Homozygous Familial Hypercholesterolemia: The Impact of Novel Treatments

In Europe, a rare disease is one that affects less than 1 in 2,000 people. However, rare diseases collectively affect approximately 30 million people in the EU.\(^1\) In the past, those with rare diseases were bereft of therapeutic options. Significant barriers existed, not least the risk versus reward imbalance when developing a treatment for a rare disease. The drug development process involves a high regulatory burden, and the financial incentives were meagre. This landscape has changed as the development of treatments for rare diseases has been incentivised by regulatory agencies, research funding bodies and healthcare systems.\(^2\)

Homozygous familial hypercholesterolemia (HoFH) is a prototypical example of the shifting focus in the field of cardiovascular medicine. While heterozygous familial hypercholesterolemia is amongst the most common genetic conditions, HoFH is estimated to affect between one in 300,000 to one million people worldwide.\(^3\) The condition is a manifestation of two mutant alleles of genes responsible for cholesterol metabolism. The abnormal lipid levels from birth lead to early onset atherosclerosis and subsequent cardiovascular events. Pharmacological treatment options have been limited to small molecule therapies, notably statins, and lipoprotein apheresis. The latter is resource intensive and impacts on the patients quality of life.\(^4\) Novel treatments of HoFH have been tested in a number of randomised controlled trials. However, similar to other rare diseases, an adequate assessment of clinical outcomes is not feasible due to the small sample sizes.

In this issue, D’Erasmo et al. present data from the Italian LIPIGEN-FH Registry. The registry was established in 2009 and includes data from more than fifty lipid clinics. This registry information detailing clinical practice is of considerable value and is welcome. It reports findings from 139 patients with HoFH. This is in the context of the recent implementation of novel pharmacological treatments for hypercholesterolemia, namely PCSK9 inhibitors, lomitapide and evinacumab. 80% of the cohort had a genetic diagnosis of HoFH while 20% were diagnosed as HoFH based on clinical criteria. 26.6% of the study cohort had simple homozygous genotype, and nine of these (25%) were null genotypes minimal or no LDL receptor function. This is important to note in terms of response to treatments with mechanisms of action dependent on LDL-R function.
This study can be juxtaposed to, and compliments, two recent articles which should be read in conjunction with this work. These are a report on the worldwide experience of HoFH by the Homozygous Familial Hypercholesterolaemia International Clinical Collaborators and 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia. In keeping with the EAS update, the authors highlight the utilisation of treatment combinations, with statins and ezetimibe as the initial foundation. Using combinations achieved a reduction in LDL-C of almost 60% from the baseline visit and a 73% reduction from untreated LDL-C levels. 15.8% of patients were on four agents, underlining this management strategy of multiple synergistic treatments. The greatest reductions in LDL-C were seen in those on combinations including novel treatments, with a 90% reduction reported with PCSK9i-lomitapide-evinacumab combination.

The availability of novel treatments to clinicians and patients is apparent and of significant interest to those managing severe hyperlipidaemia. 77.6% of patients were on novel treatments at the last study visit compared with 9.4% at the baseline visit. This is evidence of the incorporation of these treatments into management plans in the setting of specialist lipid clinics. Comparatively, 32.9% of those in the worldwide cohort reported by the Homozygous Familial Hypercholesterolaemia International Clinical Collaborators were on these three treatments. Among those from high income countries this is 44%, versus 19.5% for non-high income countries. This highlights the greater access to and utilization of these treatments in LIPIGEN-FH Registry, and the value of this information to those in healthcare systems without this access.

A key question for other jurisdictions is whether these treatments provide tangible improvements in clinical outcomes. This is not clarified by the high-quality evidence from RCTs, nor, as yet, from larger studies such as that reported by the Homozygous Familial Hypercholesterolaemia International Clinical Collaborators. D’Erasmus et al. present finding to suggest a lower rate of cardiovascular events following initiation of novel therapies. The composite endpoint MACE-plus is reported. This definition of cardiovascular outcomes was specified to capture a broad perspective of clinical endpoints and facilitate statistical analysis. The analysis compares the event rate in the five years before specialist input to five years of follow-up thereafter. The pre-post analysis found a reduction in MACE-plus with a hazard ratio of 0.56 (95% CI 0.12 to 0.90). This result was corroborated by a comparison of this cohort with a previous cohort from the same registry.

The implications of the results are consistent. Novel treatments reduce LDL-C, we know this. This translates into a reduction in cardiovascular events. This is expected in terms of the biological processes involved, namely cholesterol metabolism. The effects of treatments targeting these processes are evident from large RCTs of cholesterol lowering treatments such
as statins and PCSK9 inhibitors. The data presented by the authors quantifies these effects in clinical practice. Of course, this analysis has numerous limitations, many of which are not trivial. The authors note the potential for inherent bias and confounders due to the observational design and the research settings which are specialist centres. The time exposed to novel treatments was not uniform, nor was the choice of treatments. Gaps in the data also exist, such as date of treatment onset, incomplete patient data and the omission of Italian HoFH patients from centres not contributing to the registry.

However, the report reinforces the importance of combination treatments, the effect of novel treatments and the subsequent biochemical and clinical outcomes when novel treatments are implemented. Importantly, when compared to international norms, it highlights the inequity of access to novel treatments. It is essential to consider the condition at hand - those with HoFH have a very high-risk of cardiovascular morbidity and mortality. Those treating patient with HoFH, and those providing the resources to do so, must ensure this risk is reduced to the lowest possible level.

Where to from here? The authors call for larger and longer investigations to establish the cardiovascular benefit of combined treatments. These may be feasible through the work of the Homozygous Familial Hypercholesterolaemia International Clinical Collaborators. Alternatively, data from registries such as SAFEHEART (Spain), the Canadian FH registry and CASCADE FH may be combined to improve statistical power. Data examining the integration of novel treatments into routine practice is very informative for health systems which have yet to facilitate access to these treatments. Despite the limitations of this report, these results in a real-world setting are important for those practicing in the area of cardiovascular disease prevention.

References
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