

Research Progress of Drugs for the Treatment of Gout

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Abstract: Gout is directly related to hyperuricemia caused by purine metabolism disorder and/or reduced uric acid excretion, and belongs to the category of metabolic rheumatism. Currently, there are many drugs on the market for the treatment of hyperuricemia and gout, but most of them are chemical synthetic drugs. The main direction of chemical drugs targeted at gout attacks is to inhibit enzyme action or use hormones to relieve pain during gout attacks, and control cytokine/inflammatory cell movement and function to reduce inflammatory response. The treatment in interphase and chronic phase is mainly uric acid lowering treatment. The chemical drugs used to reduce uric acid are mainly divided into three categories: inhibiting the synthesis of uric acid, promoting the excretion of uric acid and promoting the decomposition of uric acid. However, at present, the therapeutic effect of traditional Chinese medicine and biological drugs is gradually obvious. This paper mainly reviews the shortcomings of chemical drugs, traditional Chinese medicine and drug use in the treatment of gout and hyperuricemia, aiming to provide reference for the clinical treatment of hyperuricemia and gout.

Keywords: Gout; Uric Acid; Treatment.

1. Introduction

According to the 2018 edition of the European Alliance against Rheumatism Evidence-Based Expert Recommendation Update on Gout Diagnosis, the overall clinical presentation of gout is divided into four stages: Asymptomatic hyperuricemia (no MSU crystal deposition), asymptomatic MSU crystal deposition (no gouty arthritis attack), gouty arthritis attack and interattack (MSU crystal deposition), chronic gouty arthritis (gouty lithiasis, bone destruction, etc.) [1]. During asymptomatic HUA, the only symptom is that the blood uric acid level is too high, which exceeds the normal level. However, if the high uric acid level is maintained for a long time, the uric acid in the blood will be precipitated in the form of urate and gather in tissues such as joints. It is only when uric acid levels fluctuate greatly that mono-sodium urate (MSU) crystals deposited in joints and other tissues, recognized by innate immune cells as foreign bodies, cause the first attack of gout. Because MSU is different from microorganisms, pathogens, etc., it cannot be destroyed by immune cells, so as long as MSU is still present, it will cause repeated inflammation. Attacks of gout caused by MSU are often joint inflammation.

2. Chemicals to Treat Gout

2.1. Drugs to Inhibit Pain

During the interval of gout attack and chronic arthritis, it is mainly to control the blood uric acid content by inhibiting the action of xanthine oxidase, so as to prevent or slow down the probability of gout attack. The method is effective, but the side effects with it will also bring great burden and damage to the human body. The chemical drugs used to treat acute gouty arthritis include colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoid and adrenocorticotropin. Colchicine was once the first choice of drugs, which can reduce or terminate the chemokines secreted by white blood cells or synovial endothelial cells after phagocytosis of urate, and has obvious anti-inflammatory and analgesic effects. Although high-dose colchicine is more effective in the

treatment of gouty arthritis, it is also most likely to cause human poisoning, so it is generally used in low-dose colchicine. Non-steroidal anti-inflammatory drugs mainly include indometacin, butazon, etc., which have mild efficacy and have gradually replaced colchicine. Glucocorticoid or adrenocorticotropin is generally used for short-term use. Adrenocorticosteroids can promote uric acid excretion, but long-term use is easy to increase blood pressure and blood sugar.

2.2. Drugs that Inhibit Uric Acid Synthesis

The representative drugs that inhibit the synthesis of uric acid are allopurinol, febuxotan and oxypurine. Allopurinol is similar in structure to hypoxanthine and competes with hypoxanthine for xanthine oxidase. As xanthine oxidase activity decreases, the synthesis of uric acid decreases. However, for different populations, there are also many adverse symptoms during allopurinol treatment, especially allopurinol hypersensitivity syndrome, which is prone to occur in the initial period of administration, and exfoliative dermatitis is its main manifestation, in addition to gastrointestinal symptoms, rash, liver damage and other reactions [2]. Febuxotan is a non-purine xanthine oxidase inhibitor, which can inhibit the activity of xanthine oxidase without affecting other purine and pyrimidine synthesis and metabolism enzymes. However, there is a clinical probability of causing cardiovascular diseases [3]. In patients with gout and major cardiovascular co-existing diseases, All-cause mortality and cardiovascular mortality due to febuxostat are higher than allopurinol mortality [2]. In addition, the US Drug Administration has also issued warnings on the labels of non-buxotent products in order to reduce the death rate caused by the wrong use of drugs [4]. Oxypurine, also known as oxypurine, is an active metabolite of allopurinol, and its mechanism of action is also to produce competitive inhibition with hypoxanthine, thereby reducing xanthine oxidase activity and reducing uric acid synthesis. Oxypurine is often used in patients with hypersensitivity or insensitivity to allopurinol treatment, but it can also cause adverse reactions in the central nervous system and gastrointestinal tract^[5].

2.3. Drugs that Promote Uric Acid Excretion

Representative drugs that promote uric acid excretion include benbromarone, prosulfa, and losartan. The chemical drugs that inhibit uric acid excretion mainly act on the kidney, usually inhibiting the reabsorption of uric acid in the renal tubules, which is easy to cause the accumulation of urate crystals in the urinary tract, causing renal colic and renal function damage [5]. However, the treatment of benbromarone has little damage to renal function, and the adverse reactions caused by it are mainly concentrated in the stomach and intestines, which may cause explosive hepatitis in special cases [3]. Compared with allopurinol, the uric acid lowering effect of prosulfa is weaker, and it belongs to sulfonamides, which will cause cross-allergic reaction with sulfonamides. Patients allergic to sulfonamides should not choose this drug for treatment, which will also cause rash, fever, gastrointestinal reactions, such as nausea and vomiting, and competitively inhibit the excretion of salicylic acids, thiazines and oral hypoglycemic drugs. For example, penicillin and cephalosporins are secreted in renal tubules, thereby enhancing the blood concentration of these drugs [2]. Losartan is an alkaline drug, which can increase the pH in the urine, improve the solubility of uric acid in the urine, and reduce the amount of uric acid in the body. Similar to benbromarone and Prosulfa, losartan can also cause adverse reactions in the gastrointestinal tract, nervous system and other parts, resulting in increased blood potassium content, and long-term use may lead to anemia [3].

2.4. Drugs that Promote Uric Acid Breakdown

The representative drugs that promote the breakdown of uric acid are prekacase and labrase. Both of them are uricases, and their mechanism of action is to oxidize uric acid to allantoin in vitro to achieve the effect of reducing uric acid, but their price is too expensive and they are not listed in China [4]. Uricase reduces uric acid quickly, and during chronic gouty arthritis, it is not a good thing to reduce uric acid too fast, because the sudden decrease of uric acid rate in the blood will dissolve sodium urate crystals outside the blood, and it is more likely to induce acute gout attacks during the dissolution process. In addition, it is antigenic, easy to cause hypersensitivity reaction and drug resistance, and has a short half-life. There are great limitations in clinical application [5].

3. Chinese Medicine for Gout

Traditional Chinese medicine treatment of such diseases is not divided into detailed periods, are unified drug use. Chinese medicine has a certain description of gout, and the word gout has been proposed as early as the Jin Yuan period, according to Zhu Danxi's symptoms are more similar to modern gout, "Danxi Xin Fa" recorded: "gout, the limbs of the hundred walking pain, the Fang book called the White Tiger festival syndrome is also" [6], there are also drugs used to treat gout, single Chinese medicine or multi-Chinese medicine combined use. In addition, during asymptomatic HUA, the only symptom is that the blood uric acid level is too high, which exceeds the normal level. However, if the high uric acid level is maintained for a long time, the uric acid in the blood will be deposited in the form of urate to the joints, etc. Only when the uric acid level fluctuates greatly, the first attack of gout may be caused. After repeated gout attacks and interattack periods, the first attack of gout may occur. Eventually, a gouty stone with urate crystals as its core is

formed. The whole process of gout development begins with the increase of uric acid content, and the development of gout is also the high content of uric acid in the blood, so the fundamental prevention of gout is the control of uric acid content. During hyperuricemia, controlling uric acid content within the normal level is the key step to prevent hyperuricemia from turning into gout. Unfortunately, in reality, after the first attack of gout, generally after a period of time, the second attack will occur. Very few people only have the first attack, and there are no other subsequent symptoms of gout until the appearance of gouty stone. This means that the gout has reached an advanced stage, at which time even surgery cannot cure the gout, and surgery is not a necessary means, and will not be used. When gout attacks, it is accompanied by intense pain. Therefore, for gout attacks, interattacks and chronic gouty arthritis, relieving inflammation and controlling pain is the primary choice at this time, but it cannot prevent the next attack of gout. In the future, it is necessary to carefully select drugs to control uric acid and slowly reduce the level of uric acid to normal level, so as to prevent the recurrence of gout. The active ingredients of Chinese herbs or natural plants may be a promising breakthrough in the treatment of gout.

Chinese herbs are rich in flavonoids, polyphenols, polysaccharides, triterpenes, cellulose and other chemical components, which can effectively inhibit the activation of inflammatory cells and reduce the level of pro-inflammatory cytokines, and may be effective in alleviating the attack of gout [7]. Although there is no name of hyperuricemia in traditional Chinese medicine, it is believed that this disease is mainly caused by overeating fatty, thick and greasy products, external invasion of cold and dampness, spleen and stomach transportation dysfunction, internal phlegm and dampness, and then erosion of bone, resulting in bone destruction, which is similar to the attack of gouty arthritis caused by modern hyperuricemia [6].

The use of traditional Chinese medicine to treat gout has been studied for a long time. Many of them use compound traditional Chinese medicine. For example, in *Wumen Sanhuang Decoction*, Huangbai and Huangqin are used to clear heat and dry dampness, purge fire and detoxify. Cooked Rehmannia, raw rhubarb tonifying kidney and nourishing Yin, eliminating stasis and channeling, combined for minister medicine; Preventing and removing dampness and wind, detumescence and water, Shanci mushroom and Tuckaia detumescence and detoxification, all three are adjuvant drugs; Liang Guoqiang et al used *Wumen Sanhuang Decoction* to intervene in rats with high uric acid, and the results showed that the levels of serum uric acid and creatinine in rats with high uric acid decreased. The mechanism of action is that *Sanhuang decoction* can down-regulate the expression of URAT1 in kidney tissue of rats with high uric acid, and increase the expression of OAT1 and OAT3 proteins, increase the secretion and excretion of uric acid, and reduce reabsorption [8]. Previous studies have confirmed that single Chinese herbs do have the effect of lowering uric acid. Plum blossom is rich in polyphenols, whose chemical components mainly include flavonoids, phenylpropanes, organic acids, volatile components, etc. Among them, flavonoids represented by isoquercetin and hypericum seedling and phenylpropanoid compounds represented by chlorogenic acid are the main chemical components currently isolated and identified [9]. Zheng Xiaowei, Xia Daozong et al have shown that the biological total flavonoids derived from green plum

flower have excellent biological antioxidant capacity and significant inhibitory activity of xanthine oxidase [10]. The study of hyperuricemia mice with *Ganoderma lucidum* and *Pachycoia* extract showed that *Ganoderma lucidum* and *pachycoia* extract could effectively reduce the blood uric acid content and promote the excretion of uric acid from urine of hyperuricemia mice. The active ingredient in *Polygonum cuspidatum* can reduce the levels of pro-inflammatory cytokines IL-1 β , IL-6 and TNF- α , reduce the activity of xanthine oxidase in liver, decrease the expression of URAT1 and GLUT9 in kidney, and increase the expression of OAT1 protein, thereby protecting renal function [11].

The disadvantage of Chinese medicine in treating hyperuricemia or gout is that the components of Chinese medicine are complex, and the specific components can not be directly known, and the research on pharmacologic aspects is not thorough.

4. Conclusion

There are many drugs for the treatment of hyperuricemia and gout on the market at present, but most of them are chemical synthetic drugs, the main purpose and effect of drugs are clear, mainly for a certain target for treatment, but at the same time, it will increase the burden of normal organ operation, and there are hidden dangers in the safe use of drugs for users. The components of traditional Chinese medicine are complex, the target of action is many, and the effect of the treatment of diseases is more mild, but it is not clear which specific components play a role, and the effectiveness is not always effective, so there is still a lot of space in the development and utilization of traditional Chinese medicine, the specific treatment can be combined with the advantages of traditional Chinese and western medicine, according to the specific conditions of patients to choose drugs.

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