Clinical study of Repatha: it does not affect patients' cognitive function and significantly reduce blood lipid and prevent coronary atherosclerosis

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Abstract. Hyperlipidemia has always been one of the serious factors endangering human health. It is a high-risk factor for coronary heart disease, myocardial infarction, cerebral infarction and other diseases. Blood lipid management is very important for the control of cardiovascular and cerebrovascular diseases. Repatha, as a new type of hypolipidemic drug, has shown good effects and no serious adverse reactions in clinical trials. Although at present, drugs that reduce LDL-C, especially statins, play an important role in the prevention of cardiovascular disease, however, a considerable proportion of patients still failed to reach the LDL-C target value specified in the relevant guidelines. Amgen recently released phase III clinical trial data that shows the good curative effect of repatha in combination with statins on patients with hyperlipidemia. Repatha (evolocumab), a PCSK9 inhibitor, is a necessary adjunctive treatment option for patients with inherited high cholesterol who cannot control their high LDL-C with other lipid-lowering agents alone. This review focused on hyperlipidemia and its clinical manifestations. Repatha's basic information, clinical trial process, data and results were also included.

Keywords: Clinical, Hyperlipidemia, Treatment.

1. INTRODUCTION

Hyperlipidemia is usually prone to heart emergencies, including high-risk diseases such as acute coronary syndrome. Recent study reported that there has long been a debate that low levels of low-density lipoprotein cholesterol (LDL-C) may have a negative impact on memory or other cognitive functions [1]. The ability of liver to metabolize LDL-C decreases, which leads to the accumulation of cholesterol, which is one of the important reasons for hyperlipidemia. Hyperlipidemia can be divided into primary and secondary. Primary is related to congenital and heredity. It is caused by the abnormality of receptors, enzymes or apolipoproteins involved in lipoprotein transport and metabolism due to single gene defects or polygenic defects, or due to environmental factors (diet, nutrition, drugs) and unknown mechanisms. Secondary multiple diseases occur in metabolic disorders (diabetes, hypertension, myxoedema, hypothyroidism, obesity, liver and kidney diseases, and adrenocortical hyperfunction), or are related to other factors such as age, gender, season, drinking, smoking, diet, physical activity, mental tension, emotional activity, etc. The clinical manifestations of hyperlipidemia are mainly xanthoma caused by lipid deposition in dermis and Arteriosclerosis Caused by lipid deposition in vascular endothelium. Although hyperlipidemia can cause xanthoma, its incidence is not very high; The occurrence and development of atherosclerosis is a slow and gradual process. Therefore, under normal circumstances, most patients have no obvious symptoms and abnormal signs. Many people found the increase of plasma lipoprotein level only when they carried out blood biochemical test for other reasons.

Repatha is a complete human monoclonal antibody that inhibits the preprotein invertase subtilisin / Kexin 9 (PCSK9). Repatha binds PCSK9 and inhibits the binding of PCSK9 to LDL receptors on the surface of the liver. PCSK9 is a protein that targets LDL receptor degradation, thereby reducing the liver's ability to remove LDL-C or "bad" cholesterol from the blood [2]. In the absence of PCSK9, there are more LDL receptors on the surface of hepatocytes to remove LDL-C from the blood.

Some researchers found that Repatha in clinical trials, compared with placebo, not only showed the preventive effect of reducing blood lipid and preventing heart and coronary artery disease, but

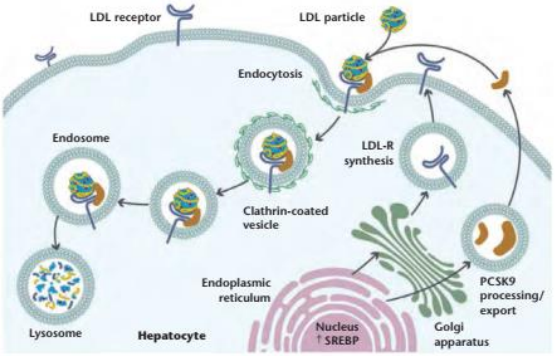
also showed acceptable adverse reactions. The results showed that the addition of Repatha to enhance statin treatment could significantly reduce the risk of these events by 20%. Like other drugs, Repatha can also produce adverse reactions. As a therapeutic protein, Repatha may exist and become an immunogen. When the human body recognizes repatha as an immunogen, it may cause the abnormal secretion of body antibodies, resulting in allergic reactions, which is also one of the common adverse reactions of therapeutic drugs [3].

Repatha has another effect in reducing blood lipids and can significantly remove atherosclerotic plaque. However, Repatha also showed some disadvantages in clinical trials, such as nasopharyngitis, upper respiratory tract infection, influenza and back pain. The primary efficacy endpoint was the combination of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina pectoris or coronary revascularization. The secondary efficacy endpoint was a combination of cardiovascular death, myocardial infarction, or stroke. The median follow-up time was 2.2 years [4]. It can be seen that Repatha is not plain sailing in clinical trials, but from multiple groups of placebo-controlled trials, it can be seen that patients with atherosclerotic cardiovascular disease can benefit from LDL cholesterol levels lower than current treatment targets.

This review focused on Repatha's clinical phase III trial, including the methods used in the trial, population, trial cycle and trial results. This review will show the data obtained by Repatha in the placebo control group of clinical trials and in combination with statins, some adverse reactions in the test will also be reflected. The data obtained from the trials will be displayed in tabular form. From the test results, Repatha can effectively reduce the LDL-C level of patients and has good safety. This paper discussed its latest clinical research.

2. The mechanism of PCSK9 Inhibitors regulate serum LDL cholesterol (LDL-C)

PCSK9 inhibitor is a protein that can act against other proteins in the body. Hepatocytes in the human liver produce receptors that clear excess cholesterol, and one of the PCSK9 proteins can destroy this receptor. The PCSK9 inhibitor can take this as the target. The drug will lock the PCSK9 protein, prevent this process, and make the cholesterol scavenging receptor play a role, so as to reduce the content of LDL-C in the blood. Reducing the number of free PCSK9 that can bind to LDL receptors will result in less degradation of LDL receptors, more LDL receptors on the surface of hepatocytes and less circulating LDL-C [5]. PCSK9 has high curative effect. It can be used alone or in combination with other drugs, such as statins.



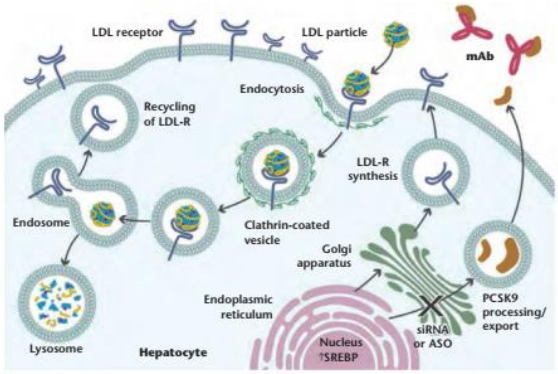


Figure 1. LDL receptor life cycle with PCSK9 inhibited.

3. Clinical Trials

As the clinical trials were conducted on a large scale, with different ethnic groups and different age groups selectedthe, adverse reaction rate observed in clinical trials can not be directly compared with the incidence of clinical trials of another drug, and may not reflect the incidence observed in practice [6]. The following are the selected population and adverse reactions in the clinical trial.

The data describe below are reflected in eight placebo-controlled trials, including 2651 patients treated with Repatha. 557 exposed for 6 months and 515 exposed for 1 year (median treatment time 12 weeks) were included as well. The median age of the population was 57 years old. 49% of the population were women, 85% were white, 6% were black, 8% were Asian, and 25 were other races.

3.1. Trials 1: Adverse reactions in a 52 week controlled trial

The long-term, double-blind, completely controlled trial was used. In the trial, 559 patients received 420mg Repatha subcutaneously once a month. The mean age was 56 years (range: 22 to 75 years old), 23% were older than 65 years old, 52% were women, 80% were white, 8% were black, 6% were Asian, and 6% were Hispanic [7]. According to Table 1, at least 3% of Repatha treated patients reported adverse reactions more frequently than placebo treated patients. Adverse reaction in 2.2% of Repatha treated patients resulted in termination of treatment and 1% of placebo treated patients. From these data, it can be seen that repatha can significantly reduce the probability of cardiovascular disease. In Study 2, Repatha treated patients had greater than or equal to 3% and more frequent adverse reactions than placebo

Table 1. Experimental data of adverse reactions in a Repatha vs Placebo controlled trial

	Placebo (N=302) %	**Repatha (N=599) %**
Nasopharyngitis	9.6	10.5
Upper respiratory tract Infection	6.3	9.3
Influenza	6.3	7.5
Back pain	5.6	6.2
Injection site reaction	5.0	5.7
Cough	3.6	4.5
Urinary tract infection	3.6	4.5
Sinusitis	3.0	4.2
Headache	3.6	4.0
Myalgia	3.0	4.0
Dizziness	2.6	3.7
Musculoskeletal pain	3.0	3.3

Hypertension	2.3	3.2
Diarrhea	2.6	3.0
Gastroenteritis	2.0	3.0

3.2. Trials 2: Adverse reactions

In these trials, 993 patients received 140mg of Repatha subcutaneously every 2 weeks and 1059 patients received 420mg of Repatha subcutaneously every month. The mean age was 57 years old (range, 18 to 80 years old), 29% were older than 65 years, 49% were women, 85% were white, 5% were hispanic [8]. At least 1% of Repatha treated patients and more frequently reported adverse reactions than placebo treated patients are shown in table 2

Table 2. Placebo controlled adverse reaction trial data of Repatha at different injection frequencies

	Placebo (N=1224) %	**Repatha * (N=2052) %**
Nasopharyngitis	3.9	4.0
Back pain	2.2	2.3
Upper respiratory tract infection	2.0	2.1
Arthralgia	1.6	1.8
Sicchasia	1.2	1.8
Fatigue	1.0	1.6
Muscle spasm	1.2	1.3
Urinary tract injection	1.2	1.3
Cough	0.7	1.2
Influenza	1.1	1.2
Contusion	0.5	1.0

3.3. Trials 3

In order to find out whether Repatha combined with statins has better curative effect, a controlled trial of statins alone and combined with Repatha was carried out. This study was a multicenter, double-blind, randomized controlled trial in which patients were initially randomized to an open specific statin regimen for a 4-week lipid stabilization period, followed by random subcutaneously injection of Repatha 140mg every 2 weeks, Repatha 420mg once a month, or placebo for 12 weeks. The results showed that the average change of the volume percentage of non-infarct related atherosclerotic plaques decreased significantly, and the coronary plaques of non infarct related arteries subsided significantly [9], but further research is still needed to understand whether Repatha can improve the clinical results of this population.

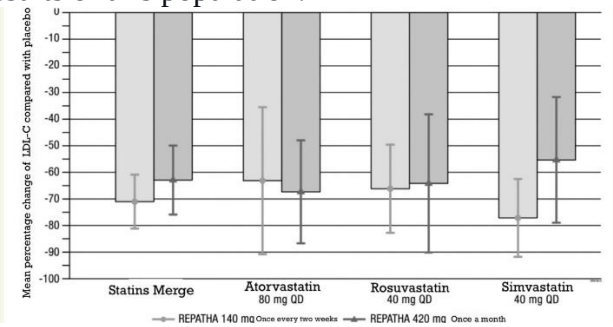


Figure 2. Mean percentage change of LDL-C compared with placebo.

3.4. Phase II and III clinical trial studies for alirocumab and evolocumab

The efficacy of the PCSK9 inhibitors to reduce LDL-C is related to the dose of the PCSK9 inhibitor, the baseline free PCSK9 level, the baseline LDL-C level, and the timing of the LDL-C measurement relative to the time of administration of the PCSK9 inhibitor. When considering the study variables

[10], the efficacy of alirocumab and evolocumab was similar, when combined with statins, both drugs can reduce LDL-C by about 55% - 65% compared with the baseline level. In the absence of statins, the percentage reduction of LDL-C is usually small, but there is a deviation due to the higher baseline value as the denominator of the percentage reduction of LDL-C. Compared with evolocumab, alirocumab may need additional doses in clinical trials. 16.8% of patients had titration up to 150 mg q2w at week 12. 75 / 150 mg aliromumab reduced LDL-C by 247.2%; 27% of patients need to increase titration because LDL cholesterol is 70 mg / dl, but only 2% of patients have LDL-C levels of 100 mg / dl. In the case of evolocumab, the efficacy of two available doses of evolocumab (140 mg q2w and 420 mg Q4w) is basically the same. The efficacy variables used were patient groups, including patients with HEFH, patients with homozygous FH (HOFH), patients with hypercholesterolemia taking statins and patients without monotherapy taking statins [11]. At the end of 52 weeks, the LDL-C reductions compared with placebo for the groups were as fol lows: diet alone: 255.7% ± 4.2%; atorvastatin, 10 mg: 261.6% ± 2.6%; atorvastatin, 80 mg: 256.8% ± 5.3%; and atorvastatin, 80 mg + ezeti mibe, 10 mg: 248.5% ± 5.2%. The GAUSS-2 study included patients who were intolerant to statins, but 18% of patients took low-dose statins. After 12 weeks, the average percentage of LDL-C reduction in Evo locomab group, 140 mg q2w group and 420 mg Q4w group was 256.1% and 255.3%, respectively. From the results, evolocumab combined with statins showed better efficacy and less side effects. As a new type of PCSK9 inhibitor, it has better development space and has better prospects in reducing the risk of cardiovascular disease and preventing coronary atherosclerosis. As a representative drug of evolocumab, repatha's ability in the treatment of hyperlipidemia is worth looking forward to. It is not only a new drug, but also has good curative effect. Although some adverse reactions may occur in clinical trials, the proportion is low and does not affect the safety of repatha as a whole

4. limitation and future development

Although Repatha showed a good cure for hyperlipidemia and significantly reduced the LDL-C level of patients in clinical trials, it also occasionally showed serious adverse reactions, such as myocardial infarction, sudden death, unstable angina pectoris and other potentially fatal symptoms [12]. In addition, the therapeutic effect of Repatha in combination with statins was significantly higher than that alone, this means that patients need to receive at least two drugs at the same time in order to significantly reduce blood lipids. Patients may face adverse reactions caused by multiple drugs, which can reduce blood lipids and lead to other diseases. Another possible outcome is a major adverse limb event, defined as acute limb ischemia, major amputation, or emergency peripheral revascularization of ischemia. On the other hand, the price of Repatha is currently very high, which means that its scope of use is limited. The high price means that many patients can't afford Repatha to treat their own hyperlipidemia. The reasons for the high price of Repatha may be that the production process still needs to be improved, the production raw materials are difficult to obtain, the purification process has great losses, the production is difficult, and the technical requirements are high. In the future development, the production technology of Repatha may not be limited to the cell fusion of immune animals, but more advanced molecular synthesis technology [13]. Repatha is synthesized at the molecular level, rather than relying on animals to produce monoclonal antibodies. In addition, the production process can also be improved. The first is the method of obtaining monoclonal antibodies. At present, monoclonal antibodies are mainly obtained by in vivo induction method, and then a large number of monoclonal antibodies are obtained by in vitro culture method. If the post freezing and thawing technology has been well developed and will not damage the protein structure and activity of post freezing and thawing, then a large number of hybridoma cells produced in the induction stage in vivo can be preserved. Whether the follow-up is produced by more advanced cloning technology or in vitro culture method, the production cost can be greatly saved, so as to achieve the purpose of reducing the product price. At present, Repatha has very favorable safety in the treatment of hyperlipidemia. On the basis of clinical trial evidence, LDL lowering with PCSK9 inhibitors is

recommended for high-risk patients with LDL-C levels ≥70 mg/dl on maximally tolerated oral therapies including statins and/or ezetimibe. Osler-1 test showed that Repatha had consistently excellent efficacy [14], tolerance and safety in reducing LDL-C in the study with the longest duration of PCSK9 inhibitor reported so far, and no neutralizing antibody was detected. Repatha, as a new type of lipid-lowering drug, combined with statins, provides a new treatment scheme for patients with hyperlipidemia. In the future, it will bring more opportunities for patients to recover. With the maturity of technology and the reduction of production cost, more and more patients will have the opportunity to use Repatha.

5. Conclusion

Repatha and other anti-PCSK9 antibodies reduced adverse cardiovascular outcomes in clinical trials of high-risk patients over <3 years median treatment duration. It can be concluded from the tabular data that the incidence of major cardiovascular events was 12.2% in the Repatha treatment group and 15.3% in the placebo group. To some extent, the use of Repatha can reduce the incidence of cardiovascular events. At 52 weeks, Repatha added to diet alone, to low-dose atorvastatin, or to high-dose atorvastatin with or without ezetimibe significantly reduced LDL cholesterol levels in patients with a range of cardiovascular risks. in spite of guidelines recommend that patients with acute coronary syndrome (ACS) begin high-intensity statin therapy in hospital, the target level of low-density lipoprotein cholesterol (LDL-C) is usually not achieved. Repatha is a fast low-density lipoprotein-c lowering drug [15]. Although there were some adverse reactions in the trial, it effectively reduced the level of LDL-C in the trial combined with statins, and there were no serious adverse reactions. Repatha is a new drug with high price and small audience, which are common problems. However, with the continuous improvement of drugs and the continuous improvement of national drug management system, repatha's ability in the treatment of hyperlipidemia will be more accepted by the public.

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