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Progress in the Treatment of Primary Biliary Cholangitis

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Abstract: ***Primary biliary cholangitis (PBC) is a chronic, progressive, and rare autoimmune inflammatory disease of the interlobular bile duct, leading to bile stasis and secondary damage to liver cells. Ursodeoxycholic acid (UDCA) is currently the only drug approved for the treatment of PBC, but about 40% of patients still have poor response to UDCA treatment. Based on this situation, research on the treatment of PBC has been continuously deepened in recent years. This article reviews the progress of PBC treatment.***

Keywords: Primary biliary cholangitis; Treatment; Ursodeoxycholic acid; Obeticolic acid; Betrate drugs.

1. Ursodeoxycholic Acid

UDCA, as a secondary bile acid, was the only first-line drug approved by the US Food and Drug Administration (FDA) for the treatment of PBC before obeticolic acid was approved for use in PBC in 2016. The therapeutic effect of UDCA is currently not fully understood, but its factors of action include protection of liver cells and bile duct cells, as well as promotion of hydrophilic bile acid pool and hydrophobic bile acid replacement [1]. Once diagnosed with PBC, a single dose standard treatment regimen of 13-15mg/kg/d should be given, and long-term use is required. If it cannot be tolerated, it can be taken in divided doses. Relevant evidence suggests that without any clinical intervention after diagnosis of PBC, liver histological staging can progress to one stage every 1.5 years [2]. The first clinical randomized controlled trial observed that serum biochemical indicators in 73 PBC patients significantly decreased after 2 years of regular treatment with UDCA doses (13-15mg/kg/d) compared to the placebo group. Meanwhile, UDCA can improve cerebral ischemia and hypoxia in PBC patients and regulate gut microbiota. Duszynski et al. found using near-infrared spectroscopy that elevated levels of cerebral hemoglobin, cerebral hypoxia, and changes in cerebral vascular activity were present in some PBC patients. These conditions were partially reversed in biochemical responders treated with UDCA.

2. Farnesol X Receptor (FXR) Activator

FXR is a highly expressed nuclear receptor in intestinal and liver cells, which regulates lipid metabolism, maintains the homeostasis of the bile acid environment, and can also regulate the metabolism of sugars and amino acids. In addition, FXR activation can promote insulin sensitivity, thereby reducing hepatic gluconeogenesis and glycogen breakdown, and exerting a protective effect on

liver cells. Based on this mechanism of action, FXR agonists can be used for the treatment of PBC.

Obeticolic acid (OCA) is a semi synthetic bile acid derivative derived from the naturally occurring human bile acid chenodeoxycholic acid. It exhibits high selectivity towards FXR and regulates bile acid homeostasis by modulating genes involved in bile acid synthesis, absorption, uptake, and transport. The development of OCA has brought new hope to PBC patients with poor response to UDCA treatment, but compared with UDCA monotherapy for PBC, the addition of OCA results in more common and dose-dependent itching symptoms. Additionally, its high treatment cost may also limit its application in PBC patients.

3. Peroxisome Proliferator Activated Receptor Activator

Studies have shown that beta drugs, as agonists of nuclear receptor peroxidase proliferator activated receptor alpha, can regulate bile acid metabolism. Many small-scale clinical observational studies have evaluated the potential efficacy of beta drugs in PBC, with the majority coming from Japan. Related experiments have shown that the combination of UDCA and fenofibrate can significantly improve liver biochemical indicators and triglyceride levels in PBC patients, but the relief of skin itching is not significant. Therefore, attention should be paid to the occurrence of adverse reactions during long-term combination therapy. At present, benzocaine has been used as a second-line drug for PBC treatment in Japan. The American Association for the Study of the Liver and the European Association for the Study of the Liver (EASL) consider beta drugs as an alternative treatment for patients with poor UDCA response, but the British Gastrointestinal Association has not made this recommendation.

4. Immunosuppressants

Immunosuppressants are used to treat PBC patients while also suppressing the normal immune system. Research has shown that adverse events during the treatment of PBC with azathioprine cannot be ignored, such as rash, severe diarrhea, and bone marrow suppression. However, clinical symptoms such as itching have not been significantly improved, and the benefits outweigh the risks. A meta-analysis showed that colchicine did not improve mortality and liver transplant rates in PBC patients compared to the placebo group. A meta-analysis compared 370 patients using methotrexate with a placebo group, and the results showed that although methotrexate can alleviate clinical symptoms of itching, it has no effect on improving patients' biochemical indicators and increasing survival rates. A large-scale randomized, double-blind comparative experiment between methotrexate combined with UDCA and placebo combined with UDCA was terminated prematurely due to ineffectiveness.

5. Biological Agents

Although the etiology of PBC is currently unclear, abnormalities in cellular and humoral immunity have been confirmed to be involved in the occurrence of PBC. In recent years, research on emerging biologics has gradually emerged based on the possible causes of PBC. Rituximab is a chimeric mouse/human monoclonal antibody targeting the CD20 antigen on the surface of normal and malignant B cells and their precursors. It selectively depletes B cells through complement dependent and antibody dependent, cell-mediated cytotoxicity. Preliminary experimental data suggests that rituximab is beneficial for patients with autoimmune hepatitis. In a small study targeting PBC patients with poor UDCA response, it was found to reduce serum levels of AMA, ALP, and IgM. Although the above results indicate good tolerance to rituximab in PBC patients, the efficacy is limited, and therefore the use of this drug in PBC patients is not recommended. Further research has found that during the

treatment of PBC with rituximab, some patients may experience complications of inflammatory bowel disease, which is a noteworthy adverse reaction.

6. Budesonide

As a synthetic steroid, budesonide's high first pass metabolism in the liver limits its systemic side effects. The experimental results indicate that budesonide is associated with improvements in liver chemistry and histology. In a 3-year clinical trial, it was found that the combination therapy group of budesonide (6mg/d) and standard dose UDCA reduced liver fibrosis by 25%, while the UDCA monotherapy group increased it by 70%. In addition, two other small studies also had similar conclusions, indicating that combination therapy can improve liver histology. Another study found that only ALP slightly decreased after 1 year of treatment with budesonide, while the Mayo score prognostic index significantly increased, bone mass significantly decreased, and for advanced patients, the incidence of portal vein thrombosis increased.

7. Summary and Prospect

At present, all patients diagnosed with PBC should receive UDCA treatment and regularly monitor biochemical indicators. People are full of expectations for emerging drugs for treating PBC, and a large amount of research, including different molecules, is underway, with results expected to be announced in the coming years. In summary, through continuous understanding and exploration of PBC, many targets derived from a deeper understanding of the pathophysiology of the disease have been discovered, providing different new treatment methods that are currently under evaluation.

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