Endokrynologia Polska
DOI: 10.5603/EP.a2021.0055
Volume/Tom 72; Number/Numer 3/2021
ISSN 0423–104X, e-ISSN 2299–8306

The treatment of heterozygous familial hypercholesterolaemia — a local perspective

Łukasz Bułdak

Department of Internal Medicine and Clinical Pharmacology, Medical University of Silesia, Katowice, Poland

Familial hypercholesterolaemia is a clinical entity resulting from mutations in the genetic code of proteins associated with lipid metabolism. Interestingly, it is one of the most common genetic disease in the Polish population. The estimated incidence of heterozygous familial hypercholesterolaemia (HeFH) in Poland is around 1:250, and recent results of the TERCET study showed that as many as 1.6% (1 in 63) of patients with very high cardiovascular risk have HeFH [1]. The most common mutations responsible for the development of the disease include LDL receptors, which are responsible for uptake of LDL from bloodstream, and less commonly the disease is a result of mutations in apoB100 or proprotein convertase subtilisin/kexin type 9 (PCSK9), leading also to reduced clearance of LDLs. Despite its relative high prevalence and straightforward clinical diagnosis, it is often recognized when complications of longstanding hypercholesterolaemia have already occurred (i.e. myocardial infarction, ischaemic stroke). Those are generally irreversible and lead to loss of life and increased economic burden of healthcare systems.

Nowadays, the validated algorithm published by the Dutch Lipid Clinic Network (DLCN) is one of the most commonly employed diagnostic tools [2]. It comprises 5 sections that cover the patient's personal history of premature cardiovascular diseases (CVD), family history, physical examination (focus on arcus cornealis and tendinous xanthomata), highest LDL-cholesterol level in anamnesis, and, optionally, the result of a genetic test for mutations of LDL-R, apoB, or PCSK9. A score above 8 points enables us to give a definite diagnosis of familial hypercholesterolaemia. From a clinical point of view, it is essential to screen subjects in our clinical practice for high-score features in this diagnostic tool, i.e. LDL-C >325 mg/dL (8 points), tendinous xanthomata (6 points), and arcus cornealis prior to 45 years of age (4 points). If they are present, we should perform profound anamnesis to exclude or confirm the FH. In some cases, when the patient has a borderline result for the diagnosis, genetic testing may be performed (available in large commercial diagnostic companies and as a part of screening/scientific grants) [3]. A positive result for the above-mentioned mutations provides 8 points. Naturally, during the work-up, secondary causes of hyperlipidaemia must be excluded [4]. Patients with diagnosed FH should be encouraged to screen members of their closest family (including children) for FH (e.g. lipid profile). Early lifestyle and pharmacologic intervention improve outcomes even in the paediatric population [5].

One of the most important actions in the treatment of hypercholesterolaemia (regardless of the genetic background) is to establish a treatment goal for our patient. A detailed description of the process is provided by the EAS/ESC guidelines [6]. Briefly, a patient with CVD should be treated intensely to achieve LDL-C level below 55 mg% (in some cases even below 40 mg%). In patients without history of CVD the threshold is generally higher, but even in patients with moderate cardiovascular risk LDL-C should be below 100 mg%. The diagnosis of FH classifies the patient, at least, to a high CV risk group (LDL-C < 70 mg%).

We are lacking comprehensive management of familial hypercholesterolaemia in outpatient setting, similar to the one that was developed for thyroid disorders [7]. Nevertheless, the initiation of high-dose, high-intensity statin therapy (i.e. 20–40 mg rosuvastatin or 40–80 mg atorvastatin) is the first-line treatment. In optimal conditions (including absence of side effects), this therapy may reduce the LDL-C by around 50%. The second step is based on the addition of ezetimibe to the treatment regimen. This drug is well tolerated and reduces LDL-C by a further 15%. In the majority of patients without FH, combined treatment leads to an acceptable LDL-C level. However, despite the combined treatment in patients with FH (especially those who cannot tolerate maximal statin doses) we often face inadequate control of lipid profile. At this point, the best treatment option is to introduce a PCSK9 inhibitor. Currently available

Łukasz Bułdak, Department of Internal Medicine and Clinical Pharmacology, Medical University of Silesia, Medyków 18, 40–752 Katowice, Poland; e-maul: lbuldak@gmail.com

PCSK9 inhibitors belong to the class of monoclonal antibodies (i.e. alirocumab and evolocumab). They are extremely effective as LDL-C lowering drugs (up to 85% as a part of combined therapy), which is accompanied by improvements in cardiovascular outcomes [6]. The major disadvantage of those therapies is their high cost (around 2000 PLN per month). Fortunately, a healthcare-funded treatment program for patients with lipid disorders (B101) has been introduced by the Ministry of Health via the National Health Fund [8]. The program gives hope for those who are not fortuitous enough and do not achieve treatment goals using maximally tolerated high-intensity statin and ezetimibe. Two cohorts of patients may be included: (1) adult patients with definite diagnosis of heterozygous hypercholesterolaemia according to the DLCN, who, despite high-intensity combined lipid therapy (statin + ezetimibe), have LDL-C > 160 mg%; and (2) adult patients who have LDL-C > 100 mg% on maximally tolerated high-intensity lipid lowering therapy (statin + ezetimibe), who have suffered from myocardial infarction in the previous 12 months, with concomitant advanced lesions in coronary arteries or atherosclerosis in other vascular beds (brain and extremities). The inclusion criteria are strict, which significantly limits the number of patients that might benefit from the novel treatment. In selected cases physicians can also apply to the National Health Fund for reimbursement of therapy with PCSK9 inhibitors in patients who have not fulfilled the criteria of the B101 program. The procedure (Emergency Access to Drug Technologies) is cumbersome and time-consuming. The application must be verified by a District or National Consultant in the respective field of medicine (e.g. cardiology). However, after approval the patient may be granted access to the drug without additional cost. Therefore, it is worth remembering about such a possibility.

The benefits of PCSK9 inhibitors have been shown in several large-scale clinical trials. The impact of both available drugs is similar. In patients with HeFH the mean reduction in LDL-C level during the treatment with PCSK9 monoclonal antibodies was 50.4% (41.4–59.3) [9]. This was transferred into a 19% (RR: 0.81, 95% CI: 0.76–0.87) reduction in myocardial infarctions and 25% (RR: 0.75, 95% CI: 0.65–0.85) reduction in strokes [10].

There are few other treatment options for patients with severe hypercholesterolaemia. In some cases, apheresis may be considered, but the procedure is invasive and expensive. Several "orphan drugs" have also been introduced, but their availability is limited [11]. Fortunately, we are on the brink of approval of bempedoic acid [12], which is an effective lipid lowering drug also in statin-intolerant patients. Several compounds are currently in the late phases of clinical trials, e.g. inclisiran — a small interfering RNA against PCSK9, and vupanorsen — an antisense oligonucleotide against angiopoietin-like 3 (ANGPTL3) protein, or evinacumab — a monoclonal antibody against ANGPTL3 [13]. All of these compounds may become useful in the treatment of HeFH.

In summary, it is vital to be aware of the fact that familial hypercholesterolaemia is not as uncommon as we may think. Specific treatment goals should be established shortly after the diagnosis. The treatment is stratified and often requires combined therapy, including PCSK9 inhibitors. Currently, we have an option, although limited, to treat patients with state-of-the-art, reimbursed pharmacotherapy according to the B101 program provided by the National Health Fund or Emergency Access to Drug Technologies. Further improvements in the care of patients are anticipated with the approval of novel drugs.

Conflict of interest

None to declare.

References

1. Dyrbuś K, Gąsior M, Desperak P, et al. The prevalence and management of familial hypercholesterolemia in patients with acute coronary syndrome in the Polish tertiary centre: Results from the TERCET registry with 19,781 individuals. Atherosclerosis. 2019; 288: 33–41, doi: 10.1016/j.atherosclerosis.2019.06.899, indexed in Pubmed: 31319356.
2. Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. Curr Opin Lipidol. 2012; 23(4): 282–289, doi: 10.1097/MOL.0b013e3283556c33, indexed in Pubmed: 22801386.
3. Krajowe Centrum Hipercholesterolemii Rodzinnej. http://hipercholesterolemia.com.pl/Kontakt,67 (11.05.2021).
4. Bułdak Ł, Marek B, Kajdaniuk D, et al. Endocrine diseases as causes of secondary hyperlipidemia. Endokrynol Pol. 2019; 70(6): 511–519, doi: 10.5603/EP.a2019.0041, indexed in Pubmed: 31891414.
5. Hennig M, Brandt-Varma A, Wołoszyn-Durkiewicz A, et al. Monitoring the Effects of Hypolipidemic Treatment in Children with Familial Hypercholesterolemia in Poland. Life (Basel). 2020; 10(11), doi: 10.3390/life10110270, indexed in Pubmed: 33158089.
6. Averna M, Banach M, Bruckert E, et al. Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients: A statement from a European Atherosclerosis Society Task Force. Atherosclerosis. 2021 [Epub ahead of print], doi: 10.1016/j.atherosclerosis.2021.03.039, indexed in Pubmed: 33892925.
7. Zygmunt A, Dąbrowski J, Lewiński A. Specialist thyroid package 1 (PS1) in outpatient endocrine care. Endokrynol Pol. 2020; 71(6): 485–496, doi: 10.5603/EP.a2020.0078, indexed in Pubmed: 33378069.
8. Leczenie inhibitorami PCSK-9 pacjentów z zaburzeniami lipidowymi (ICD-10 E78.01, I21, I22, I25). https://www.gov.pl/attachment/9ad24526-c366-4b32-b4b0-8eb9a62c9d00 (11.05.2021).
9. Brandts J, Dharmayat K, Vallejo-Vaz A, et al. A meta-analysis of medications directed against PCSK9 in familial hypercholesterolemia. Atherosclerosis. 2021; 325: 46–56, doi: 10.1016/j.atherosclerosis.2021.03.042, indexed in Pubmed: 33901739.
10. Cordero A, Rodríguez-Mañero M, Fácila L, et al. Prevention of myocardial infarction and stroke with PCSK9 inhibitors treatment: a metanalysis of recent randomized clinical trials. J Diabetes Metab Disord. 2020; 19(2): 759–765, doi: 10.1007/s40200-020-00557-6, indexed in Pubmed: 33520801.
11. Okopień B, Bułdak Ł, Bołdys A. Current and future trends in the lipid lowering therapy. Pharmacol Rep. 2016; 68(4): 737–747, doi: 10.1016/j.pharep.2016.03.016, indexed in Pubmed: 27180022.
12. Banach M, Duell PB, Gotto AM, et al. Association of Bempedoic Acid Administration With Atherogenic Lipid Levels in Phase 3 Randomized Clinical Trials of Patients With Hypercholesterolemia. JAMA Cardiol. 2020; 5(10): 1124–1135, doi: 10.1001/jamacardio.2020.2314, indexed in Pubmed: 32609313.
13. Surma S, Romańczyk M, Filipiak KJ. Angiopoietin-like proteins inhibitors: New horizons in the treatment of atherogenic dyslipidemia and familial hypercholesterolemia. Cardiol J. 2021 [Epub ahead of print], doi: 10.5603/CJ.a2021.0006, indexed in Pubmed: 33470417.