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Advances in the Research on Drugs Targeting Uric Acid Transporters for the Treatment of Hyperuricemia

Wenyu Huo[1,a], Ying Fu[2,b]

[1]Beijing Luhe Hospital, Capital Medical University, Beijing, 101149, China
[2]Center for Endocrine Metabolism and Immune Diseases, Beijing Luhe Hospital, Capital Medical University, Beijing, 101149, China
[a]18902009698@163.com, [b]fuyingrlyfe@163.com

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Abstract: Hyperuricemia is a metabolic disease characterized by disordered purine metabolism or impaired uric acid excretion. Its incidence has been steadily increasing, and it has become another common metabolic disease following diabetes. Hyperuricemia is a systemic disease affecting multiple systems. Elevated serum uric acid levels are likely associated with a series of complications, including gout, metabolic syndrome, kidney disease, diabetes mellitus, cardiovascular disease, among others. Therefore, actively intervene in uric acid levels and reduce uric acid deposition in the body is imperative. This review summarizes advances of medications targeting uric acid transport proteins for hyperuricemia, focusing on drug efficacy, adverse effects and complications, with a view to providing helps for the clinical management of hyperuricemia.

1. Introduction

Hyperuricemia pathogenesis is complex, mainly involving the production and excretion of uric acid as well as genetic factors. [1]

Impaired uric acid excretion is a key factor in hyperuricemia, which is mainly associated with renal diseases and abnormalities in uric acid transporter proteins. Based on the mechanism, drugs have been developed to act on the uric acid transporter proteins in the renal tubules to achieve the purpose of lowering serum uric acid (sUA) by promoting uric acid secretion and inhibiting uric acid reabsorption.

2. Drugs that target uric acid transport proteins

2.1. Probenecid

Probenecid mainly reduces uric acid reabsorption by inhibiting the activity of URAT1, but it also inhibits the activities of OAT1 and OAT3, which reduces the effect of promoting uric acid excretion. As one of the earliest uricosuric drug used clinically, probenecid offers additional pharmacological effects, such as activating transient receptor potential vanilloid 2 (TRPV2) to exert positive inotropic effects on the heart[2]. Therefore, the role of probenecid in hyperuricemia patients combined with

cardiovascular disease deserves to be further exploratio. A cohort study of elderly gout patients compared cardiovascular risks of probenecid and allopurinol found that probenecid appeared to be more beneficial in reducing the incidence of cardiovascular disease and had better uric acid-lowering efficacy[3], but observational studies are needed to confirm it.

2.2. Benzbromarone

Benzbromarone inhibits the metabolic activity of URAT-1 and reduces renal tubular reabsorption of uric acid. A retrospective cohort study from Taiwan (2003–2015) analyzing asymptomatic hyperuricemia patients aged 20–84 showed that compared with allopurinol, benzbromarone was more effective in reducing the risk of chronic kidney disease[4].Moreover, it performed better in relatively young and healthy gouty patients of renal underexcretion-type (excretion rate < 5.5% and uric acid excretion ≤ 600 mg/day / 1.73m²). [5]

However, due to its low receptor selectivity and hepatotoxicity, it is currently necessary to develop new analogues with stronger efficacy and safety. JNS4, with a low inhibition of other transport proteins, has a superior uric acid - lowering effect in a mouse model of hyperuricemia with good pharmacokinetic properties and low toxicity[6].

2.3. Lesinurad

Lesinurad is a URAT1 inhibitor. Lesinurad has obtained approval in the United States and the European Union for combination use with XOI to treat hyperuricemia patients who have failed to achieve target sUA with monotherapy. Lesinurad is often combined with febuxostat or allopurinol. The CRYSTAL study substantiated the efficacy and safety characteristics regarding combination of lesinurad and febuxostat in treatment[7] ,with no significant increase in hepatic injury and cardiovascular adverse events[8]. Compared with monotherapy, the combination therapy is more likely effective in the lower sUA control and tophus revolution. However, Sriranganathan, MK et al. summarized the studies reported (as of August 28, 2020) on lesinurad for tophus treatment and questioned its efficacy and safety [9]. Therefore, further research is needed to determine its appropriateness for treating patients with gouty tophi. Currently, the FDA has approved Ironwood's combination medication Duzallo for patients with poor response to allopurinol alone. Since lesinurad has low activities in vitro and in vivo but a reliable scaffold structure, it provides a foundation for developing derivatives. One such compound, Thiophenopyrimidine 29, showed a 2-fold increase in lowering sUA activity in vivo by potently inhibiting both URAT1 and GLUT9[10].

2.4. Verinurad

Verinurad, as a derivative of lesinurad, shows promising efficacy and safety and is currently in clinical trials. It is recommended for combination with febuxostat or allopurinol. Two phase II trials showed that although Verinurad can continuously reduce the sUA when used alone, the incidence of renal adverse events is higher than that of placebo group possibly resulting from excessive uric acid excretion[11]. However, combined with allopurinol, it shows good tolerance across races and can effectively reduce sUA and increase uUA excretion [12]. Stack, A. G et al. found that combining verinurad with febuxostat, not only has a better uric acid - lowering effect, but also can reduce albumin-to-creatinine ratios in type II diabetes patients, showing potential renoprotective effects [13]. So verinurad not only offers benefits beyond lowering sUA, but also shows a certain role in treating renal complications, which deserves further research.

2.5. Dotinurad

Dotinurad, developed in Japan in 2018, is a URAT1- selective inhibitor with minimal effects on other uric acid transporters. Kuriyama, S. et al. found that Dotinurad was noninferior to benzbromarone and febuxostat in terms of efficacy in both underexcretion and overproduction types of hyperuricemia. It is also suitable for patients with chronic liver or kidney diseases, only causing mild to moderate disorders[14]. Five Phase II and III clinical trials (in Table 1) confirmed that Dotinurad is effective even in patients with comorbid hypertension, and that no drug interactions were observed between Dotinurad and common antihypertensive drugs such as thiazide diuretics or ARBs[15]. Additionally, Dotinurad can helps lower blood glucose and lipid levels,improve liver and adipose tissue metabolism by inhibiting URAT1 in the heart and liver, thereby slowing down the process of cardiovascular disease and chronic kidney disease[16].

2.6. SGLT2 inhibitors

SGLT2 inhibitors reduce uric acid reabsorption by downregulating URAT1 via the PDZK1 pathway, and increase uric acid secretion by upregulating ABCG2 in the intestine and kidney via the PDZK1, SIRT1 and AMPK pathways. It also directly inhibits uric acid formation to lower sUA. In addition, they have anti-inflammatory, anti - myocardial and metabolic improvement properties[17].Moreover,SGLT2 inhibitors can delay renal fibrosis in hyperuricemic nephropathy by activating the ERRα - OAT1 axis [18].

2.7. SHR4640

SHR4640 is a highly selective URAT1 inhibitor currently in clinical trials. A Phase II trial validated its efficacy of different doses. A total of 362 participants were grouped and given 2.5 mg, 5 mg, or 10 mg of SHR4640； 50 mg of benzbromarone or placebo once daily. Results showed that the 5 mg and 10 mg SHR4640 groups performed better than the benzbromarone group. In terms of the uric acid-lowering effect, SHR4640 were better; in terms of safety, the incidence of adverse events was comparable across groups, without severe events reported. The serum creatinine increasing in the 10mg SHR4640 group was significantly higher compared to other groups, but most changes were transient and reversible[19]. The combination of SHR4640 and febuxostat also showed excellent ability to reduce sUA and good tolerance[20] , making it a promising candidate for future therapies.

2.8. Other drugs still in development

CC18002 is an active compound targeting URAT1. It has been validated that CC18002 exhibits comparable urate-lowering activity to benzbromarone in subacute hyperuricemia mice, without affecting the activity of XOIs[21].It can be further developed as a drug for combination with XOIs.

HP501 is a highly selective URAT1 inhibitor. Clinical trials demonstrated its good tolerability and that the concentration of SUA can be reduced by up to about 50% within the tested dose range. It also has a synergistic effect with febuxostat in lowering uric acid, which indicates the potential for combination[22].Another study conducted on Chinese men with hyperuricemia showed that a dose of 90 mg would achieve the maximum uric acid-lowering effect, providing a reference for future trial designs[23].

Dual-targeting drugs of GLUT9 and URAT1 are also currently under investigation. Compounds such as CDER167, iso-psoralen chalcone derivative 27b, and KPH2f have demonstrated promising efficacy and safety, warranting further research.

Since about two-thirds of uric acid is excreted by the kidneys, and the rest through the intestines

and bile[24].Increasing renal uric acid excretion may cause renal injury,so research on intestinal uric acid transporter proteins and intestinal flora has become a new direction in drug development. Shao ping JIA et al. explored the use of saRNA to activate ABCG2 expression, aiming to enhance uric acid transport in renal and intestinal cells[25]. Zhen ping, Zou et al. used a hyperuricemic mouse model to test the effect of YES301, an E. coli overexpressing the xanthine transporter protein XanQ2. The result indicated that it was as effective as allopurinol but caused fewer adverse effects[26]. Increasing intestinal uric acid excretion through probiotics provides a new strategy for lowering SUA. The approach combining with conventional drugs may offer a solution for refractory hyperuricemia and mitigate the renal injury associated with high doses or prolonged use of uricosuric drugs.

3. Summary and outlook

Current research demonstrates that drugs exhibit significant efficacy in reducing serum uric acid levels in clinical settings. However, these agents are associated with certain adverse effects and risks. Thus, further investigation into their efficacy and safety, particularly in patients with comorbidities, is essential to provide a foundation for personalized treatment strategies. This evidence will support clinicians in making more informed therapeutic decisions. Additionally, with advances in molecular biology and genomics, the development of novel compounds based on traditional agents is underway. The safety, efficacy, and potential benefits of these emerging therapeutics are highly anticipated.

Table 1: Clinic trails of Clinical trials of drugs for hyperuricemia

<table>
<tr><th>Trial</th><th>Design</th><th>Enrollment</th><th>Interventions</th><th>Endpoint/result</th><th>Conclusion</th><th>Duration</th></tr>
<tr><td>NCT01510769</td><td>phase III multicenter, multinational, randomized, double-blind, placebo-controlled</td><td>1. sUA ≥8 mg/dl (not taking urate-lowering therapy) ≥6 mg/dl (taking urate-lowering therapy) 2.≥1 measurable tophus</td><td>screening period: Febuxostat 80 mg once daily and prophylaxis for 3 weeks placebo plus febuxostat 80 mg (N=109), Lesinurad 200 mg plus febuxostat 80 mg (N=106), Lesinurad 400 mg plus febuxostat 80 mg (N=109).</td><td>Primary：the portion of patients with sUA<5 mg/dl at month 6
Secondary: reduction of tophus, etc.
Result：<table><tr><th></th><th>placebo</th><th>Lesinurad 200 mg</th><th>Lesinurad 400 mg</th></tr><tr><td>sUA</td><td>46.8%</td><td>56.6%.</td><td>76.1%</td></tr><tr><td>reduced area</td><td>28.3%</td><td>50.1%</td><td>52.9%</td></tr></table></td><td>The combination of lesinurad and febuxostat is more effective in lowering sUA and reducing the size of tophus</td><td>screening period: 35 days treatment period: 12 months</td></tr>
<tr><td>NCT02344862
NCT02416167
NCT03100318
NCT03372200</td><td rowspan="2">phase II and III</td><td>222 patients</td><td rowspan="2">0.25 - 4mg daily in different groups</td><td rowspan="2">Primary: the proportion of patients with sUA≤6mg/dL
Secondary: blood stress, heart, drug safety, etc.</td><td><6mg/dL:<table><tr><th>2mg</th><th>4mg</th></tr><tr><td>82.8%</td><td>100.0%</td></tr></table></td><td rowspan="2">Dotinurad effectively reduces sUA in hypertensive patients, with higher compliance at the 4mg dose.</td><td>8-14 weeks</td></tr>
<tr><td>NCT03006445</td><td>154 patients</td><td><table><tr><th>2mg</th><th>4mg</th></tr><tr><td>88.7%</td><td>90.5%</td></tr></table></td><td>34 or 58 weeks</td></tr>
</table>

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