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A Review on Treatments of Gout for Future Aspects

Manpreet Singh**, *Madan L. Kaushik
Department of Pharmacology, CT Institute of Pharmaceutical Sciences, Shahpur, Jalandhar, Punjab, India

Abstract

Gout is the most common inflammatory arthritis in adults, and is caused by excess uric acid pools in the body, which leads to the formation of monosodium urate (MSU) crystals and their deposition in and around joints where they induce inflammation, leading to acute gout attacks. The extreme inflammatory burden and pain of an acute gout attack can be unbearable. The prevalence of gout appears to be increasing and may affect up to 8 million people in the United States and this disease mainly occurs in men aged more than 50, affecting approximately 1–2% of adult men in the western world. The development of novel therapies for gout after 40 years has opened new understanding of this disease. A study from Vellore revealed that 15.8% of the affected patients are less than 30 years. The quality of care for many patients with gout is unfortunately not in keeping with current guidelines. Rather than providing a comprehensive overview of gout, this review focuses on various classes of drugs used in the treatment of gout such as short-term and long treatments with allopathic medicines and alternative medicines.

Keywords: *Gout, monosodium urate crystals, allopathic medicines, alternative medicines*

****Author for Correspondence*** E-mail: arora.manpreet.ms@gmail.com

INTRODUCTION

Gout is a common inflammatory disease which is characterized by acute arthritis and hyperuricemia due to disorder of purine metabolism. It is caused by the deposition of monosodium urate crystal in tissues, soft tissue masses, and other factors such as kidney stones and urate nephropathy are also responsible to cause arthritis. Attacks of pain, erythema, and swelling of one or a few joints in the lower extremities are prominent clinical manifestations of acute gout [1]. This disease is mainly occurring in men aged more than 50, affecting approximately 1–2% of adult men in the western world. The acute onset pain is in joint, erythema and swelling of the first metatarsophalangeal joint. Incidence of gout in India is not fully understood [2]. The prevalence is 0.12% as per international and national surveys against rheumatism, community oriented program for control of rheumatic diseases study in Bhigwan village of India. A study from Vellore revealed that 15.8% of the affected patients are less than 30 years of age; urban Indian population is involved more than the rural population and due to increased prevalence of metabolic disorder in younger population, the first attack of gout occurs a ten times earlier to them. Additional Indian study showed that level of high uric acid is associated with laboratory and anthropometric parameters of metabolic syndrome [3]. High uric acid level is the main cause of gout. In humans, uric acid is derived from xanthine by the action of xanthine oxidase, and it is the end product of purine metabolism. Uric acid is mainly excreted by the kidneys, and therefore serum levels increase when renal function is impaired [4]. Uric acid levels increase in case of excessive intake of purine rich foods, fructose, or alcohol. Other causes of hyperuricemia are conditions associated with high cell turnover, that is, lymphoproliferative disease. In hyperuricemia, uric acid level is considered as >6.5 or 7.0 mg/dl (>416 mmol/l) in men and >6.0 mg/dl (>360 mmol/l) in women. The various treatments are available for gout but no one can cure; now the society is looking for other alternatives [5].

ETIOLOGY OF GOUT

Several factors are responsible for monosodium urate crystals to form. Gout is a complex disease. There are a variety of factors that can play a role in causing the gout.

Certain conditions, such as blood and metabolism disorders are also a cause to produce too much uric acid. Drinking too much alcohol can also lead to excess uric acid. Certain foods can also cause gout when you eat too much of them [6, 7]. These include: shellfish, red meat, organ meat, sweet juices and salt. There are different types of diseases which may lead to cause gout such as type-2 diabetes, hypertension, hyperlipidemia, cardiovascular disease, renal disease, and obesity suggest that gout and its necessary precursor hyperuricemia may play an important role in the demonstration of the metabolic syndrome and some other factors such as trauma, repetitive microtrauma, arthritis, infection, lack of tissue perfusion, lower blood pH, or lower tissue temperature act as the local factors [8].

TREATMENTS OF GOUT

Gout flare medications are include colchicine, non-steroidal anti-inflammatory drugs and steroids, which can be taken together in severe cases and they are most efficient when taken early after the flare onset [9].

Allopathic Treatment Classified on the Basis of Duration

Short-term and Long term treatments:

Short-Term Therapy

Colchicine: If taken before 12 h after flare onset, 1.8 mg of colchicine has been shown to be more effective than the traditional higher doses. In some conditions, the combination of colchicine with other drugs such as cyclosporine, ketoconazole, erythromycin, diltiazem or verapamil reduce the dose of colchicine [10].

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): Aspirin, celecoxib, diclofenac, diflunisal, etodolac, ibuprofen, indomethacin, ketoprofen, ketorolac, nabumetone, naproxen, oxaprozin, piroxicam, salsalate, sulindac and tolmet are the drugs which belong to the class of NSAIDs. Nonsteroidal anti-inflammatory drugs block the COX enzymes and reduce prostaglandins throughout the body and their efficacy is largely accepted [11].

Steroids: Oral, parenteral, and intra-articular steroids are used to treat acute gout and corticosteroids such as prednisone are generally given because this is a safer approach than using NSAIDs. Adrenocortcotropic hormone can also be injected in the muscle or intravenously for the treatment of gout [12].

IL-1 Blockers: are the drugs which reduce the level of urate in serum and then treat gout, IL-1 inhibition for acute gout are those for whom conventional flare therapies are ineffective. Various drugs are used such cryopyrin, rilonacept, canakinumab, anakinra, triamcinolone acetonide and canakinumab. Among these drugs, canakinumab is more effective than a single dose of intramuscular triamcinolone for treating an acute gout flare [13].

Single Therapy: In a prospective study of joint aspirations in patients with gout on urate-lowering therapy, the recommended therapeutic Serum Urate Lowering drugs are [14].

Long-Term Treatments

Allopurinol: Allopurinol is an oral xanthine oxidase inhibitor, first introduced to the clinic in the sixties. Perhaps one of the more contentious interactions between rheumatologists and nephrologists relates to allopurinol dosing in the setting of CKD. Allopurinol and other xanthine oxidase inhibitors should not be prescribed with azathioprine and 6-mercaptopurine, as xanthine oxidase is involved in the metabolism of these drugs [15].

Febuxostat: Febuxostat was the first new urate-lowering drug to be approved in the United States in over 40 years. It is a xanthine oxidase inhibitor and therefore has the same mechanism of action as allopurinol. It may be an option if patient develops side effects from allopurinol or has kidney disease. Like allopurinol, febuxostat decreases the amount of uric acid made in the body. It is also started at a lower dose, which may be increased if uric acid levels remain high. Side effects can include nausea and joint or muscle pain [16].

Probenecid: Probenecid has been the first commercialized urate lowering drug and was at first a very popular drug. When allopurinol became available, probenecid was much less used because it had to be given in divided doses and required high fluid intakes and adjustment of the urine pH. It acts on the kidneys to help the body to eliminate uric acid. The medication is taken daily and may be combined with antibiotics to boost

effectiveness. The common side effects include nausea, kidney stones, skin rashes, upset stomach and headaches [17].

Lesinurad: Lesinurad acts orally and helps the body to eliminate uric acid. It is used with xanthine oxidase inhibitor (XOI), such as allopurinol and febuxostat to increases the effects for those people whose gout is not controlled by optimally-dosed XOIs alone. The common side effects of this drug include headache, flu symptoms, increased level of blood creatinine, gastroesophageal reflux disease, kidney-related side effects and kidney stones [18].

Pegloticase: This is used when standard medications are unable to lower the uric acid level, a condition known as refractory chronic gout. It is an effective than other drugs and it reduces uric acid quickly and lowers its levels than other medications. The drug is administered every two weeks by intravenous (IV) infusion. Side effects of this drug can include gout flares, nausea, painful knee, sore throat, constipation, infusion reactions, vomiting and chest pain [19].

Combined Therapy

In severe stage of gout, short-term therapy is not useful for treating the gout. Thereafter in this stage, we use the combination therapy of short-term and long-term medicines for the treatment of chronic or severe gout [20].

Treatment of Gout with Herbal Plants

Herbal plants are the best alternative source for the treatment of gout, the list of used plants is given below in Table 1 [21].

Table 1: *Herbal Plants for the Treatment of Gout.*

S. No.	Plants Used	Botanical Name	Family	Chemical Constituent
1.	Alfalfa	*Medicago sativa*	*Fabaceae*	Soyaspogenol A-E, Medicageic acid, Hedragenin
2.	Cherry tree	*Prunus avium*	*Rosaceae*	Cyanogenic glycoside
3.	European Ash	*Fraxinus excelsior*	*Oleaceae*	Iridoids, Secoirridoids, Flavonoids,
4.	Grapevine	*Vitis vinifera*	*Vitaceae*	Nerol, Citronellal, Linalool
5.	Autumn crocus	*Colchicum autumnale*	*Liliaceae*	Colchicine, Demecolcine
6.	Birch	*Betula alba*	*Poaceae*	Hyproside, Quercitin, Myricetin
7.	Garlic	*Allium sativum*	*Liliaceae*	Allyl propyl disulphide
8.	Horsetail	*Equisetum arvense*	*Equisetaceae*	Hexahydrofernesyl acetone
9.	Lemon tree	*Citrus limonis*	*Rutaceae*	Limonin, Citral
10.	Onion	*Allium sepa*	*Amaryldaceae*	Quercetin, Allins
11.	Red vine	*Vitis vinifera*	*Vitaceae*	ε-viniferins, Resverartrol
12.	Potato	*Solanum tuberosum*	*Solanaceae*	Starch, Solasodine
13.	Sarsaparilla	*Similax aspera*	*Liliaceae*	Similogenin, Sarsapogenin
14.	Oats	*Avena sativa*	*Poaceae*	Avenine, Trigonelline
15.	Cowslip	*Primula officinalis*	*Primulaceae*	GABA, Glutamine, Glycine
16.	Celery	*Apium graveolens*	*Umbelliferae*	Sedanoic acid, Sedanolide
17.	Dandelion	*Taraxacum officinale*	*Compositae*	Inulin
18.	Devil's claw	*Harpagophytum procumbens*	*Pedaliaceae*	Herpagoside, Harpagophylum
19.	Elm	*Populus nigra*	*Saliaceae*	α/β-Herpagoside, Eudesmol
20.	Juniper	*Juniperus communis*	*Cypressance*	A-pinene, camphene
21.	Linden	*Tilia cordata*	*Tiliaceae*	Fanesol
22.	Mossy	*Paronychia kapela*	*Carophyllaceae*	Flavonoids, Tocopherols
23.	Nettle	*Urtica dioica*	*Urticaceae*	Scopoletin
24.	Willow	*Salix fragilis*	*Saliaceae*	Salicin
25.	Vervain	*Verbena officinalis*	*Verbenaceae*	Verbenalin and Aucubin

Marketed Formulations of Herbal Drugs for the Treatment of Gout

The list of marketed drugs has given below in Table 2 [22].

Table 2: *List of Marketed Formulations of Herbal Drugs for the Treatment of Gout.*

S. No.	Common Name	Marketed Formulation
1.	*Ashwagandha*	*Ashwagandha Powder*
2.	*Ashwagandha*	*Ashwagandharishta*
3.	*Liquarice*	*Respinova*
4.	*Liquarice*	*Yasti madhu*
5.	*Oroxylum indicum*	*Anxocure*
6.	*Nirgundi*	
7.	*Shillakai*	Joint AID plus
8.	*Guggle*	
9.	*Sonth*	

Treatment of Gout with Physiotherapy

The physiotherapy management could be an effective treatment for gout arthritis in various stages. Physiotherapy can help the patient to manage the symptoms of gout in a various ways. Physiotherapy controlling the pain, reducing inflammation, reducing tiredness, Improving the strength and range of movement and also improving cardiovascular fitness levels. There are two main exercises such as *Stretching exercises and Strength Exercises* which is helpful for the treatment of gout [23].

Treatment of Gout with Replacement of Joint Therapy

In the severe stage of gout, knee aspirations were performed and the synovial fluid appeared yellow and cloudy. If gout affects the knee joint, a knee replacement might likely become necessary [24]. The surgeon reports that the intraoperative appearance of the tissue was that of infection. No obvious chalky deposits were appreciated [25]. The patient was evaluated by the infectious disease service and was treated with 6 weeks of intravenous cefazolin (Ancef) via a peripherally inserted central catheter and had physical therapy/occupational therapy at home. The postoperatively reports reduction of pain and examination showed decreased erythema and increased motion [26].

Treatment of Gout with Acupuncture

Acupuncture is an effective or very useful technique for the treatment of acute gout attacks. It is an important technique found particularly helpful in the reduction of pain, inflammation and, improves blood circulation [27]. The therapy was applied alone or in combination with other treatments e.g. Chinese herbal medicine, acupoint injection, and local blocking therapy [28].

Treatment of Gout with Laser Therapy

Low Intensity Laser Therapy (LILT) is a new technique used for the treatment of gout. The proper application of this therapy is found to significantly reduce the pain and swelling associated with acute outbreaks of gout immediately, with naturally associated elimination of the requirement for pharmaceuticals [29]. LILT acts rapidly to reduce the inflammation on the surrounding joints, in addition to relieving the debilitating pain. The visible or near-infrared photons are thought to be absorbed by chromophores within the cells such as cytochrome *c* oxidase located in the mitochondria [30]. Alterations in the activity of cytochrome *c* oxidase results in increased production of adenosine triphosphate (ATP), a major source of cellular energy, which leads to normalization of cell function, pain relief, and healing [31].

CONCLUSION

Guidelines for the management of gout developed by the ACP primary care in comparison to the rheumatology society gout guidelines groups are discordant, despite assessment of largely the same evidence, with the exception of trials of pegloticase. To understand gout, and consequently to manage it, has been a challenge to the skill of physicians along the history of medicine. Recent advances in this field that took the shape of continuous progress, have recently witnessed quantum leaps. There are many therapies which are used for the treatment of gout. The aim of this review is to introduce the current therapy for gout. Various therapies have been recommended to treat the gout, such as allopathic treatment, treatment with herbal marketed formulation, physiotherapy, acupuncture and laser therapy. The scientist has recently new approach to inform the

diagnosis and management of gout. Now there is a resurgence of interest in improving its management. This review article may be beneficial for future aspects to treat the gout disease.

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