Research Progress on the Role of Atorvastatin in the Treatment of Coronary Heart Disease

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Abstract: The basic pathological change of coronary heart disease is atherosclerosis, and the main risk factor is abnormal lipid metabolism. Atorvastatin is the most commonly used lipid-lowering drug. This paper mainly describes the research progress of atorvastatin in terms of pharmacological effects, dosing and deficiencies.

Keywords: Atorvastatin; Coronary Heart Disease; Treatment

1. Coronary heart disease overview

Coronary atherosclerotic heart disease (CHD) is a disease in which atherosclerosis of the coronary arteries causes luminal narrowing or occlusion leading to myocardial ischemia and hypoxia, followed by myocardial necrosis, resulting in chest pain, angina and other discomfort, and is one of the more common and urgent types of cardiovascular diseases. If not treated in time, it can have serious consequences, such as heart failure, various arrhythmias, and even death. Studies have shown that this disease is caused by multiple factors, such as smoking,hypertension,hyperglycemia, hyperlipidemia, age, and gender. Among them, abnormal lipid metabolism is its basic pathological factor and the most important risk factor. It is now generally accepted that cholesterol,triglycerides(TG), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) and Lp (α) are involved in the progression of atherosclerosis. The basic pathological changes are lipid deposition under the intima to form lipid pattern, and then fibrous tissue proliferation to cover the lipid surface to form a fibrous cap, and smooth muscle proliferation in the intima to cause lumen thickening and narrowing, forming a stable angina. If the plaque ruptures, a thrombus will be formed, which can cause acute coronary events and serious harm. Therefore, lipid lowering is the core treatment. Clinically used lipid-lowering drugs can be divided into those that mainly lower TC and LDL, those that mainly lower TG and VLDL, and those that lower LP(α), etc. Atorvastatin is the former. Current research on atorvastatin focuses on the pharmacological effects of the drug, the efficacy of patients' blood lipids, cardiac function and other factors, and the comparison of the lipid-lowering effect at different doses, as well as its side effects and shortcomings.

2. Pharmacological effects of atorvastatin

Statins are also known as hydroxymethylglutarate monoacyl coenzyme A (HMG-CoA) reductase inhibitors. Among the statins, atorvastatin is the most commonly used. Its main effect is to lower blood lipids, followed by non-lipid-regulating effects. It is widely used in clinical practice because of its significant effect and low side effects.

2.1 Hypolipidemic effect of atorvastatin

Atorvastatin is the most commonly used lipid-lowering drug in clinical practice and has significant lipid-regulating effects. Jinlong Zhang proposed in 2022 that it can reduce blood viscosity, improve hemodynamics and thus prevent thrombosis, and is an important component of secondary prevention after PCI. At therapeutic doses, it primarily lowers

cholesterol and low-density lipoprotein (LDL), and to a lesser extent triglycerides (TG), with a slight increase in high-density lipoprotein (HDL). The effect of the drug starts in about two weeks and reaches a peak in 4-6 weeks, requiring long-term use. Cholesterol is mainly synthesized in the liver, and the key enzyme for synthesis is HMG-CoA reductase. HMG-CoA reductase is the target of atorvastatin, because the drug or its metabolites are similar in spatial structure to the substrate HMG-CoA and have a much greater affinity for the reductase than HMG-CoA, so they can compete with the substrate for inhibition, thus impeding cholesterol synthesis. Cholesterol in the blood is mainly transported by low-density lipoprotein (LDL) as a carrier (LDL-C), mediated into the cell with the help of LDL receptors on the liver cell membrane. When plasma cholesterol is lowered, the LDL receptor on the surface of hepatocytes is increased or its activity is enhanced through a negative feedback mechanism to lower LDL. LDL is mainly converted from VLDL and therefore causes a secondary acceleration of VLDL metabolism.VLDL and LDL have similar physiological functions, i.e. transport of endogenous cholesterol and triacylglycerol (TG), which also leads to a further decrease in TG. HDL is synthesized primarily by the liver and small intestine and, unlike LDL and VLDL, is responsible for transporting cholesterol from extrahepatic tissue cells. The first step is binding to the cell surface, and some studies suggest that this process may be mediated by HDL receptors, but does not enter the cell, but rather by some sort of signaling that moves intracellular cholesterol to the cell surface and then into HDL. The increase in HDL may be an indirect result of the decrease in VLDL, as the cholesterol in the body is continuously transferred from celiac (CM) and VLDL to HDL through a series of conversions after the release of neonatal HDL into the blood. In addition, small and dense low-density lipoprotein cholesterol (sdLDL-C) is also involved in the development process of AS. There are few reports related to the effect of atorvastatin on the expression level of sdLDL-C. Wanjiang Tan studied the expression level of this substance in patients with coronary artery disease and the effect of the drug after administration in 2019. His study showed that sdLDL-C was an independent predictor of the development of cardiovascular disease and that atorvastatin may alter sdLDL-C levels and thus have a positive effect on disease regression. Numerous clinical trials have shown that postoperative use of atorvastatin in patients with coronary artery disease or acute infarction significantly decreased serum TC, TG and LDL-C and slightly increased HDL, while patients' LVEF increased ($P<0.05$), significantly reducing patient mortality. Therefore, atorvastatin can play a role in endothelial protection, delaying atherosclerosis, protecting target organs and improving prognosis. This drug can be used to prevent and treat a variety of atherosclerotic cardiovascular diseases, such as acute coronary syndrome (ACS), stable angina pectoris, and post-PCI.

2.2 Non-lipid-modulating effects of atorvastatin

A large body of clinical evidence suggests that CHD occurs not only due to lipid accumulation, but also due to myocardial damage and vascular endothelial cell damage from inflammatory responses and cellular damage from oxidative substances. For example, Zhang ZG et al. mentioned in 2017 that PCI is often accompanied by some myocardial injury, and that vascular endothelial system injury and inflammatory response play an important role in adverse cardiovascular events after PCI. Other studies such as macrophages engulf LDL-C and oxidize it during endothelial injury, forming peroxides and superoxide ions, while atorvastatin exerts antioxidant effects by scavenging oxygen free radicals. Moreover, macrophages can secrete many inflammatory mediators, such as PDGF, FGF, TNF-α, IL-1, etc. Liu Suge et al. mentioned in 2019 that TNF-α inhibits myocardial contraction and mediates ventricular remodeling; excessive hs-CRP leads to coagulation system activation and vascular endothelial injury; Hcy damages endothelial cells and promotes smooth muscle proliferation. The above inflammatory substances decreased significantly after treatment with atorvastatin. Atorvastatin also attenuates the inflammatory response by inhibiting the adhesion and secretion function of monocytes-macrophages. Wang Shan mentioned in 2019 that serum C-reactive protein may be an independent predictor of coronary heart disease occurrence, and IL-6 may also be involved. The clinical trials observed that these two indicators were significantly lower with atorvastatin than before

the use of the drug. Cao A. et al. proposed in 2017 that hs-CRP is an important indicator of the level of inflammation in the response organism and the level is positively correlated with the degree of lesions. The level of this indicator decreased significantly after one month of oral atorvastatin. In conclusion, a number of studies have shown that atorvastatin is effective in suppressing the inflammatory response, improving cardiac function and preventing vascular and ventricular remodeling in patients.

3. Comparison of the efficacy of atorvastatin at different doses

There are more clinical comparative studies on the therapeutic effects of conventional and higher doses of atorvastatin. Most of them are based on 20 mg/d as the conventional dose and 40 mg/d as the higher or moderate dose. Zhao Pei et al. noted in 2017 that Europeans and Americans are more tolerant of atorvastatin than Asians, and given that China is a large country with liver disease, patients are not easily given intensive treatment with atorvastatin, usually not at a dose of 80 mg/d. Its clinical study showed that atorvastatin lowered TC, TG, LDL-C and hs-CRP in both the experimental group (40 mg/d) and the control group (20 mg/d), but the modulatory and anti-inflammatory effects were more pronounced in the experimental group than in the control group ($P<0.05$), with fewer side effects and no significant differences. Liu, Bin and Su, Hailong in 2022 suggested that there is still a significant proportion of patients with suboptimal doses of statin lipid modulation using conventional doses. Their study used the same approach and came to similar conclusions: serum CDF-15 and PTX3 levels were reduced in both groups and were more significant ($P<0.05$) in the observation group (40 mg/d) than in the control group (20 mg/d), with fewer side effects and no significant differences. They also compared the patients' left heart function, LVEF was significantly higher, LVESD, LVEDD and plasma NT-proBNP levels were significantly lower after treatment, and the observation group was significantly better than the control group. Regarding left heart function, Liu Suge et al. performed a similar clinical trial and showed that the magnitude of changes in LVESD, LVEDD and NT-proBNP in the high-dose (40mg/d) treatment group was significantly greater than that in the low-dose (20 mg/d) group, and LVEF was greater than that in the low-dose group. The same experiment was done by Zhang Lianfang, Mu Mian, Liu Lihua and others, and the conclusions obtained were consistent. All of the above results indicate that treatment with 40 mg/d atorvastatin after PCI in patients with coronary artery disease is safe and effective, with significant lipid-lowering and anti-inflammatory effects compared to 20 mg. However, this option is not yet widespread, and its specific efficacy and risk level need to be further studied. In addition, Huali Wang studied the therapeutic effect of small doses (10 mg/d) in 2022. The results showed that the patients in the small dose group (10 mg/d) had lower cardiac function indexes and higher NT-proBNP levels, with better clinical outcomes than the high dose group (40 mg/d). It was concluded that low-dose atorvastatin therapy is of high value in elderly patients with chronic heart failure in coronary artery disease.

4. Side effects, shortcomings and outlook of atorvastatin

4.1 Side effects

In the above clinical observation experiments, some patients experienced temporary reactions such as gastrointestinal reactions, skin flushing, headache and insomnia. A small number of people have asymptomatic transaminase elevation, indicating that the drug has a certain degree of hepatotoxicity, regular liver function tests are required during the use of the drug, and people with a history of liver disease should use with caution. This class of drugs can also cause muscle adverse reactions, manifested as myalgia, myositis and rhabdomyolysis, and those with muscle discomfort or weakness need to test for creatine kinase (CK) and reduce or discontinue the drug if necessary. However, overall, atorvastatin has few and mild adverse effects, a wide range of safety, and can reduce overall mortality, making it a first-line agent for lipid lowering.

4.2 Drawbacks

Atorvastatin has some hepatotoxicity, but the overall side effects are small and the clinical application is less restricted. Wei Gaohui et al. concluded that adverse effects of statin therapy are more likely to occur in elderly patients (over 80 years of age). Choruo Zhang and Feilong Dai proposed in 2022 that atorvastatin is orally administered via gastric mucosal clearance and hepatic first-pass elimination effect with low systemic utilization, and its use alone may prolong the therapeutic cycle and limit the clinical application, so it was proposed to be combined with trimetazidine. Trimetazidine has myocardial protective effects and reduces oxidative damage. Combined with atorvastatin, it can play a synergistic role to improve myocardial cell metabolism, restore normal blood supply to the myocardium and improve cardiac function. Zhang Churuo and Dai Feilong divided the patients into the combined trimetazidine group and the atorvastatin alone group to observe the efficacy of the two groups in the experiment. The study showed that LVEF, LVSD, and ET-1 were higher in the combination group than in the atorvastatin group, and LVEDD, NO, TC, and LDL-C were lower than in the atorvastatin group ($P<0.05$), suggesting that the combination was more effective than atorvastatin alone. And in terms of safety, the combination of drugs will not increase the adverse drug reactions, high safety. The same study was done by Yang Jun et al. in 2019, which noted that trimetazidine has a relatively long onset of action after dosing, and that the combination with atorvastatin can effectively take advantage of both to achieve a fast and long-lasting onset of action. In addition, Bin Liu and Hailong Su in 2022 mentioned a variety of novel biomarkers, such as PCSK9 and Sortilin. PCSK9 is a preprotein convertase that degrades the LDL-C receptor on the surface of hepatocytes, decreases the metabolism of LDL by the liver, and causes elevation of peripheral LDL. Sortilin is a lysosomal sorting receptor that induces VLDL synthesis and release, promotes LDL-C elevation, and accelerates LDLR degradation by interacting with PCSK9. They detected an increase in PCSK9 levels after treatment with atorvastatin in the trial, which is one of the reasons for its limiting lipid-regulating effect. Therefore, some investigators have proposed that the use of conventional doses of atorvastatin in combination with PCSK9 inhibitors. There have also been many recent studies on the effects of statins on glucose metabolism. Liu Sining and Tian Xuefeng et al. showed that fasting blood glucose and Hb1Ac levels increased and fasting insulin levels decreased in the atorvastatin group 12 weeks after treatment compared with those before treatment ($P<0.05$), indicating that long-term statin use may have an effect on glucose metabolism. Their study also showed that regular doses of atorvastatin did not increase the risk of new-onset glucose metabolism abnormalities in patients with ACS, but that moderate doses increased. If you need to take atorvastatin for a long time, you need to test the patient's glucose metabolism first, and use the drug to lower blood sugar at the same time. In contrast, pitavastatin has little effect on non-diabetic CHD glucose metabolism and does not increase the risk of new-onset diabetes in patients with CHD. In addition, atorvastatin has limited HDL-elevating effects and is weaker than pitavastatin. Pitavastatin is also less hepatotoxic than atorvastatin and has a better clinical application.

4.3 Conclusion and Outlook

CHD has become a hot disease of global concern. Atorvastatin is the first choice of clinical lipid-lowering drug, with significant lipid-lowering effect, small side effects and high safety. There are certain shortcomings and better treatment options are being investigated clinically. Such as coadministration of trimetazidine, PCSK9 inhibitors, and switching to other statins. In 2017, a new domestic self-developed lipid-lowering drug, PCSK9 inhibitor, has been qualified for clinical trials and will surely play an important role.

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