PCSK9 and its clinical importance with the new therapeutic targets against dyslipidemia

A PCSK9 e sua relevância clínica com os novos alvos terapêuticos contra a dislipidemia

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ABSTRACT

This is a remarkable progress; since the finding of statins, there was no new way of reducing, significantly, cholesterol and LDL fraction. It is also clear that this decrease, by statins, is related to future cardiovascular lesions, being useful in its primary and secondary prophylaxis. The authors presented studies on research to promote the falling of blood cholesterol by means of antibodies, which inhibit the pro-protein PCSK9, as well as agents that act performing the RNA interference. We had two advantages immediately: for patients with myopathy associated with statins, and the fact of being injected every 15 days, that may contribute to better treatment adherence.

Keywords: Dyslipidemias; Lipoproteins; Cholesterol, LDL

RESUMO

Este é um progresso sensível; desde a descoberta das estatinas, não havia novas maneiras de diminuir, de maneira significativa, o colesterol e a fração LDL. Também está claro que essa redução, pelas estatinas, tem relação com futuras lesões cardiovasculares, sendo útil na profilaxia primária e secundária destas. Os autores apresentaram estudos sobre pesquisas para promover a queda do colesterol sanguíneo por meio de anticorpos que inibem a pró-proteína PCSK9, bem como agentes que atuam realizando a interferência no RNA. Duas vantagens se afiguram imediatamente: para pacientes que têm a miopatia relacionada às estatinas e por ser droga injetável a cada 15 dias, o que pode colaborar para maior adesão ao tratamento.

Descritores: Dislipidemias; Lipoproteínas; LDL-colesterol

INTRODUCTION

The proprotein convertase subtilisin/kexin type 9, also known as PCSK9, is an enzyme that is encoded by gene PCSK9[1] in humans, and has orthologous genes found in virtually all species. This gene encodes a proprotein convertase from the proteinase K subfamily, of the secretory subtilase family. The encoded protein is synthesized as a soluble zymogen, which undergoes an intramolecular self-catalytic processing in the endoplasmic reticulum. This protein plays an essential role in regulation of cholesterol homeostasis. PCSK9 binds to the repetition domain *A*, of the epidermal growth factor (EGF-A), to the low-density lipoprotein receptor (R-LDL), inducing degradation of this receptor. These reduced R-LDL levels result in decreased metabolism of low-density lipoproteins (LDL-cholesterol - LDL-c), which could lead to hypercholesterolemia[2,3].

CLINICAL RELEVANCE

Inhibiting function of PCSK9 is explored as a way to reduce cholesterol levels. Research has advanced in studying antibodies against this enzyme, aiming at its inhibition. It is worth mentioning that the use of statins is well established in clinical practice. Statins interfere in cholesterol production by inhibiting the enzyme HMG-CoA reductase[4] and stimulating the production of LDL receptors; meanwhile, these antibodies allow more LDL receptors to be available[5].

Currently, four different therapeutic targets against PCSK9 are under investigation; in that, Ac anti-PCSK9 – REGN727/SAR236553 (Regeneron Pharmaceuticals/ Sanofi) has more data available[6].

The most recent phase II study was published online on October 31, 2012, in the New England Journal of Medicine, and was carried out by a tem led by Dr. Eli Roth. The project involved 92 patients, with

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LDL levels ≥100mg/dL after receiving atorvastatin 10 mg for at least 7 weeks. They were randomized for 8-week treatment, at the ratio of 1:1:1 – receiving atorvastatin 80mg/day + REGN727/SAR236553; atorvastatin 10mg/day + REGN727/SAR236553 and atorvastatin 80mg/day + placebo. The drug REGN727/SAR236553 was administered every two weeks, subcutaneously. The exclusion criteria included type-1 *diabetes mellitus*, uncontrolled type-2 *diabetes mellitus* (glycated hemoglobin >8.5%) or on insulin, triglycerides >350mg/dL or any cardiovascular events in the past 6 months before the study. The results on the monoclonal antibody anti-PCSK9 REGN727/SAR236553 showed important reduction in LDL levels, in both associations (atorvastatin 10mg and 80mg) in patients with primary dyslipidemia (Table 1). In the placebo group, the drop was by 2.7% only. Like in previous studies with the same therapy, there was a decrease by approximately one-third lipoprotein-a Lp (a) levels in patients who received the antibody[7].

The Odyssey study with this antibody is on its phase III since July 2012. A total of 22000 patients will be enrolled, distributed throughout 2000 centers all over the world (United States, Europe, Canada, Australia, Asia and South America, including Brazil). It is conducted by Professor Dr Henry Ginsberg, of the Columbia University Medical Center, in New York.

Another way to inhibit the action of PCSK9 would be to use the therapeutic targets that act interfering in RNA, that is, RNA interference (RNAi)[8]. The RNAi is a great advance in medicine, and represents understanding of how genes are switched on and off in the cells, and provides a totally new approach to discovery and development of new medications. Its discovery was announced as "a great scientific advance that occurs once in every ten or more years" and it represents one of the most promising findings, being awarded the Nobel Prize of Physiology, in 2006[9,10]. Alnylam Pharmaceuticals recently demonstrated in initial clinical trials (Phase 1), the positive results of the new drug ALN-PCS, which has the same action, and effectively inhibits this proprotein.

New studies will be published soon, enabling a better evaluation of these promising therapeutic targets.

Table 1. Reductions in LDL-cholesterol in patients with primary dyslipidemia

Groups	Reduction in LDL levels from baseline (%)	p value (*versus* atorvastatin 80mg + placebo)
Atorvastatin 80mg + antibody	73.2	<0.001
Atorvastatin 10mg + antibody	66.2	<0.001
Atorvastatin 80mg + placebo	17.3	—

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