantly improved the accuracy of detecting and monitoring urate deposits. Biologic and immunomodulatory approaches, such as uricase-based pharmaceuticals and IL-1β antagonists, are emerging as effective treatment alternatives for cases resistant to conventional therapy.

Aim of the study.

The review seeks to emphasise recent advancements in the diagnosis and treatment of gout, concentrating on the clinical importance of cutting-edge imaging modalities and new biologic therapies in enhancing management and long-term results in refractory cases.

Materials and methods.

This narrative review is based on a selective analysis of literature (2018–2025) sourced from PubMed and Scopus. Research focused on advanced imaging techniques (DECT, ultrasound) and innovative treatments for refractory gout, including immunomodulatory and biologic strategies, was emphasised. Recent advancements in diagnosis and therapy were evidenced by the integration of high-quality observational studies, randomised trials, and clinical recommendations.

Conclusions

Progress in pharmacogenetic profiling, biological therapy, and innovative urate-lowering medications is transforming the treatment of gout, particularly in refractory patients. Ultrasound

and DECT enhance the accuracy of treatment, surveillance, and early detection. Incorporating these advancements into customised tactics may produce improved disability prevention and outcomes.
Key words: hyperuricemia, gout arthritis, DECT

Introduction

Gouty arthritis is a common inflammatory disorder marked by the accumulation of monosodium urate crystals in the joints, frequently causing severe pain and inflammation. Traditional therapy methods, including nonsteroidal anti-inflammatory medications, corticosteroids, and urate-lowering medicines like allopurinol and febuxostat, frequently exhibit limitations such as adverse effects, drug interactions, and inadequate patient adherence [1] .

Gout is the primary kind of inflammatory arthritis in males. Due to chronic hyperuricemia, uric acid crystals accumulate in the intra-articular and periarticular regions, thereby activating the innate immune system. The clinically significant sudden onset of monoarticular arthritis in the lower extremities strongly indicates a gout episode. Gouty arthritis is associated with significant morbidity and mortality and results from chronic hyperuricemia [2,3] . Ultrasonography can facilitate the early identification of crystal deposition in joint cartilage [4] . The identification of uric acid crystals in synovial fluid via polarisation microscopy is indicative of gout, even in the absence of intracellular uric acid crystals [3] . Gout persists as a global health concern despite the availability of effective treatments. Its prevalence, influenced by genetic predispositions, is also linked to alcohol consumption, obesity, and hypertension, which exacerbate the incidence of gout and hyperuricemia in African and Asian nations. Gout is closely related to metabolic syndrome, obesity, hypertension, insulin resistance, and various other cardiometabolic disorders, along with dietary factors. Rapid-acting anti-inflammatory medications are accessible for the acute management of attacks; however, the fundamental approach involves sustained pharmacological treatment of hyperuricemia from the initial episode onwards [3,5] . This review outlines the clinically pertinent information regarding the pathogenesis, diagnosis, and treatment of gout based on the existing data.

Risk factors:

Hyperuricemia

Hyperuricemia plays a predominant role in the aetiology of gout 6] . Hyperuricemia, characterised by a serum urate content of 6.8 mg/dL (0.408 mmol/L) or above, is a metabolic anomaly that contributes to the onset of gout [7] . The chance of gout occurrence in the joint is influenced by the urate tissue content, the pH level, the temperature of the joint fluid, its macromolecular structure, and the concentrations of sodium ions and proteins [8] . Although the gender disparity diminishes with age, men exhibit a markedly higher susceptibility to gout than women, with frequency among women rising post-menopause [3]. The prevalence significantly escalates with age, affecting over 12% of guys aged 70–79 years, in contrast to less than 3% in men under 50 years [9,10] . When categorised by age, there were increases in incidence among individuals over 65 years in both genders. Although gout prevalence increased among both sexes over the decade, men remained to shoulder the predominant burden of the disease. In individuals under 65, men exhibited a prevalence four times greater than women (4:1 ratio), however in the elderly demographic (> 65), the gender disparity narrowed to one woman for every three men with gout and/or hyperuricemia (3:1 ratio) [11] .

Lifestyle/diet

Numerous studies have identified nutrition as a risk factor for gout, owing to its tendency to elevate urate levels in bodily fluids [12] . Gibson et al. performed a controlled study analysing the eating patterns of gout patients, uncovering differences in alcohol consumption relative to healthy controls. Their research sought to ascertain whether patients with gout possess a diet

that is unique in quality or quantity, utilising a meticulous dietary questionnaire. In a seven-day nutritional assessment, gout patients exhibited significantly higher alcohol consumption, particularly beer, in comparison to healthy controls. More than 60 grammes of alcohol (almost 2.5 litres of beer) were consumed daily by over 40% of the gout cohort. Furthermore, this increased alcohol consumption significantly enhanced daily purine intake, hence worsening hyperuricemia [13] . Dairy products seem to provide a preventive benefit, but excessive consumption of meat and fish correlates with elevated uric acid levels. Significantly, no correlation existed between blood uric acid levels and overall protein intake [14] .

Sociodemographic characteristics

Multiple demographic factors influence the onset of gout. Numerous epidemiological studies have demonstrated that the incidence of gout escalates with increasing age. Ethnic variations in nutrition, comorbidity patterns, and genetics may heighten vulnerability to gout [15] . Various socioeconomic characteristics have been identified as being correlated with gout. Numerous European research indicate that rural inhabitants exhibit a diminished risk of gout compared to their urban counterparts [16] .

Genetics

Numerous investigations on the genetic underpinnings of gout and genome-wide association studies (GWAS) have concentrated on the renal excretion of uric acid, validating the significance of renal uric acid excretion in regulating serum uric acid (SUA) levels and the susceptibility to gout. Genome-wide analyses have revealed 28 genetic loci associated with hyperuricemia. Two principal routes regulate uric acid levels: renal and gastrointestinal excretion, with glycolysis also playing a role. Key genes encompass SLC2A9, which influences uric acid excretion and antioxidant defence, and ABCG2, associated with extra-renal uric acid under-excretion. Additional genes such as PDZK1, SLC22A11, and INHBB are likewise implicated. The genetic mechanisms underlying the relationship between hyperuricemia and gout remain ambiguous. No genome-wide investigation has particularly examined gout cases in individuals with hyperuricemia, which could enhance the understanding of genetic predispositions to gout[17].

Pathogenesis

The predominant etiology of gout is the compromised renal excretion of uric acid, which may be precipitated by chronic kidney disease, diuretics, low-dose aspirin, or genetic anomalies in renal transporters. Excessive uric acid generation is the primary reason in approximately 10% of cases, associated with cytolysis during chemotherapy, elevated purine turnover, or enzymatic problems. Foods abundant in purines, such as beer and red meat, can facilitate both processes.

Men (9:1) constitute the principal victims of the disease, typically aged between 40 and 60. Gout is rare in women before menopause, likely due to the uricosuric effects of oestrogen. Individuals with crystal deposits may encounter exacerbations due to mechanical trauma or damage. Analogous to matches that ignite under particular conditions, monosodium urate (MSU) crystals may remain dormant for years without triggering flares; yet, neutrophil activity in reaction to these crystals induces acute inflammation 18] .

Monosodium urate (MSU), soluble up to approximately 7.0 mg/dL, is the predominant type of uric acid present in physiological fluids at a pH of 7.4. The development and deposition of MSU crystals is the primary pathogenic mechanism of gout. MSU crystals initiate the formation of deposits on joint surfaces, referred to as microtophi, when urate levels exceed the threshold of hyperuricemia. MSU crystals are elongated objects that are swiftly identified and engulfed by human phagocytes [19] . The elevated sodium concentrations in the crystals cause a significant rise in cellular sodium content upon absorption by phagocytes. These crystals induce the secretion of proinflammatory cytokines, specifically interleukin (IL)-1β, which promotes inflammation. The swift and intense inflammatory reaction of the body to MSU crystal

accumulation presents clinically as an acute gout episode [20]. It is advisable to decrease urate levels gradually, as crystals remain unstable for about a month after an attack, and a quick reduction may precipitate more flares. With appropriate management, gout episodes diminish, crystals disintegrate, and urate concentrations decrease to below 6.0 mg/dL over time. Unhealthy lifestyle choices complicate the attainment of remission [21]. Gouty arthritis may advance to a chronic, deformative, and physically incapacitating condition characterised by the formation of disfiguring tophi, joint damage, and enduring agony [22].

Acute gout impacts other joints and adjacent tissues while typically inducing sudden, severe joint pain, predominantly in the big toe. MSU crystals are predominantly located in the plantar areas of the first and second metatarsal heads and the base of the first phalanx (>30%), as well as in the medial quadrant of the first metatarsal head (60%) in cases with tophaceous gout. Infrequently (1%), the third and fourth metatarsophalangeal joints, especially their lateral quadrants, are impacted. The greatest crystal accumulation is located in the medial/plantar quadrants, metatarsal heads, and first metatarsophalangeal joint [23].The identification of needle-shaped, negatively birefringent monosodium urate crystals in synovial fluid substantiates the diagnosis. Patients may feel well even while crystals accumulate silently between attacks. If untreated, gout may progress into a chronic illness characterised by the formation of solid deposits of monosodium urate (tophi) in tissues, including tendons and joints. Approximately 20% of patients develop urate nephropathy or renal calculi. Gout adversely affects quality of life and is strongly linked to metabolic syndrome and several health issues, including renal disease, diabetes, and cardiovascular illnesses[24].

Imaging diagnostics

Every imaging modality possesses a distinct function. Radiographs can reveal characteristic erosions and tophi in advanced stages of gout. Ultrasound plays a significant role in the diagnosis and evaluation of gout. Dual-energy computed tomography (DECT) facilitates accurate imaging of monosodium urate (MSU) deposits and assesses disease severity. MRI can evaluate non-specific inflammatory and structural alterations. Ultrasound and DECT are highlighted within diagnostic algorithms, and the significance of imaging is evolving according to new breakthroughs and evidence[25]. Over the past decade, dual-energy computed tomography (DECT) has become an essential noninvasive diagnostic tool for gout, facilitating the precise identification of monosodium urate (MSU) crystal formations. The quality of DECT picture interpretation has markedly enhanced over time, as evidenced by a retrospective assessment of two patient cohorts (2013 vs. 2019). Owing to enhanced spectral separation facilitated by advanced scanners and the growing expertise of radiologists, the proportion of ambiguous results in 2019 was markedly reduced compared to 2013 (16.0% vs. 33.0%, $p < 0.001$). The incidence of joint aspiration following negative DECT results was significantly reduced in 2019 (2.1% compared to 17.4%, $p = 0.02$), suggesting that clinicians exhibited greater confidence in the reliability of this imaging modality. The technological developments in third-generation DECT scanners, including enhanced voltage separation, superior filtration, and refined image reconstruction, are chiefly accountable for this increasing clinical confidence. These advancements provide enhanced resolution, reduced artefacts, and improved material differentiation—particularly in areas such as thickening skin or nail beds that are susceptible to false positives. Automated 3D, colour-coded imagery enhances diagnostic clarity. DECT uniquely differentiates MSU crystals from other deposits, such as calcium pyrophosphate, and has superior sensitivity and specificity compared to established procedures like radiography and ultrasonography. Consequently, it is presently the most comprehensive imaging technique for diagnosing gout. Importantly, particularly in atypical instances, the 2015 ACR/EULAR criteria now recognise DECT findings as equivalent to crystal verification with joint aspiration. A post hoc blinded study of DECT scans from 2013 and 2019 confirmed that reduced diagnostic

uncertainty resulted from improved technology rather than reader variability [26] .The GOUT-DECTUS study evaluated the kinetics of tophus volume reduction as determined by dual-energy computed tomography (DECT) and ultrasound (US) in gout patients on treat-to-target (T2T) urate-lowering treatment (ULT) over a period of 24 months. after baseline, as well as after 6, 12, and 24 months, ultrasonography (US) and dual-energy computed tomography (DECT) imaging of the knees and feet was conducted on a cohort of 55 patients who were naïve to urate-lowering therapy (ULT). Complete resolution of tophus cores was seen between months 12 and 24, indicating that DECT facilitated more rapid and precise identification of monosodium urate (MSU) crystal breakdown. Conversely, despite the reduction in volume, the US was still capable of identifying tophus structures. This discrepancy can be elucidated by the observation that DECT solely identifies the MSU crystals, whereas ultrasound detects both the crystalline core and the adjacent inflammatory tissue. The study concludes that DECT delivers precise volumetric assessments of MSU burden and serves as an exceptional instrument for monitoring treatment response in gout. While the US remains valuable, it may overstate the persistence of a disease due to its unpredictability and susceptibility to non-crystalline elements. These findings endorse the utilisation of DECT in the prolonged therapy of gout and underscore the necessity of meticulous interpretation of imaging data [27] .

DECT is beneficial for assessing intra-articular MSU deposits, but ultrasonography exhibits greater sensitivity for the early identification of dispersed MSU deposits [28] . It possesses the capability to identify vascular MSU deposition. This is associated with greater coronary calcium scores and increased Framingham cardiovascular risk [29] . In certain cases, it may be essential to utilise both methods concurrently to enhance the diagnostic imaging algorithm for gout. The US is more cost-effective and more readily accessible than DECT, and it has demonstrated greater sensitivity for early illness detection especially in cases with low quantities of MSU deposits. It facilitates the identification of soft tissue inflammation, potentially aiding in the evaluation of therapeutic response. DECT may not be accessible on the same day for the majority of institutions, and clinicians may wish to commence therapy. It is thus recommended to utilise ultrasound as the primary diagnostic tool in patients with suspected acute gout. Nevertheless, DECT exhibits superior sensitivity and specificity compared to ultrasound in identifying MSU deposits in specific areas. A standardised approach utilising DECT following ultrasound in ambiguous circumstances can attain high accuracy in diagnosing or ruling out gout, eliminating the necessity for intrusive treatments [30] .

Investigators from the CRYSTALILLE cohort assessed the relevance of two negative dual-energy CT (DECT) thresholds for monosodium urate (MSU) crystal deposition (<0.01 cm^3 and <0.1 cm^3) in gout patients initiating urate-lowering therapy (ULT) in a study conducted by Victor Laurent and associates (Rheumatology, 2025). At the 0.1 cm^3 threshold, 43% of the 211 ULT-naïve individuals had no identifiable MSU crystals. Overall, these individuals were younger, exhibited fewer cardiovascular comorbidities, experienced shorter symptom durations, and encountered fewer exacerbations throughout a 24-month period. DECT-negative patients required reduced dosages of urate-lowering therapy, despite achieving comparable urate targets across groups. DECT negativity may signify a less severe gout phenotype, as the 0.1 cm^3 threshold exhibited superior clinical value compared to the 0.01 cm^3 threshold [31] . Crystal identification is essential to differentiate gout from other crystalline arthropathies, such as calcium pyrophosphate dihydrate and basic calcium phosphate crystal deposition disorders. The established gold standard for diagnosis is polarised light microscopy. Nonetheless, acquiring synovial fluid or tophaceous material is not always practicable in routine settings [32] . Ultrasound is an effective clinical method for identifying monosodium urate (MSU) crystal deposits in joints to aid in the diagnosis of gout. Hyperechoic aggregate (HAG) is regarded as an initial indicator of monosodium urate (MSU) crystal accumulation in joints, while the double contour sign (DCS) and tophi are associated with bone degradation. Initiating urate-lowering

therapy early may effectively diminish hyperuricemia and partially avert synovitis and synovial hypertrophy. Urate-lowering therapy (ULT) should be contemplated when gout patients exhibit DCS or tophi in their joints [4] . Fundamental US research indicates that MSU deposits and US-detected inflammation are independent predictors of gout flares over a 12-month period [33] . In individuals with asymptomatic hyperuricemia, imaging of the first metatarsophalangeal joint (1MTP) and femoral condyle for double contour, along with the 1MTP for tophus, exhibits the highest prevalence and discrimination relative to those with normouricemia [34] . Ultrasound characteristics of urate crystal accumulation, as opposed to soft tissue inflammation or bone disintegration, correlate with clinical indicators of foot-related functional impairment and disability, even in the absence of clinical signs of acute inflammatory arthritis. This association remained consistent irrespective of whether the participant was diagnosed with gout or asymptomatic hyperuricaemia [35] . Urate deposition, synovitis, and bone degradation frequently occur at the MTP1 joint in individuals with gout, even in the absence of an acute flare. Individuals with asymptomatic hyperuricemia, despite lacking ultrasonography indicators of inflammation or structural joint alterations, exhibit a comparable prevalence of urate deposition [36] US may identify tophi using MRI as the standard, exhibiting sensitivity to change. The dual contour sign detected on cartilage signifies gout and is susceptible to changes. Synovial pathology is acknowledged in gout, with evidence suggesting that intrasynovial hyperechogenicity signifies the condition. The US had lesser sensitivity than MRI in identifying cortical erosions in gout, although it outperformed standard radiography. The interobserver reliability, upon evaluation, ranged from medium to considerable agreement for soft tissue changes and was graded as very good for the assessment of tophi, double contours, and erosions. Ultrasound is a potential tool that may be employed in the diagnosis and treatment of gout. Additional investigation is necessary to assess responsiveness, reliability, and feasibility [37] . The sensitivity of ultrasound for diagnosing gouty arthritis in the hand and wrist is constrained, especially for extra-articular urate deposition. The DCS is the most sensitive indicator for evaluating gouty arthritis of the hand and wrist with ultrasound [38] .

Zhang et al. established that the sensitivity of ultrasound (US) was much superior to that of dual-energy computed tomography (DECT) in detecting monosodium urate (MSU) deposition in the early-stage cohort, however in the middle- and late-stage cohorts, the sensitivities of US and DECT were comparable. The United States should be the primary option for diagnosing acute gouty arthritis, particularly in patients with early-stage illness [39] .

Conventional Management and Clinical Challenges in Gout

Although the physician and patient being able to readily identify acute gouty arthritis, mistakes in choosing the optimal medicine and dosage frequently occur. The clinical phases of gout encompass asymptomatic hyperuricemia, intermittent gouty arthritis, and chronic tophaceous gout. The management of gout is generally initiated following the initial episode of arthritis, commonly referred to as podagra. The objectives of treatment are to mitigate pain and inflammation during acute episodes, avert subsequent attacks, and reduce uric acid levels. Confusion often occurs due to the dual uses of certain drugs, such as colchicine, which can both cure an acute attack and prevent subsequent episodes [40] . Nonetheless, an increasing proportion of patients find traditional treatments inefficient or contraindicated, primarily due to comorbidities. Gouty arthritis can significantly impair health-related quality of life, particularly in people with refractory illness [41] .

Given that gouty arthritis is typically diagnosed and managed in primary care, practitioners must have a thorough awareness of its clinical presentations, risk factors, differential diagnosis, and therapeutic options for effective management. The effectiveness of current therapies for gouty arthritis is occasionally impeded by the potential aggravation of the condition caused by

drugs for comorbidities, along with the adverse effects and contraindications linked to present treatment options [42] . The care of hyperuricemic individuals, whether asymptomatic or suffering from gout, primarily concentrates on sustaining blood urate levels within a subsaturating range (often <6 mg/dL) to prevent or mitigate the clinical consequences of urate crystal formation and deposition [43] . Systemic corticosteroids are often utilised to treat acute gouty arthritis in many people with comorbidities that exclude the use of NSAIDs or colchicine. Intra-articular injections are appropriate for monoarticular or oligoarticular disorders. The suitable length of anti-inflammatory therapy and comprehensive patient education are essential elements of effective acute gout management. The evaluation and treatment of hyperuricemia should begin after the resolution of all acute gout symptoms and when the patient is stable on a daily regimen of NSAIDs or colchicine [44] . Indications for extended urate-lowering therapy encompass chronic renal disease, recurring flare-ups occurring biannually or more frequently, urolithiasis, the presence of tophi, chronic gouty arthritis, and joint degeneration. Allopurinol and febuxostat are utilised to prevent flare-ups; however, febuxostat is associated with an increase in all-cause and cardiovascular mortality, making it generally not recommended [45] . Recent pharmaceuticals are demonstrating efficacy and complementing their predecessors. Additional critical aspects of its care encompass patient education, dietary modifications, lifestyle alterations, and the discontinuation of hyperuricemic medications [46] .

Innovative Therapies and Precision Medicine for Gout

Recent advancements in gout treatment demonstrate an increased emphasis on precision medicine, immunomodulation, and a more thorough integration of hereditary and lifestyle factors. A 2023 systematic review and meta-analysis evaluated the safety of initiating urate-lowering therapy (ULT) during acute flares, revealing no significant differences in pain, flare duration, or recurrence within 30 days between early and delayed treatment groups, despite existing limitations regarding its applicability to patients with tophaceous gout or renal impairment[47]. Attaining serum urate objectives and preventing flares continues to be challenging, particularly in individuals with concomitant conditions, despite the availability of effective therapies. Investigated promising pharmaceuticals encompass arhalofenate, exhibiting both anti-inflammatory and urate-lowering properties, and dotinurad, potentially beneficial for renal impairment. The therapeutic potential is evidenced by advancements in uricase-based formulations exhibiting reduced immunogenicity and tigulixostat, an innovative xanthine oxidase inhibitor. Additionally, many IL-1β inhibitors, gut uricase inhibitors, and NLRP3 inflammasome inhibitors, such as dapansutrile, are under investigation for acute flares [48].

The 2025 Chinese guidelines for gout and hyperuricemia highlight personalised urate-lowering therapy options based on the specific type of urate imbalance and endorse febuxostat as the primary treatment for asymptomatic hyperuricemia. Examples of innovative recommendations include aiming for serum urate levels between 180 and 300 μmol/L and preferring citrate over sodium bicarbonate for urine alkalinisation when pH is below 6.0. The guidelines also address biomarkers for flare prediction in high-risk populations to facilitate a more individualised treatment approach [49].

Alternative and complementary medicines are gaining popularity beyond pharmacological approaches. Initial studies indicate that canakinumab, ozone therapy, and herbal treatments such as Citrullus colocynthis have enhanced safety profiles and anti-inflammatory effectiveness. Despite the limitations of limited sample sizes, short follow-up periods, and population homogeneity, adjuvant methods such as physical exercise, warm ginger compresses, polyphenol-rich diets, and traditional Eastern medicine may provide tolerable long-term advantages. Pharmacogenetics is becoming recognised: genetic variants such as those in SLC2A9, SLC22A12, and HLA-B*58:01 influence urate management, medication metabolism, and the risk of adverse reactions, underscoring the importance of genetic screening in future healthcare frameworks. Standardisation of protocols and comprehensive, longitudinal

randomised controlled trials are essential for integrating these treatments into mainstream care[50] .

In patients previously exposed, efforts to reinstate pegloticase efficacy via co-treatment with methotrexate have proven largely ineffective. In the ADVANCE trial, only one of the eleven uncontrolled gout patients had a sustained urate response after receiving pegloticase combined with MTX, underscoring the need of commencing immunosuppression before the initial administration of pegloticase to prevent antibody development and infusion responses [51].

Finally, while still not incorporated into conventional treatment protocols, novel drugs that selectively inhibit URAT1 and agents with secondary uricosuric properties (such SGLT2 inhibitors, losartan, and fenofibrate) are beginning to emerge [52] .

Immunomodulation and biological treatment for refractory gout

Pegloticase and Methotrexate: Improving Uncontrolled Gout Treatment Results

Pegloticase, a recombinant uricase enzyme, has demonstrated significant urate-lowering effects in patients with treatment-resistant gout. The development of anti-drug antibodies (ADAs) typically diminishes its long-term efficacy, leading to infusion responses and therapy failure. A possible strategy to diminish immunogenicity is the co-administration of methotrexate (MTX). MTX (15 mg/week) was initiated four weeks before the administration of pegloticase and was maintained throughout the treatment in an open-label multicenter trial. Consequently, 78.6% of patients sustained serum urate (sUA) levels below 6 mg/dL for a minimum of 80% of the duration throughout Month 6 without encountering any novel safety concerns. MTX may enhance the endurance and efficacy of pegloticase in treatment-naïve patients, as demonstrated by the significant disparity with previous monotherapy results, which indicated a mere 42% response rate [53] .

This technique appears to be significantly less effective in treating patients who have previously failed pegloticase monotherapy. In the ADVANCE open-label trial, just one patient sustained urate control at six months, while 91% of patients discontinued pegloticase+MTX prematurely due to infusion complications or insufficient response. Anti-PEG antibodies were generally associated with an unfavourable therapeutic response and manifested immediately after treatment re-initiation. The data indicate a restricted capacity to reverse immunogenicity after the establishment of immunological memory, notwithstanding the potential influence of MTX on the reduced antibody titers in the sole responder. The study recommends initiating immunomodulation before to the initial administration of pegloticase, rather than pursuing rescue therapy following treatment failure [54]

These results align with the MIRROR study, which showed that in biologic-naïve populations, adjunctive MTX therapy improves response rates and reduces infusion-related problems. These results together question the efficacy of pegloticase reintroduction in ADA-positive individuals and underscore the importance of early immunological intervention in biologic therapy for gout.

A 2023 systematic analysis by Tai et al. assessed the timing of urate-lowering treatment (ULT) during acute gout flares and found no significant differences in pain, flare length, or recurrence between early and delayed beginning of ULT across six randomised controlled studies. The external validity is constrained by the removal of individuals with tophaceous gout and renal impairment, despite a seemingly identical safety profile across groups. These findings suggest that initiating urate-lowering therapy during a flare is typically safe and may be feasible for certain individuals; however, further study is necessary to inform treatment decisions in more complex populations [55] .

Physical activity

A vital component of daily life, physical activity is often compromised in gout patients, especially during acute flare-ups. The lower extremities, including the ankle, knee, and first metatarsophalangeal joint, are most frequently affected by gout attacks, which are frequently marked by abrupt, severe joint pain and swelling. Because of this, patients frequently report

severe limitations in activities related to mobility, such as walking, climbing stairs, shifting positions, and doing household chores. Particularly for those who experience frequent or polyarticular flares, these limitations can have a significant negative influence on social engagement, independence, and occupational productivity [56] . Although the mean age of participants was under 60 years, Becker et al. showed that physical functioning scores were significantly lower and more like those of people 75 years or older in patients with treatment-failure gout. This implies that a subgroup of patients with poorly managed disease may experience a significant and early loss of physical function [57] .

The episodic nature of gout is evident in the fact that many patients report little to no functional limitations in between flare-ups, despite the fact that disability is most noticeable during flare-ups [56] . Disability measurement is made more difficult by this sporadic disease course, especially when standard instruments with brief recall periods are used. For instance, despite being widely used in rheumatology, the Health Assessment Questionnaire-Disability Index (HAQ-DI) was not created specifically for gout and might not accurately reflect the disease's functional impact. Many of the HAQ-DI items, as demonstrated in the study by ten Klooster et al., concentrate on upper extremity function, which is frequently unaffected in gout, and neglect to include important mobility-related tasks that patients commonly struggle with, like standing for extended periods of time, riding a bicycle, or operating a vehicle during flares. Furthermore, flares that occur outside of the HAQ-DI's one-week recall period may be completely missed, underestimating disability in both clinical and research contexts [58] .

These results emphasize how crucial it is to use disease-appropriate tools that take into account the type and timing of disability associated with gout.

Conclusions

Recent advancements in the management of gouty arthritis signify a significant paradigm shift, especially for individuals with refractory or treatment-resistant illness. Traditional therapies such as NSAIDs, colchicine, corticosteroids, and xanthine oxidase inhibitors remain crucial; nevertheless, comorbidities, inadequate adherence, and adverse effects sometimes restrict their effectiveness. Due to the rising incidence of gout, particularly in elderly and metabolically vulnerable groups, there is a want for more precise, enduring, and tailored treatment strategies. Biologic and immunomodulatory medicines, which address the fundamental inflammatory pathways and may alter disease progression in patients unresponsive to traditional treatments, represent some of the most promising advancements. Pegloticase, a recombinant uricase enzyme, exhibits significant urate-lowering capabilities; nevertheless, its pronounced immunogenicity has constrained its use. Emerging evidence clearly supports the co-administration of methotrexate to suppress the production of anti-drug antibodies, hence enhancing the safety and durability of pegloticase therapy in patients not yet receiving biologics. These findings underscore the importance of initiating immunomodulatory medication prior to initial exposure, rather than resorting to rescue therapy following treatment failure.

The treatment landscape is being broadened by novel pharmacological drugs, some of which possess both urate-lowering and anti-inflammatory properties. Agents in this category comprise arhalofenate, dotinurad, IL-1β inhibitors, and NLRP3 inflammasome antagonists. Concurrently, pharmacogenetic profiling is emerging as an essential instrument for directing drug selection according to individual genetic predispositions, reducing adverse effects, and personalising treatment.

The integration of biologic medicines represents a groundbreaking advancement in the management of gout, especially for individuals with severe, recurring, or tophaceous conditions. Future treatment algorithms will likely prioritise the early identification of high-risk patients,

the initiation of urate-lowering therapy during acute flares when suitable, and the prompt implementation of biologic or adjunctive immunomodulatory strategies to avert long-term disability as personalised medicine evolves. Prolonged observational studies and further extensive randomised trials are essential to establish these advancements as standard practice.
The clinical care of gout has significantly improved due to advancements in diagnostics, particularly in imaging, with therapeutic innovations. Dual-energy computed tomography (DECT) enables highly specific, noninvasive detection of monosodium urate (MSU) deposits, facilitates accurate quantification of crystal load over time, and assists in early diagnosis, including atypical instances. Musculoskeletal ultrasonography (US) is an economical and readily accessible diagnostic and monitoring technology, capable of identifying features such as the double contour sign, tophi, and joint inflammation. The integration of DECT and US enhances diagnosis accuracy, promotes treat-to-target strategies, and reduces the necessity for invasive procedures such as joint suction. With the advancement of imaging technologies, it is essential to integrate them into standard gout evaluations to guide individualised treatment decisions and measure the efficacy of biologic therapy.

After conclusions

Author's contribution:

Conceptualization, methodology, software, check, formal analysis, investigation, resources, data curation, writing-rough preparation, visualization, project administration, supervision: Julia Sieniawska,

Author have read and agreed with the published version of the manuscript

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