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Review on Allopurinol in the Treatment of Gout

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ABSTRACT

Gout and pain are synonymous, and a study in this issue of the *BJP* reports a novel anti-nociceptive effect of allopurinol, the drug most commonly used to treat gout. Allopurinol works by inhibiting xanthine oxidase (XO), the enzyme responsible for converting hypoxanthine to uric acid which is deposited as crystals in the joints of gout sufferers. Hypoxanthine is a metabolite of, and a possible precursor to, adenosine. find that acute inhibition of XO with allopurinol produces a modest adenosine A_1 receptor-mediated anti-nociceptive effect in common tests of chemical and thermal nociception in mice. A concomitant increase in cerebrospinal fluid levels of adenosine supports their hypothesis that inhibiting XO increases adenosine levels via salvage from hypoxanthine. Elevating endogenous adenosine levels by inhibiting metabolism is a well-established strategy for producing anti-nociception in many preclinical models, but inhibiting XO is likely to be particularly beneficial in some chronic pain states because of the pro-nociceptive reactive oxygen species that are produced by XO activity. Thus, allopurinol may have unexpected benefits in pain associated with chronic inflammation, diabetes and vascular dysfunction.

Keywords- allopurinol, analgesia, xanthine oxidase, adenosine, anti-nociception, mouse**.**

I. INTRODUCTION

Gout distinguished itself in the history of Homo sapiens since time immemorial. It appeared in medical records very early in the history of medical writing, and was also mentioned in the biographies of many famous names. It was depicted as the fate of a life of affluence as much as the challenge to a physician's skill, and truly it was. Modern ages witnessed remarkable progress in managing gout. More recently, thanks to quantum leaps in molecular biology, diagnostic modalities, and pharmacotherapy, we enjoy deeper understanding of the disease and a more sophisticated armamentarium.

Gout is a systemic disease that results from the deposition of monosodium urate crystals (MSU) in tissues. Increased serum uric acid (SUA) above a specific threshold is a requirement for the formation of uric acid crystals. Despite the fact that hyperuricemia is the main pathogenic defect in gout, many people with hyperuricemia do not develop gout or even form UA crystals. In fact, only 5% of people with hyperuriceamia above 9 mg/dL develop gout. Accordingly, it is thought that other factors such as genetic predisposition share in the incidence of gout [1], [2].

MSU crystals can be deposited in all tissues mainly in and around the joints forming tophi. Gout is mainly diagnosed by identification of the pathognomonic MSU crystals by joint fluid aspiration or in tophi aspirate. Early presentation of gout is an acute joint inflammation that is quickly relieved by NSAIDs or colchicine. Renal stones and tophi are late presentations. Lowering SUA levels below deposition threshold either by dietary modification and using serum uric acid lowering drugs is the main goal in management of gout.

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This results in dissolution of MSU crystals preventing further attacks [3], [4].

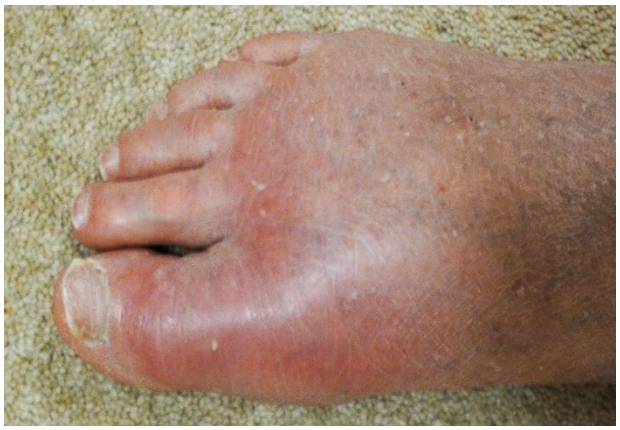

Fig: 1 Gout disease

II. EPIDEMIOLOGY OF GOUT

- Global Prevalence:
  - Gout is the most common inflammatory arthritis in adults, with studies estimating a global prevalence of 1-4%. The prevalence varies by region, age, sex, and socioeconomic factors.
  - In Western countries, the prevalence has been reported to be higher. For example, in the United States, the prevalence of gout in adults is approximately 3.9% (according to the 2015-2016 National Health and Nutrition Examination Survey, NHANES). This translates to an estimated 8.3 million adults affected by gout.
  - In Europe, the prevalence ranges between 1-3% in different countries, with variations based on national dietary habits and healthcare access.
- Age and Gender Distribution:
  - Gout is most common in men, with a male-to-female ratio of about 3:1. Men typically develop gout at an earlier age, usually between 30-50 years, whereas women tend to develop the condition later in life, often after menopause, due to the protective effect of estrogen on uric acid metabolism.
  - The incidence of gout increases significantly with age, particularly after the age of 60, affecting both men and women, but more frequently in men.
- Trends in Prevalence and Incidence:
  - Recent data indicate an increase in the prevalence of gout over the past few decades. This rise has been attributed to factors such as aging populations, increased rates of obesity, dietary changes, and improved access to healthcare.
  - Hyperuricemia, the primary risk factor for gout, has also become more common due to lifestyle factors, including high purine diets, alcohol consumption, and the growing prevalence of conditions like hypertension, diabetes, and chronic kidney disease (CKD), all of which increase the risk of gout.

III. GLOBAL DISTRIBUTION

- **Western Countries:**
  - In the United States, gout is most prevalent in older adults and in individuals who are overweight or obese. The rise in gout cases is largely attributed to the increasing prevalence of obesity and metabolic diseases. It is most common in men aged 30-50 and women after menopause.
- **Asia**:
  - Gout has traditionally been less common in Asian populations, but its prevalence is rising in countries such as Japan, China, and South Korea, likely due to changing diets (increased intake of purine-rich foods and alcohol) and higher rates of obesity.
  - In China, the prevalence of gout has increased significantly in urban populations, especially in areas with higher socioeconomic status.
- **Africa**:

Gout is less common in sub-Saharan Africa, although it has been increasing in some countries due to the rising rates of obesity, hypertension, and diabetes. There is less data available from rural regions, where dietary patterns may differ significantly from urban areas.

- **Middle East:**

The prevalence of gout is relatively high in the Middle East, partly due to dietary habits rich in purine-containing foods and the high prevalence of obesity and diabetes in the region.

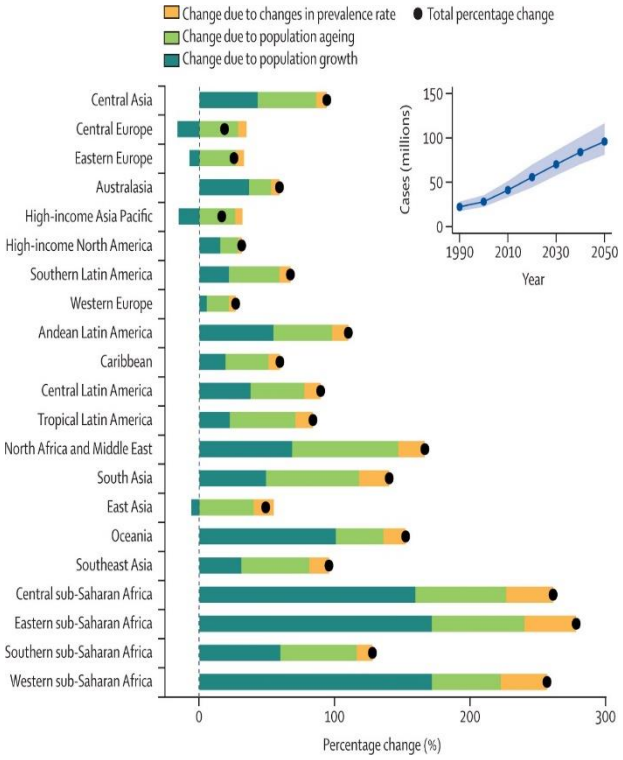

Fig: 2 Global cases of gout forecast to year 2050 and decomposition of changes in case counts by region, 2022–50

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IV. MECHANISM OF ACTION IN GOUT

Gout is a form of inflammatory arthritis that occurs due to the deposition of monosodium urate (MSU) crystals in the joints and tissues, resulting in painful inflammation. The underlying mechanism of gout involves hyperuricemia—an elevated concentration of uric acid in the blood—which leads to the formation of MSU crystals that trigger the inflammatory response.

Here is an outline of the mechanisms involved in the development of gout:

1. Hyperuricemia: The Primary Cause of Gout

Gout is closely associated with hyperuricemia, which occurs when serum uric acid levels exceed the normal range. Normal uric acid levels typically range from 3.5-7.2 mg/dL (in blood), and levels above 6.8 mg/dL (the saturation point) can lead to the formation of uric acid crystals.

Uric acid is a product of the breakdown of purines, which are found in certain foods and are produced by the body. Normally, uric acid is filtered by the kidneys and excreted in the urine. However, in hyperuricemia, there is either:

1. Increased production of uric acid, often due to a high intake of purine-rich foods (e.g., red meat, seafood, alcohol), metabolic disorders, or excessive cell turnover.
2. Decreased excretion of uric acid, often due to renal dysfunction, dehydration, or the use of diuretics, which impair the kidneys' ability to eliminate uric acid.

When uric acid levels exceed the saturation threshold (6.8 mg/dL), uric acid forms monosodium urate (MSU) crystals.

V. FORMATION AND DEPOSITION OF MONOSODIUM URATE CRYSTALS

- **Crystal Formation**:
  - When the uric acid concentration in the blood exceeds its solubility limit, monosodium urate (MSU) crystals form. These needle-like crystals can deposit in the joints, especially in cooler areas like the big toe, where the temperature is lower.
- **Crystal Deposition**:
  - The deposition of MSU crystals in joint tissues, tendons, and other tissues leads to the hallmark of gout—inflammation. These crystals act as foreign bodies, and the body's immune system reacts to their presence, leading to inflammation and pain.

Inflammatory Response: Activation of the Immune System

Once MSU crystals have deposited in the joints, they trigger a strong inflammatory response through the activation of the body's innate immune system, primarily by macrophages and neutrophils.

1. ***Phagocytosis by Macrophages:***
   - The MSU crystals are recognized by macrophages, which are immune cells that engulf and attempt to eliminate the crystals. This process of engulfing the crystals is called phagocytosis.
   - MSU crystals activate the NLRP3 inflammasome, a protein complex that plays a critical role in the innate immune response.
   - The activation of the inflammasome leads to the production and release of interleukin-1 beta (IL-1β), a pro-inflammatory cytokine that is central to the inflammatory response in gout.
2. **Cytokine Release and Inflammation**:
   - IL-1β and other pro-inflammatory cytokines (e.g., TNF-α, IL-6) are released by macrophages, causing the local inflammation.
   - Neutrophils, another type of immune cell, are recruited to the site of crystal deposition by these cytokines. These neutrophils further contribute to inflammation by releasing reactive oxygen species (ROS) and proteolytic enzymes that cause tissue damage.
3. **Joint Inflammation**:
   - The inflammatory cascade leads to the classic signs of gout: pain, redness, swelling, and heat in the affected joint. The acute pain in gout often occurs suddenly and is intense, leading to episodes of acute gouty arthritis.

Chronic Gout and Tophi Formation

- **Chronic Gout**:
  - In individuals with long-standing hyperuricemia, repeated episodes of acute gouty arthritis may occur, leading to chronic inflammation in the affected joints. Over time, this can result in joint damage and deformity.
- **Tophi Formation**:
  - With prolonged or untreated gout, tophi (urate crystal deposits) may form under the skin or in other tissues such as cartilage and tendons. These tophi are often visible as firm, painless lumps and can cause significant joint damage if left untreated.
  - Tophi can form in areas such as the auricle of the ear, elbows, hands, and feet.

Acute Gout Flare: The Role of Crystal-Induced Inflammation

- **Acute Flare**:
  - An acute gout attack (or flare) is a sudden, intense episode of joint pain and swelling. It is usually triggered by the rapid increase in uric acid levels, dehydration, trauma, or the consumption of foods or drinks high in purines (e.g., red meat, alcohol, sugary drinks).
  - During an acute attack, the MSU crystals cause intense local inflammation, leading to the hallmark symptoms of gout: redness, swelling, warmth, and severe pain in the affected joint, often the first metatarsophalangeal joint.

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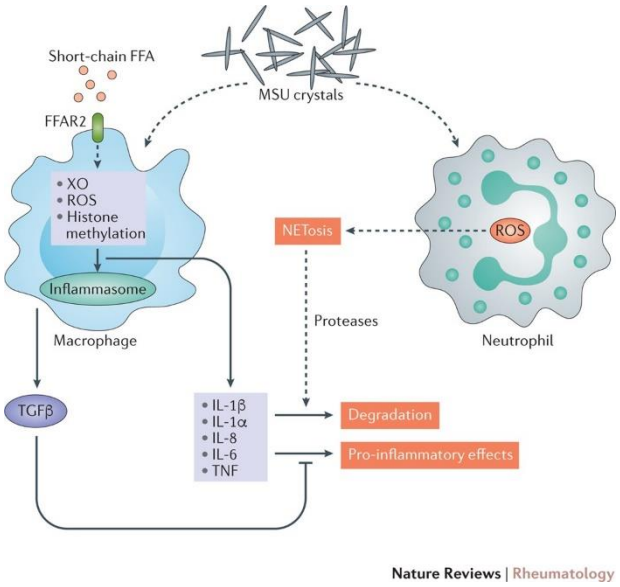

Fig: 2 M.O.A of gout disease

Efficacy of Allopurinol in Gout Treatment

1. **Uric Acid Lowering:**

○ Allopurinol is effective in lowering serum uric acid levels. It is typically prescribed to maintain serum uric acid below 6 mg/dL, a target that is associated with reduced risk of gout flares and tophi formation.

○ Studies show that allopurinol can significantly reduce serum uric acid levels within 1-2 weeks of initiation, and it remains effective in preventing further gout attacks when used long-term.

2. **Prevention of Acute Gout Attacks:**

○ While allopurinol is effective in preventing future gout attacks by lowering uric acid, it should not be used during an acute flare due to the potential for exacerbating inflammation. Instead, it is introduced once the acute attack has been managed.

○ Long-term use of allopurinol reduces the frequency of acute flares and decreases the incidence of tophi formation, leading to improved joint function over time.

3. **Effectiveness in Chronic Gout:**

○ In chronic gout, allopurinol is highly effective in reducing the frequency of attacks and the size of tophi. Long-term therapy has been shown to reduce the overall burden of the disease and improve quality of life.

○ Studies suggest that allopurinol can significantly reduce the risk of joint damage, especially when started early in the course of the disease.

4. **Combination with Other Therapies:**

○ Allopurinol is often used in combination with nonsteroidal anti-inflammatory drugs (NSAIDs) or colchicine during the initiation phase to prevent acute flare-ups while uric acid levels are being lowered.

○ It can also be combined with other urate-lowering therapies, such as febuxostat (another xanthine oxidase inhibitor) or probenecid (a uricosuric agent), in cases where allopurinol alone is insufficient.

1. **Common Side Effects:**

○ Allopurinol is generally well-tolerated, but common side effects include gastrointestinal symptoms (nausea, diarrhea) and rash. These side effects are usually mild and resolve with dose adjustment or discontinuation.

2. **Severe Reactions:**

○ Rare but serious adverse effects include hypersensitivity reactions, which can manifest as a rash, fever, and more severe conditions such as toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome (SJS).

○ Allopurinol hypersensitivity syndrome (AHS) is a life-threatening reaction that can cause renal failure, hepatitis, and hematological abnormalities. Patients should be monitored closely, especially in the first few months of therapy.

3. **Renal Considerations:**

○ Allopurinol is excreted by the kidneys, and dosing adjustments are necessary in patients with renal impairment. In these cases, the dose of allopurinol should be reduced to prevent toxicity.

○ Allopurinol has been associated with acute kidney injury in rare cases, particularly when initiated during an acute gout flare, so its use in such settings requires caution.

4. **Drug Interactions:**

○ Allopurinol can interact with several drugs, including azathioprine and mercaptopurine, which are metabolized by xanthine oxidase. These drugs can accumulate in the body when taken concurrently with allopurinol, leading to increased toxicity. Careful dose adjustments are required when these drugs are used together.

○ It can also interact with warfarin, potentially enhancing its anticoagulant effects.

Dosing and Administration

- Allopurinol is typically started at a low dose (e.g., 100 mg per day) to minimize the risk of side effects and titrated upward as needed to achieve target uric acid levels.
- The typical maintenance dose ranges from 200 mg to 800 mg per day, depending on the patient's response and the presence of renal impairment.
- Renal dose adjustments: In patients with impaired renal function, the dose of allopurinol should be adjusted based on the degree of renal impairment. The drug should be used cautiously in patients with eGFR (estimated glomerular filtration rate) below 30 mL/min.

Considerations and Contraindications

- Contraindications: Allopurinol should be used cautiously or avoided in patients with a history of severe hypersensitivity reactions to the drug, as these reactions can be life-threatening.
- Pregnancy: Allopurinol is classified as a Category C drug during pregnancy, meaning it should only be used if the potential benefit outweighs the risk. It is not known to be teratogenic, but should be avoided unless necessary.

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VI. CONCLUSION

Allopurinol remains a cornerstone in the management of chronic gout and hyperuricemia due to its proven efficacy in lowering uric acid levels and preventing future gout attacks and long-term complications like joint damage and tophi formation. It is generally well-tolerated, with relatively few severe side effects. However, its use requires careful monitoring, especially in patients with renal impairment and those at risk for hypersensitivity reactions. When used appropriately, allopurinol significantly improves the quality of life for patients with gout by reducing the frequency of flare-ups and preventing disease progression.

Despite its long-standing role in gout management, future research is needed to explore its use in combination therapies, dosing strategies, and its effectiveness in various subpopulations of patients with gout.

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