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Recent Advancements in the Field of Gout and Hyperuricemia: A Narrative Review

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ABSTRACT

Gout is one of the most complex and leading types of crystal arthropathy that can cause inflammatory arthritis. Mostly, it is linked with diminished quality of life related to health and wellbeing along with functional weakening. Several studies have established the influence of gout and correlated situations on patient mortality and morbidity. In the common population, gout is still under-treated and under-diagnosed condition unfortunately. Despite great developments in treatment approaches, several patients with gout are inadequately controlled or inappropriately managed and consequently hyperuricemia flares are persistent. The advancement of innovative imaging interventions, urate-lowering treatments, and a well insight of the gout pathogenesis increase the prospect of improved treatment and better outcomes. In this narrative review, the recent advancements are spotlighted in the diagnostics and management of gout and hyperuricemia along with discussion on the innovative therapeutics.

Key words: Gout, Hyperuricemia, Advanced clinical management

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INTRODUCTION

In recent years, the prevalence and incidence of gout and hyperuricemia have increased, which reflect the risk factors of population level along with the social transmission of prejudicing dietary behavior and habits [1]. Aside sophisticated management guiding principles, several efficient medications, and better understanding of treatment procedures to the physicians, a number of patients are remained unable to achieve therapeutic objectives [2]. Luckily, the increasing occurrence of gout has carried a transformed interest in its nature, diagnostics, and therapeutic management. In this descriptive review, certain advancements in gout recently reported including development of therapeutic approaches, novel genetic screening, and the progress of advanced gout management strategies [3].

Advanced understanding of hyperuricemia and management

The levels of serum urate (sUA) can be evaluated with the help of metabolic balance, production, and excretion over the gastrointestinal region particularly kidneys [4]. Within the people who developed primary hyperuricemia (not acquired causes of chronic kidney disorders or excessive urate production), up to 90% have urate elevation because of insufficient excretion [5]. Latest physiologic and genetic studies have extended the insights into the modes of actions in which uric acid is carried out throughout the renal tubule. Despite nearly 100% of urate transporting through a vigorous kidney is being filtrated through the glomerulus, about 5-10% is truly excreted [6].

Amongst gout patients with primary underexcretion, these statistics are even lower within the range of 3-5%. In

responding the increasing sUA levels, the fractional excretion of urate (FEUA) also be disposed to increase to provide an adjustment mechanism for sUA after serum burdens [7]. Nevertheless, FEUA seems to be less reactive to sUA variations at high ranges of sUA and in the situation of primary underexcretion, which is fundamentally low FEUA [8]. Above all, the gout patients have frequently reported with less responsive renal excretory system for increasing levels of sUA, repetitively contribute to the hyperuricemia pathogenesis [9].

The management of urate at the kidney level befalls principally in the proximal convoluted tubule (PCT), in which function of transporting either to secrete (such as, MRP, NPT1, NPT4, OAT1, OAT2, and OAT3) or reabsorb (such as, OAT4, URAT1, GLUT9, and OAT10) uric acid throughout the tubular endothelium. URAT1 transporter is fundamental to maintain sUA levels among the entire class of reabsorbing transporters [10]. Patients with inactivating mutations or deficiencies of the URAT1 transporter establish evidently lower levels of sUA than those of healthy people. In addition, medications for example probenecid, lesinurad, and losartan increase the small excretion of uric acid and lower the sUA level through URAT1 inhibition [11].

In the hyperuricemia development, Genome-wide association studies (GWAS) associate genetic variations in OAT4, OAT10, URAT1, and GLUT9 [12]. It signifies the probability that patients with hyperuricemia comprise these transporters with improved functional variants that promote the uric acid retention [13]. Certain drugs which cause hyperuricemia (such as, pyrazinamide) seem to be functional by encouraging the retentive capacity of the pumps, especially URAT1 [14]. In contrast, although it is less definitely recognized, GWAS recommend that the secretory uric acid transporting variants including OAT13, NPT1, and MRP are also linked with hyperuricemia, apparently inferring a reduced functional state and permitting the sUA accumulation [15].

There is a deficiency of knowledge about mode of action behind urate excretion from the intestine but possibly of higher significance in patients with impaired renal excretion of uric acid [2]. The possible causes of hyperuricemia based on latest GWAS statistics have implicated impaired functional variants in the ABCG2, which is a secretory pump. Though ABCG2 was primarily found to express in the renal PCT, the advanced research suggests that it is extremely expressed in the intestinal region, perhaps provide insights into the gastrointestinal urate excretory mechanisms [16].

Advanced classification and diagnosis

In the history, the diagnostics of gout concentrated on the acute arthritic condition and did not found the potential to identify the chronic state. Recommended criteria of classification established suboptimal specificity and sensitivity, were never corroborated, or did not integrate the advancements in imaging interventions [17]. In 2015, the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) cooperatively published authorized criteria of classification that involve both aspects of chronic and acute gout, recent imaging developments, and emphasizing to make best use of specificity and sensitivity [18]. These standards allow better support the patients with gout into research and deliver a structure that can enlighten clinical diagnostics. The recognized existence of monosodium urate (MSU) crystals in a symptomatic tophus or joint is an adequate criterion to classify gout under the newly designed algorithm. In case of not meeting these criteria appropriately, a scoring system is implemented that reflects properties of chronic and acute gout, as well as recent imaging developments [19].

Advanced imaging

The technological developments in addition to a better knowledge of the gout pathophysiology have directed to improved non-invasive approaches enabling smooth the management and diagnosis of gout [20]. The growing applications of dual-energy computed tomography (DECT) and ultrasound are contributing to perfections in gout study, diagnostics, and management.18 Currently, though its practice is limited by availability and cost, DECT can offer an exact estimation of MSU crystal masses in both soft tissues and joints and allows the recognition of deposits in clinical checkup [21].

In the future, DECT can let both therapeutic monitoring and identification of occult deposits to verify terminations based on resolution of urate burden. The most advanced DECT approach (dual-source CT) brought up radiational exposure, which is not more than that of traditional CT [22]. It is because a study of an extremity that provided radiation exposure almost comparable to four months of background radiation naturally. However, this radiation exposure level can restrict the DECT applications frequently, as it may be essential during therapeutic monitoring. Consistent CT, magnetic resonance imaging, and nuclear medicine have confirmed effectiveness in supporting the diagnostics of gout, particularly in atypical appearances or cases bring about by incompetent workers [23].

Advanced drugs

Since the mid of 20th century, the gout therapeutics field came to an effective cessation during which no novel drugs were approved for therapeutic purposes. On the other hand, the early 21st century has seen a revitalization of gout treatment, commencement with developing the febuxostat as xanthine oxidase inhibitor (XOI) [24].

Advanced anti-inflammatory strategies

The synthesis of Interleukin-1 beta (IL-1β) occurs as pro-IL-1β on ribosomes as an inactive molecule whose multiple inflammatory stimuli can upregulate the overall expression [25]. When the inflammasome NOD-like receptor protein 3 (NLRP3) converted the active state of

IL-1β, it orchestrates great inflammatory response induced by crystal in acute gout. The NLRP3 inflammasome activates with the endogenous or pathogen-derivative hazard signals, which lead to activation of caspase-1 along with IL-1β activation and secretion [26]. In the acute attacks of gout, the crucial part of the NLRP3 inflammasome was identified not more than a decade before, and the mode of action by which the NLRP3 inflammasome activated by MSU crystals is still being investigated. Owning to the significant outcomes of IL-1β for the gout inflammation, the off-label practices of anti-IL-1β therapies have become common for patients with inadequate response or forbid traditional gout medicines [27].

Canakinumab

It is a monoclonal antibody that fictions to neutralize IL-1β for inflammation suppression [28]. The US Food and Drug Administration (FDA) approved it for Muckle-Wells syndrome, periodic fever syndromes, systemic idiopathic juvenile arthritis, and familial cold autoinflammatory syndrome linked with cryopyrin [29]. Different phase-3 trials of canakinumab confirmed its efficiency in prophylaxis and for acute gout during sUA-lowering treatment (ULT) [30]. Meanwhile, the canakinumab has been approved by European Medicines Agency for the similar symptoms [31].

Anakinra

It is a human recombinant IL-1β receptor approved by FDA for multi-system inflammatory syndrome in children and rheumatoid arthritis [32]. So far, there is deficiency of randomized controlled trials evaluating anakinra's effectiveness for the gout management; however uncontrolled trials and case series support its efficiency. Anakinra has been the favourite off-label anti-IL-1β approach amongst expert "goutologists", due to its comparatively low cost and short half-life than that of canakinumab [33].

Advanced approaches to lower serum urate

Since hyperuricemia is the primary condition that promotes gout, the long-span gout therapy involves almost constantly the lowering of serum therapeutically and sUA levels in tissues. Various advanced ULTs are exploring their way into the functional list of medicinal drugs.

Pegloticase

It is a pegylated recombinant uricase for uric acid degradation. In 2010, it was approved by the FDA and specified for the therapy of hyperuricaemia in adults with tophaceous or chronic gout headstrong to traditional ULT [34]. It is administered intravenous pathway in each 2 weeks. Many research confirmed the capability of pegloticase to dramatically and rapidly lowering sUA and to encourage the frequently- intense tophi resolution [35]. In randomized controlled trials, many safety concerns arose for pegloticase. As for entire ULTs, the administration of pegloticase rapidly increases the risks of gout flares. Consequently, gout flare prophylaxis is suggested for minimum the initial 6 months of pegloticase treatment [36]. Pegloticase must be prevented in patients with deficiency of glucose-6-phosphate dehydrogenase (G6PD) because its reaction produces oxidants that might raise the risks of methemoglobinemia and hemolysis in these patients [37]. Due to infusion-linked volume burdens, pegloticase must also be stopped in patients with decompensated heart failure. Infusion reactions risk is the major safety concern and the most recurrent reason of suspension in the trials [38]. Generally, these reactions are moderate but can be severe and require pre-medicine with glucocorticoids. As both infusion reactions and loss of medication efficiency indicate the development of anti-pegloticase antibodies (mostly polyethylene glycol) [39]. Meanwhile, the risks of reactions can be significantly decreased by stopping pegloticase in patients with excessive amount of sUA about 6.0 mg/dL before infusion on two successive times [40].

Lesinurad

It is a highly potent and selective inhibitor of uric acid reabsorption as it decreases sUA by inhibiting both the organic anion transporter 4 (OAT4) and the sUA-anion exchanger transporter 1 (URAT1), which function to reabsorb the sUA throughout the proximal tubule [41]. Lesinurad is highly potent and efficient more than uricosuric probenecid, even in mild renal deficiency [42]. It attained FDA approval in 2015 as a second-line therapy of gout in patients who have failed to encounter target sUA in spite of cure a traditional XOI ULT (mostly, febuxostat or allopurinol) [43].

Arhalofenate

It is a dual mechanism of action drug. Patients starting ULT are regularly prescribed contemporaneous anti-inflammatory prophylaxis to decrease the risks of gout attacks triggered by the sUA-lowering procedure [44]. In history, all gout medicines have been either sUA-lowering or anti-inflammatory. However, arhalofenate is a peroxisome proliferator-activated receptor-gamma (PPAR-γ) to some extent agonist, establishes dual anti-inflammatory and ULT expressions. Explicitly, it inhibits IL-1β expression at the time of inhibiting uric acid renal reabsorption at the OAT4, OAT10, and URAT1 transporters [45]. Different randomized controlled trials evaluated the efficiency of arhalofenate comparative to placebo and allopurinol. Although indicating a higher capability for sUA lowering as compared to placebo, it did not demonstrate benefit more than allopurinol [46]. Likewise, arhalofenate did not seem to be as efficient as conventionally administrated anti-inflammatory drugs [47]. However, the likelihood that the dual reaction of arhalofenate allows single-drug routines for almost few patients with gout may recover compliance for this disorder where patients and their doctors have been disreputably non-compliant with therapeutic management [48].

Advanced treatment guidelines

The ACR published primary guidelines for the treatment of gout in 2012. These strategies confirmed that chronic gout requires chronic management and combined the matters of ULT, anti-inflammation, and lifestyle risk managing [49]. With a stress on early gout management, the guidelines encourage evidence-based perfect practices, enhance quality of treatment, and improve safety of patient. Endorsements were reached after an official review process by an international multi-center team of gout expert physician [50]. Revolutions comprise management on the appropriate time to recruit ULT (in the situation of two attacks in the similar year or afterwards single attack in patients with second stage or higher renal illness, kidney stones, or tophi), a stress on treat-to-target approaches (an early target of not more than 6.0mg/dL and less as required to resolve tophi or regulate attacks or both) [51]. The use of pegloticase and uricosuric agents were recommended for ULTs along with confirmed off-label anti-IL-1 biologics in case of failing traditional anti-inflammatory approaches [52].

Advanced screening genetics

The most important cell surface protein, human leukocyte antigen B (HLA-B) has been reported efficient in the identification and demonstration of external antigens and crucial for immune defenses [53]. The HLA-B allele as a single variant of this gene has been highly associated with increased (>100-fold) risks for acute cutaneous and systemic side effects with allopurinol therapy. Among Thai and Han Chinese patients, this allele has been reported in 100% of patients with allopurinol hypersensitivity [54]. It was also reported in 80% of Korean patients with reactions of allopurinol hypersensitivity, that was more than 12% those of healthy controls. Hence, the present management guidelines of ACR for gout suggested examining all patients of Thai and Han Chinese lineage and all Korean origin patients with almost renal failure of 3rd stage [55].

Clinical Pharmacogenomics Implementation Consortium (CPIC) suggests avoiding prescribing that allopurinol to patients with HLA-B positive [56]. In higher risk patients, the pharmacological analysis of HLA-B genotyping recommends that this scanning approach is cost-effective. Many recent studies have reported the statistics that African, and Americans could have a higher incidence of HLA-B like certain Asian population. In another recent study, the allopurinol hypersensitivity risks in the African American and Asian subpopulations were 5 and 12 times greater, correspondingly, comparative to Europeans [57]. Consequently, ACR therapeutic guidelines suggest starting allopurinol for all patients with low dosage and titrate up progressively till a target sUA is accomplished.

Advanced risks and benefits of hyperuricemia

There is an increasing identification within the gout population of a highly causative relation between cardiovascular disease and hyperuricemia. In spite of differences in study populations and variable outcomes, nearly all of the research established that hyperuricemia is an autonomous risk factor for adversative cardiovascular results [58]. An identical adverse effect of hyperuricemia has been studied thoroughly about chronic kidney disease [59]. Studies recommend that higher concentrations of sUA influence the stage of kidney damage and are related to a greater risk of secondary hypertension. Several population-based studies and interventional trials in patients with gout and hyperuricemia, recommend that ULTs treatment can decrease the risks of different side effects [60].

Moreover, levels of sUA in multiple sclerosis patients are considerably lower than healthy controls [61]. Additional studies have uncertainly recognized identical relationships between sUA and gout and both Huntington and Parkinson diseases. However, all studies have not documented these probable useful effects [62]. As the putative neuroprotective relation between central nervous system and uric acid disorders is a comparatively novel concept, there is presently no guideline about specific sUA level, if any, may characterize a proper balance between neuroprotective benefits and comorbidity risks of gout [63]. Thus, more studies are mandatory to verify that higher levels of sUA in fact deliver a neurologic advantage and to re-assess the constitutions of healthy sUA level in gout and healthy patients [51].

CONCLUSIONS

Gout has become a forefront disease with critical implications and requires complex treatment with recent advancements in the knowledge of pathophysiology and crystal inflammation of hyperuricemia. The significance of IL-1β and the inflammasome provided great insights in the vital transporters for renal sUA management with introducing novel gout therapies with different mechanism of actions. Likewise, with increasing sympathetic of the gout genetics and the multiple sUA functions, the gout management recommendations are undergoing improvement and progression. With enhancements in knowledge of gout as both a chronic and acutely devastating illness, gout pharmaceutical developments and constant research remains to make substantial headway to produce sufficient control of sUA and inhibition of acute gout.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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Dr. Andleeb Asghar and Dr. Fahad Somaa collected data from databases. Hafiz M Zeeshan Raza prepared the manuscript and Dr. Muhammad Ibrahim proofread it well.

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