Guest Editorial

Reducing Risk in Familial Hypercholesterolaemia and Severe Dyslipidaemia: Novel Drugs Targeting PCSK9

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Elevated LDL cholesterol (LDL-C) plays a major role in the development of atherosclerotic cardiovascular disease (ASCVD). Multiple studies and meta-analyses, including randomised controlled trials, prospective cohort studies and Mendelian randomisation studies, have consistently shown an association between LDL-C and ASCVD risk that is proportional to the magnitude and duration of exposure to elevated LDL-C levels.¹

These two components – magnitude and duration – emphasise the need for early and effective LDL-C lowering in severe primary hypercholesterolaemia in order to achieve significant reductions in the risk of cardiovascular disease. However, despite the use of statins, a significant residual risk usually persists.^{2,3} Several factors, such as failure to reach LDL-C reduction goals and concerns with long-term adherence to medication, among others, highlight the need for additional treatment options that further reduce LDL-C levels while being well tolerated and accepted by patients.

Patients with familial hypercholesterolaemia (FH) are of particular interest among people with severe dyslipidaemias. This genetic disorder, resulting from mutations in genes related to LDL-C metabolism, reflects well the notion of “LDL-C levels × time of exposure”, since FH patients are exposed to high LDL-C levels from early in life.^{4,5} The burden of life-long elevated LDL-C levels results in a significantly higher risk of ASCVD, particularly premature coronary artery disease.^{4,5}

Despite compelling information supporting the risk posed by FH and recent studies suggesting FH to be far more prevalent than previously thought (around 1 in 200–300, versus previous estimates of 1 in 500 people), reports suggest that there are generally low rates of FH identification.^{4–6} This results partly from a lack of awareness and clinical suspicion, and also from insufficient formal programmes and support for FH detection and screening.⁷

In addition, a common issue that has been highlighted is the general under-treatment of FH. This is due to several factors, including lack of identification and diagnosis, delayed treatment (introduced too late) or patients not being treated with high enough levels of

medications.⁴ Statins, frequently at high-intensity doses, are the first-line therapy to reduce LDL-C in people with FH.⁴ However, FH patients have poor rates of attainment of guidelines-recommended LDL-C levels.⁸ This highlights the need for additional therapies to achieve greater reductions in LDL-C, which will, in turn, further reduce adverse cardiovascular outcomes.

Severe hypercholesterolaemia usually requires high-intensity statins and frequently also will involve combination therapy with additional drugs, such as ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, particularly in subgroups with elevated cardiovascular risk.⁹ A number of factors will influence the decision on what drug to add and when, such as the magnitude of LDL-C reduction needed (drug intensity, percentage reductions), drug availability and cost, individual risk, adherence to medication, and patient preference.

The recent approval of PCSK9 inhibitors, may have a substantial positive impact on the treatment of severe dyslipidaemia. These drugs have been developed fairly quickly over the last 2 decades, with results from two large outcome clinical trials recently available. In both ODYSSEY (alirocumab) and FOURIER (evolocumab) outcomes trials in patients with cardiovascular disease, PCSK9 inhibitors (administered every 2 weeks, usually on top of statins) were shown to produce greater LDL-C reductions, while being overall safe and well-tolerated (apart from some injection site reactions).^{10,11} This translated into a lower risk of cardiovascular events, with some data suggesting that patients at higher risk or with higher LDL-C may benefit the most from PCSK9 therapy.

Nevertheless, the cost of this therapy is still an issue, and additional data are needed on longer follow-ups, outcomes results in some subgroups (e.g. FH), and long-term daily-practice data. Thus, the identification of patients that may obtain a greater benefit has become a particular point of interest. So far, different statements have recommended that PCSK9 inhibitors should be considered in patients with substantially elevated LDL-C levels (primary elevations, including FH patients), despite maximally tolerated lipid-lowering therapy (or intolerant to therapy), with either very-high risk or established

ASCVD.^{12–14} There is an ongoing debate about whether to lower the current proposed LDL-C levels for prescribing PCSK9 inhibitors, as these cut-offs are higher than the target levels recommended in guidelines. Additionally, these recommendations were made before the results of the outcome trials were published and further updates on these recommendations are expected.

Finally, it is worth mentioning inclisiran, a promising new drug targeting PCSK9 by reducing its hepatocellular synthesis. Inclisiran has been

shown to produce sustained LDL-C reductions over a few months after one injection.¹⁵ This gives rise to the possibility that inclisiran might need to be administered only a few times a year, which ultimately could increase medication adherence and cost-effectiveness. Nevertheless, results from large clinical trials evaluating outcomes and long-term safety are required.

In this issue, R Alonso et al present an overview of FH and S Nicholls an overview of PCSK9 inhibitors for managing severe dyslipidaemias. ■

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