

Progress in the application of ezetimibe combined with statins in cardiovascular and cerebrovascular diseases

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Abstract: As one of the main risk factors of cardiovascular and cerebrovascular diseases, hyperlipidemia has a great impact on the quality of life of patients. Statins, as first-line lipid-lowering drugs, have been clinically proven, but for high-risk patients with cardiovascular and cerebrovascular diseases caused by hyperlipidemia, the optimal lipid-lowering effect cannot be achieved by increasing the basic dosage. Therefore, the therapeutic effect of the new drug Ezetimibe combined with statins is superior to that of single drug. In order to better cure this disease, a large number of relevant literatures at home and abroad were searched. The pharmacological mechanism of ezetimibe, the new way of combining with statins, the research status and advantages of cardiovascular and cerebrovascular diseases were expounded, which provided reference for the cure of cardiovascular and cerebrovascular diseases.

Keywords: Ezetimibe; Statins; Cardiovascular and cerebrovascular diseases; Reduce fat and stabilize spots

1. Introduction

In recent years, with the improvement of living standards, the number of patients with high cholesterol and blood lipid is increasing, resulting in a sharp increase in the risk of cardiovascular and cerebrovascular diseases. Cerebrovascular disease (CVD) is one of the common diseases in the middle-aged and elderly people, which has a high incidence, disability rate, and mortality [1,2]. Its clinical manifestations are usually chest tightness, shortness of breath, and compressional retrosternal pain. Hemiplegia, hemiblinidness, hemiplegia, language impairment and other related symptoms. Arteriosclerosis caused by hyperlipidemia has become the main pathophysiological mechanism of the disease, and it has become necessary to control abnormal blood lipids in patients with cardiovascular and cerebrovascular diseases. Statins, as the cornerstone of lipid-lowering therapy [3], have been widely used in clinical work. However, in recent years, with the recurrence of CVD patients, statins alone cannot achieve significant lipid-lowering effects on the basis of increasing dosage, and to some extent, they increase the occurrence of adverse reactions [4,5]. The guidelines suggest that statin combined with non-statin therapy should be considered for these patients [6]. Studies [7] have reported that ezetimibe combined with simvastatin in the treatment of acute coronary syndrome, compared with simvastatin alone, is more effective and reduces the risk of cardiovascular events. Based on ezetimibe combined with statins, this paper makes a comprehensive analysis and prospect in the clinical intervention and treatment of CVD patients, providing a new idea for clinical treatment.

2. Pharmacological mechanism of Ezetimibe

Ezeimibe is a novel selective cholesterol absorption inhibitor distributed on the brush edge of the small intestine. Through the NPC1L1 transporter, Ezeimibe selectively inhibits dietary and bile cholesterol, reduces intestinal cholesterol transport to the liver, reduces hepatic cholesterol storage, and increases blood cholesterol clearance. Transintestinal transport leads to reduced TC storage and increased liver low-density lipoprotein receptor synthesis [8,9], thereby reducing LDL-C levels, independent of diet. The main effect of imeczebe is to reduce total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C). AgarwalaA et al. [10] found that ezetimibe has been shown to reduce

LDL-C levels by 15-25% from baseline.

3. New approach to Ezetimibe in combination with statins

Ezetimibe is an exogenous cholesterol absorption inhibitor that does not inhibit liver cholesterol synthesis nor increase bile acid secretion. This clear mechanism of action is a favorable complement to the action of statins, namely 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors. HMG-CoA competitively inhibits endogenous cholesterol synthesis rate-limiting enzyme^[11], blocks intracellular hydroxyvalerate metabolic pathway, and reduces intracellular cholesterol synthesis. In this way, the number and activity of low-density lipoprotein (LDL) receptors on the surface of cell membrane can be stimulated to increase, and the serum cholesterol clearance can be increased and the level can be reduced, thus lowering cholesterol, especially LDL-C^[12].

The main pathological factors of cardiovascular and cerebrovascular diseases are lumen stenosis caused by atherosclerosis, which leads to a series of related symptoms. Treatment and prevention of arterial plaque become a risk event to reduce cardiovascular and cerebrovascular diseases. According to relevant studies^[13,14], the combination of ezetimibe and statin utilization mechanism is complementary and effective, and the combination of Ezetimibe and Statin can be synergistic and significantly reduce the risk of cardiovascular and cerebrovascular events^[15]. Therefore, to seek a new idea of lipid-lowering drugs, statin combined with ezetimibe is expected to further improve the standard rate of LDL-C treatment, so as to further treat and prevent the recurrence risk of cardiovascular and cerebrovascular disease events.

4. Clinical application in cardiovascular diseases

At present, there are various risk factors for cardiovascular diseases. Hyperlipidemia and atherosclerosis cause related diseases by blocking arteries, and lipid reduction and plaque stabilization are particularly critical for the prevention and treatment of cardiovascular diseases. The following is the description of cardiovascular diseases: acute coronary syndrome, angina combined with arrhythmia, and prevention and treatment after PCI.

4.1. Acute coronary syndrome

Acute coronary syndrome ACS is a group of syndromes caused by acute myocardial ischemia, including unstable angina pectoris, non-ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction. It refers to the rupture of unstable plaques, the loss of emboli secondary to erosion, and the blockage of coronary arteries. Acute lesions causing myocardial cell ischemia, hypoxic necrosis^[16]. Clinically, the main manifestations are radiation pain in the anterior chest and posterior back, irritability, sweating, fear, chest tightness or a sense of near-death, which often lead to arrhythmia, embolism and other complications. The condition is more serious and life-threatening.

Feng Yiqing et al.^[17] observed the clinical efficacy analysis and drug safety of patients with acute myocardial infarction of coronary heart disease treated with ezetimibe combined with rosuvastatin, and found that the effective rate of the observation group (93.33%) was significantly higher than that of the control group (77.78%), $P < 0.05$. After treatment, triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) were improved compared with before treatment, and the differences were statistically significant ($P < 0.01$). There was no significant difference in the incidence of adverse reactions between the two groups ($P > 0.05$). Mu Yu et al.^[18] analyzed 18,144 patients with acute coronary syndrome. The experimental group was given oral ezetimibe and simvastatin, and the control group was given oral simvastatin. The median follow-up time was 6 years. The trial demonstrated that simvastatin combined with ezetimibe was more effective in reducing LDL-C levels and reducing the risk of residual cardiovascular events without increasing adverse reactions. Therefore, for patients with acute coronary syndrome, combined lipid-lowering has a more ideal single drug effect, reducing the risk of recurrence of events, and providing a new diagnosis and treatment idea for clinical treatment.

4.2. Angina pectoris with cardiac insufficiency

Angina pectoris is caused by coronary artery atherosclerosis, myocardial ischemia and increased

oxygen consumption, mainly paroxysmal chest pain or suffocation in the precardiac area, acute attack of angina, inducing various arrhythmias and aggravating cardiac function load, such as atrial fibrillation, etc. [19]. Control of risk factors, for angina attack is the key.

Gao Yongxing [20] studied the clinical efficacy of ezetimibe combined with statins in the intensive lipid-lowering treatment of patients with stable angina pectoris combined with atrial fibrillation, and selected 65 patients with stable angina pectoris combined with atrial fibrillation. Compared with the statin group, combined lipid-lowering can further reduce LDL-C, with better clinical effect and safety worth promoting. Zheng Fangfang [21] studied the effects of atorvastatin combined with Ezetimibe on cardiac function and long-term prognosis of patients with coronary heart failure, and selected 120 patients with coronary heart failure as research objects. After 1 month of treatment, the left ventricular end-systolic radius (LVESD), left ventricular end-diastolic diameter (LVEDD) and left ventricular ejection fraction (LVEF) in both groups were lower than those before 1 day of treatment ($P < 0.05$) and was higher ($P < 0.05$), LVESD and LVEDD of the observation group were lower than those of the control group ($P < 0.05$), and LVEF of the observation group was higher than that of the control group ($P < 0.05$). The total effective rate of the observation group [96.67% (58/60)] was higher than that of the control group [83.33% (50/60)], and the difference was statistically significant ($P < 0.05$). There was no significant difference in the readmission rate and fatality rate at 1 and 3 years after treatment between the observation group and the control group ($P > 0.05$). Therefore, the combination of ezetimibe and statins with lipid-lowering therapy has certain significance in improving patients' cardiac function and reducing the risk of recurrent arrhythmia, so as to improve clinical efficacy.

4.3. Long-term prognosis after percutaneous coronary intervention (PCI)

As an extremely high risk group in the risk stratification of coronary heart disease after PCI, lipid reduction is effective if serum low density lipoprotein (LDL-C) is reduced to ≤ 1.80 mmol or LDL-C is decreased by $\geq 50\%$ [22], and clinical benefits are achieved. Statin therapy has limitations, and the optimal goal of lipid reduction still cannot be achieved under the premise of increasing dose. Therefore, combined lipid reduction provides a possibility for the treatment of patients after PCI.

Lin H et al. [23] evaluated the short-term effects of combined treatment with ezetimibe and simvastatin on the expression levels of LDL-C, TG and hs-CRP in patients undergoing percutaneous coronary intervention. 57 patients with percutaneous coronary intervention were selected. LDL-C and TG were significantly decreased in the observation group after administration ($P < 0.01$), while no significant changes were observed in the control group ($P > 0.05$). After treatment, LDL-C and TG in observation group decreased significantly compared with control group (-27.2% vs -14.6%, $P < 0.05$). The results were (69% vs 28.9%, $P < 0.05$) and (47.6% vs 13.2% $P < 0.05$), respectively. There were no adverse reactions such as hepatorenal toxicity and myopathy during the treatment. Feng Xinyu et al. [24] investigated the effects of different lipid-lowering programs on blood lipid and safety after percutaneous coronary intervention (PCI). After treatment, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and oxidized hyposensitive lipoprotein cholesterol (oxLDL-C) of patients were investigated. The levels of oxLDL-C/TC, oxLDL-C/LDL-C and oxLDL-C/HDL-C were significantly lower than before treatment, with statistical significance (all $P < 0.05$); The reduction of the above lipid indexes in the combination group was greater than that in the control group, the difference was statistically significant (all $P < 0.05$). Therefore, according to clinical data analysis, ezetimibe combined with statins has a relatively ideal effect of regulating lipids and stabilizing plaques in patients after PCI, which provides a good diagnosis and treatment plan for reducing the risk of recurrence of events.

5. Clinical application in cerebrovascular diseases

Cerebrovascular diseases occur in the cerebral vessels, mainly due to the related diseases caused by intracranial blood flow disorders. Hyperlipidemia has become one of the main factors in the pathogenesis, especially triglyceride (TG), total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C), which are the key factors in the pathogenesis [24]. Therefore, lipid-lowering treatment is particularly critical for the prevention of diseases. The prevention and treatment of cerebrovascular related diseases such as ischemic stroke, transient ischemic attack and amyloid cerebrovascular disease were expounded.

5.1. Ischemic stroke

Various cerebrovascular diseases cause local cerebral blood supply disorders, leading to local cerebral tissue ischemia, hypoxia, necrosis, and neurological function defects, which is a kind of clinical syndrome, which will seriously affect patients' quality of life [25]. Intracranial atherosclerosis and plaque blocking corresponding blood vessels are the common causes [26]. Its common clinical manifestations are hemisensory disorders, hemiplegia, poor speech, dysphagia and other symptoms, its onset is urgent, save ischemic penumbra, avoid or reduce primary brain injury, is the most fundamental goal of acute cerebral infarction treatment, "time is the brain", for patients with indications, should try to implement reperfusion therapy as early as possible.

Tan Zhongbing et al. [27] observed the efficacy of ezetimibe combined with lovastatin in the treatment of acute cerebral infarction and the effects on carotid intima-media thickness (IMT), lipid levels and serum inflammatory factors. After 3 months of treatment, the total effective rate of the study group (92.45%) was significantly higher than that of the control group (77.36%) ($P < 0.05$). After treatment, total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), carotid IMT, hs-CRP, TNF- α and IL-6 were significantly lower than those of the control group. After treatment, high density lipoprotein cholesterol (HDL-C) was higher than that of the control group, which confirmed that ezetimibe combined with lovastatin can improve the clinical efficacy, significantly reduce the levels of carotid IMT and inflammatory factors, and has good safety. Li et al. [28] explored the effects of intensive lipid-lowering regimen on neurological impairment, blood lipid and Vaspin levels in patients with acute cerebral infarction complicated with hypertension and dyslipidemia. NIHSS score, mRS Score and ADL-BI score in the intervention group were significantly better than those in the control group after treatment ($P < 0.05$). The blood pressure and blood lipid levels of the intervention group after treatment were significantly higher than those of the control group and before treatment ($P < 0.05$), the TNF- α and IL-6 levels of the combination group after treatment were significantly lower than those of the control group and before treatment ($P < 0.05$), and the Vaspin level of the intervention group after treatment was significantly higher than that of the control group and before treatment ($P < 0.05$). Wang Hailun [29] showed basically the same results on the analysis of the efficacy of atorvastatin combined with ezetimibe in patients with acute ischemic stroke. Therefore, it is confirmed that intensive lipid lowering regimen can effectively protect the damaged nerve function, improve the quality of life, improve blood pressure and lipid levels in patients with acute cerebral infarction.

5.2. Transient ischemic attack (TIA)

TIA is a transient neurological deficit caused by local cerebral or retinal ischemia. The clinical symptoms are generally less than 1 hour and the longest is less than 24 hours, and there is no evidence of the responsible lesion. The main factors causing TIA are atherosclerosis and artery stenosis [30]. TIA is an emergency, and the high-risk period of stroke is within 2 or 7 days after the onset of TIA. Emergency evaluation and intervention of patients can reduce the occurrence of stroke [31]. Sun Youli et al. [32] investigated the effects of ezetimibe assisted intensive lipid-regulation on blood lipid and carotid atherosclerotic plaque in patients with transient ischemic attack. After treatment, the levels of TC and LDL-C in the study group were lower than those in the control group, the difference was statistically significant ($P < 0.05$). After intensive lipid regulation in the study group, the maximum area of carotid artery plaque was (16.79 ± 2.03) mm², which was significantly smaller than that before treatment (22.72 ± 2.01) mm², the difference was statistically significant ($P < 0.05$). In the secondary prevention of TIA, Lei Yang et al. [33], for patients with TIA with intracranial vessels, carotid arteries, aortic arch or coronary atherosclerosis, low density lipoprotein cholesterol (LDL-C) can be reduced to < 1.8 mmol.L⁻¹ by using statins alone or combined with ezetimibe. Through observation, it was found that combined medication had a good preventive effect on improving cerebrovascular diseases with dyslipidemia, greatly preventing the incidence of cerebrovascular diseases, and was ideal for improving the prognosis of patients. Therefore, clinical trials have confirmed that ezetimibe combined with statins can further reduce cholesterol and reduce atherosclerotic plaque with fewer adverse reactions, which can bring clinical benefits to TIA patients.

6. Advantages and limitations of ezetimibe

Although ezetimibe has been used clinically as a therapeutic and prophylactic agent against hyperlipidemic CVD disease, it has been in clinical use for a short time compared with statins. However, its lipid-lowering effect is not inferior to that of statins, and the combined application has a

more prominent effect than single drug, which has been confirmed in relevant foreign literature [34]. NußbaumerB et al. [35] in patients with acute coronary syndrome, statins combined with Ezetimibe can significantly reduce the risk of cardiovascular events compared with statins alone. Therefore, the advantages of ezetimibe combined with statins are critical for clinical treatment.

6.1. The advantages of Ezetimibe include

According to a large number of relevant foreign literatures [36,37], ezetimibe has the following advantages in the treatment of cardiovascular and cerebrovascular diseases: (1) In renal insufficiency, mild liver insufficiency, the elderly do not need to adjust the dose to achieve lipid lowering effect. (2) It has no effect on common CYP-450 metabolic enzyme drugs. (3) There was no significant effect on the absorption of other fat soluble substances. (4) The addition of ezetimibe to statin therapy has been observed to bring net benefits and improved clinical outcomes, especially in patients with significantly increased risk of atherosclerotic cardiovascular disease and elevated LDL cholesterol levels.

6.2. The limiting point of ezetimibe

Many foreign scholars have stated caution and limitations in the treatment of blood lipid with ezetimibe [38]. These caution and limitations [39,40] are reflected in: (1) The expression of NPC1L1 transporter in animal liver is relatively low, which is different from that in human liver. This limitation of animal model needs to be further confirmed clinically. (2) Ezetimibe can selectively inhibit intestinal cholesterol and precipitate intestinal toxicity in a dose-dependent manner. This limitation may cause intestinal injury diseases, which requires caution.

7. Summary and outlook

In conclusion, ezetimibe combined with statins has a prominent effect in the treatment and prevention of cardiovascular and cerebrovascular diseases caused by hyperlipidemia. The combination of lipid lowering breaks the previous goal of lipid lowering that cannot be achieved with statins alone, provides a good treatment plan for clinical diagnosis and treatment, and greatly reduces the risk of recurrence of cardiovascular and cerebrovascular events. However, some scholars have pointed out [41] that although combined drug use has achieved certain achievements in lipid lowering, its safety and overall morbidity are still not well controlled, and the target mechanism and quantitative indicators of combined drug use are still problems that need to be solved. Therefore, in order to make more patients better and safer to take medicine, we still need to explore more.

However, at present, ezetimibe combined with lipid-lowering drugs have not been applied well in clinic, which may be related to drug price, patient compliance, drug development time, etc. Therefore, we should further apply the drugs in clinic, do long-term follow-up, so as to benefit more patients with cardiovascular and cerebrovascular diseases and improve more ideas for clinicians.

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