

Lipid lowering: PCSK9 inhibitors – new kids on the block target their breakthrough

Markus G. Mohaupt

Department of Nephrology, Hypertension and Clinical Pharmacology; Department of Clinical Research; both University of Bern, Switzerland

While primary prevention of cardiovascular disease primarily involves addressing several risk factors and should also include shared decision-making between patient and treating physician on the preferred means to achieve this goal, only extremes of the dyslipidaemias are targeted by treatment. In these cases, and in secondary prevention following cardiovascular events such as stroke, or overt coronary disease, lowering cholesterol levels by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme-A-reductase with statins is mandatory as it has provided proven benefits on clinical outcomes. This success story has four caveats:

1. Tolerable doses of a given statin may not sufficiently reduce cholesterol levels as the clinical effect is directly related to the achieved cholesterol levels.
2. Side effects, mostly myopathic, may limit appropriate dosing or even prescription of this type of drug at all and might even hamper physical activity of the affected patients, a key lifestyle modification to reduce cardiovascular risk.
3. Efficacy of statins might also depend on additional pleiotropic effects independent of the lipid-lowering capability.
4. Recently statins have also been linked to hampered glucose metabolism.

Given these and other issues Koskinas and coauthors summarised the currently available data on proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors [1]. The principle of PCSK9 inhibition has been developed incredibly fast by several companies against the background of the unsuccessful exploration of several avenues to lower lipid levels.

Proprotein convertases exist in a variety of isoforms in almost all organs and are involved in the processing of proteins or, like PCSK9, in targeting the low-density lipoprotein (LDL) receptor as a chaperone to its degradative pathway. As one might assume, inhibiting degradation of the LDL receptor acts beneficially by supporting cellular LDL cholesterol uptake and thus reducing its circulating load. An experiment of nature has already proven that subjects with an inhibitory loss-of-function mutation of the *PCSK9* gene have an interesting phenotype. Heterozygotes

are usually asymptomatic, yet present in several analyses with reduced cardiovascular disease. Worryingly, as well as LDL-cholesterol, apolipoprotein B is also reduced [2], and patients with homozygous familial hypobetalipoproteinaemia and very low apolipoprotein B levels show neurological deficits [3]. Though absence of immunodetectable PCSK9 in a compound heterozygote patient was compatible with a college degree, close monitoring of the clinical phenotype, as well as of the cardiovascular outcome, with long-term treatment with PCSK9 inhibitors is clearly recommendable [4].

As Koskinas and coworkers point out, novel treatment strategies are required in patients with statin intolerance, especially those with statin-associated myopathy, who are clearly eligible for lipid lowering therapy. Although the diagnosis of statin-associated myopathy is difficult without muscle biopsy, which shows a distinct pattern [5], the authors provide diagnostic criteria which are likely to apply in this condition and provide advice on how to proceed with conventional therapy [1].

As pointed out in the review, short-term data indicate safety with some concerns, which might be anticipated, about neurocognitive events in the evolocumab group. Though this was independent of achieved LDL-cholesterol levels, careful monitoring of neurological side effects and perhaps vitamin E levels (which might be affected with apolipoprotein B) is recommended.

PCSK9 inhibitors currently should be reserved for patients at very high risk of cardiovascular events. These include patients with familial homozygous / compound heterozygous hypercholesterolaemia who are on lipid apheresis. The regulatory approvals include patients with severe heterozygous familial hypercholesterolaemia and those with clinical atherosclerotic disease. The results of randomised trials need to indicate whether mortality endpoints are achieved as expected. As myopathy is not an issue with PCSK9 inhibition, statin intolerance due to myopathy might be considered as an indication and will probably be included in clinical recommendations, although additional studies are required to verify safety in this condition.

Given the cost of this therapy, for most patients it should be strictly reserved for severe clinical conditions. As a result of the necessity for such an approach, more affordable low

molecular weight molecules with a high oral bioavailability are currently being developed by several companies and are even in first clinical studies. Currently, the question of whether the pleiotropic effects of statins will be missed or whether even substances used in traditional medicine will undergo further investigation, must remain unanswered.

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Correspondence: Markus G. Mohaupt, MD, Division of Hypertension, Department of Nephrology, Hypertension and Clinical Pharmacology, University of Bern, CH-3010 Berne, Switzerland, [markus.mohaupt\[at\]jinsel.ch](mailto:markus.mohaupt[at]jinsel.ch)

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