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Review

Triglyceride-lowering agents ☆

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ABSTRACT

This review is the first attempt at systematization of the literature data on the structures and activities of triglyceride-lowering agents which used in medical practice or are in development. The effects and mechanisms of action of statins, squalene synthase inhibitors, fibrates, PPARα and PPARα/γ agonists, nicotinic acid, omega-3 fatty acids and some other molecular targets were considered. Unfortunately, to date, harmless and effective triglyceride-lowering drug still does not exist and there is still need for development of better triglyceride-lowering agents.

Contents

☆ This review is primarily intended for chemists, but we hope it can be useful for professionals in the medical field.

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1. Introduction

Triglycerides and cholesterol are major lipids circulating in blood. Cholesterol ensures the stability of cell membranes and is also required to develop a number of vital molecules including hormones and vitamin D. Triglycerides are necessary to maintain the energy balance. Elevated levels of these substances in the blood are the cause of various pathologies. And if in the case of increased cholesterol concentrations, the problem is clear enough,[1–8] the role of high triglyceride concentrations as a cardiovascular disease risk factor has been controversial. High levels of triglycerides are very often associated with low levels of high density cholesterol, or 'good cholesterol', which are the cause of vascular disease. High triglyceride levels are often part of the disease called metabolic syndrome. Therefore, high levels of triglycerides in the blood should be seen as a danger sign. Normal triglyceride levels may be from 40 to 199 mg/dl. Triglyceride levels between 200 and 500 mg/dl are considered 'high', the levels at 500 mg/dl or greater are considered 'very high'.

Despite their own significance, triglycerides as a target for inhibiting remain in the 'shadow' of decreasing high cholesterol levels in blood plasma. As a rule, the result of decrease in triglyceride level is a secondary or ancillary to that for cholesterol. The available literature data about triglyceride inhibitors are not systematized separately, unlike the data concerning cholesterol-lowering drugs for the treatment of hypercholesterolemia.[1–8] In this review we attempt to systematize the collection of data available in the literature about agents, lowering triglyceride levels, as used in medical practice as well and are in development. Presented consideration of triglyceride-lowering agents includes not only the result but also the established or proposed mechanism of this action.

2. Cholesterol biosynthesis blockers

Although statins and squalene synthase inhibitors are primarily compounds interrupting the chain of cholesterol synthesis and thereby reducing the cholesterol concentration in blood plasma, they are also able to effectively reduce level of triglycerides.

2.1. Statins

The mechanism of action of statins **1**–**7** (Fig. 1), which inhibit activity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), is currently well understood. This action leads to significantly reduced plasma level of low density lipoprotein (LDL), less reduced level of very low density lipoproteins (VLDL) and triglycerides, and somewhat higher level of high density lipoprotein (HDL).[1,4,9,10] Specific studies[10] suggest that statins decrease levels of triglycerides through their capacity either to decrease the rate of VLDL synthesis or to increase the rate of catabolism of lipoproteins through enhancement of activity of LDL receptors.

The clinical studies[9] showed that a dose of 40 mg per day of compounds **1**, **2** and **3** caused reduction in triglycerides in the blood of patients by 22%, 25% and 24%, respectively. The lowering effect of statins was dependent on the pretreatment baseline level of triglycerides. Thus, when patients with very high levels of triglycerides (>1000 mg/dl) were prescribed simvastatin **2**, decrease in blood plasma triglycerides by 28% was observed, with close to normal levels (162 ± 55 mg/dl) only by 18%, and patients with low levels (78 ± 25 mg/dl), even a slight increase in triglycerides was registered.[9] Treatment of patients with high triglyceride levels (⩾386 mg/dl) with atorvastatin **5** at a daily dose of 10 mg for 12 weeks resulted in a reduction in triglyceride levels by 26–28%. Further use of atorvastatin **5** (20 mg dose) had no significant effect

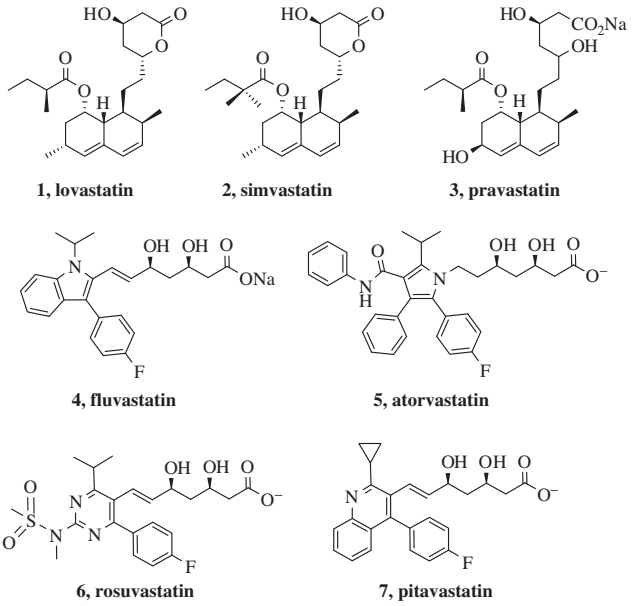

Figure 1. Structures of statins **1**–**7**.

since the total change was only 29–32%.[11] Treatment of patients with primary dyslipidemia with rosuvastatin **6** at a dose of 10 mg per day for 12 weeks resulted in an average reduction in plasma triglyceride levels by 15.2%. The effect of rosuvastatin was also dependent on the level of triglycerides in patients before treatment. A significant reduction in triglyceride levels was observed in patients with baseline ⩾120 mg/dl (about 20%), the reduction was not significant for lower levels.[10] Korean doctors had conducted studies of their hypercholesterolemic patients[12] and found that pitavastatin **7** at a once daily dose of 2 mg for 4 weeks more efficient than simvastatin **2** (20 mg once daily), since decrease in triglycerides for compounds **7** and **2** was 29.8% and 17.4%, respectively.

Although statins can significantly reduce the levels of LDL, their side effects are too aggressive. The most dangerous side effect of statins is specific myopathy, ranging from mild myalgia to extreme manifestation—rhabdomyolysis.[4,5,10] Despite the fact that statins reasonably lower triglyceride levels in patients, they are not drugs for the treatment of hypertriglyceridemia and are used to treat cardiovascular diseases. Patients with atherogenic dyslipidemia require combination of statins with drugs more effectively lowering triglycerides.[6,9]

At the end of a brief review of statins should be mentioned about the data[13] reporting that the magnesium ion is able to replace these compounds. The beneficial effects of the statin drugs are paralleled and complemented by those of the magnesium ion. Statins and Mg^{2+} inhibit HMG-CoA reductase. Magnesium, additionally, activates lecithin-cholesterol-acyl-transferase, the enzyme that lowers LDL and triglycerides levels, and also activates a desaturase, that converts omega-3 and -6 fatty acids to prostaglandins. Magnesium supplement also protects against myopathy. Temporary disorders of digestive system as the only side effect of magnesium salts are incomparable with the negative effects of statins. Yet it is clear that statins are not going to leave the market any time soon.

2.2. Squalene synthase inhibitors

Squalene synthase catalyzes the reductive dimerization of two molecules of farnesyl pyrophosphate to squalene. Squalene synthase inhibitors also inhibit the biosynthesis of cholesterol but do