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Homozygous Familial Hypercholesterolemia "Rare Disease"

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Homozygous familial hypercholesterolemia (HoFH) is an inherited disorder caused by homozygous mutations in the low-density lipoprotein receptor (LDL-R) gene. The genetic basis of this autosomal co-dominant disorder is distinguished by loss of function mutations in both LDL-R gene loci, resulting in reduced uptake and clearance of circulating low density lipoprotein cholesterol (LDL-C) by the liver. The LDL-R gene is located on chromosome 19 and more than 1,000 mutations, affecting the function of the receptor, have been described [1]. The resulting defects refer to different functions, i.e. ligand binding, transport, internalization, recycling, or total lack of receptors [2]. Types of LDL-R mutations include single amino acid substitutions, premature stop codons, large rearrangements, mutations affecting the promotor region and splicing of pre-messenger RNA. Rarely, similar clinical phenotypes occur with a recessive pattern of inheritance i.e. autosomal recessive hypercholesterolemia (ARH). In this case the mutations are located on chromosome 1. The differential diagnosis can be done only with genetic analysis [3]. The accumulation of cholesterol after birth produces several clinical manifestations, including xanthomas located on the hands, elbows, feet, Achilles tendons and cardiovascular complications, such as aortic valve disease. The combination of high total cholesterol (TC) and LDL-C can lead to early-onset accelerated atherosclerosis and premature coronary death, usually before the patient turns 30 years old. The diagnosis of this disease is performed during the first decade of life. In patients with HoFH, the main cause of morbidity and mortality is represented by coronary arteries disease. The majority of patients with HoFH will not achieve sufficient reductions in LDL-C levels even with the maximal doses of statin and non-statin therapies. These patients often require additional therapy such as LDL-C apheresis. This is an effective way to lower LDL-C levels in patients with FH who are not responsive to or are intolerant to drug therapy. Unlike statins, apheresis also lowers Lp(a) levels [4-6]. Apheresis is a procedure that physically remove plasma lipoproteins from the blood using dextran sulfate cellulose adsorption (DSA), heparin-induced extracorporeal LDL-C precipitation (HELP), immunoadsorption, double filtration plasmapheresis (DFPP), or direct adsorption of lipoproteins [7]. Unfortunately many patients with HoFH do not achieve the desired reduction of lipoproteins and the LDL-C levels return to pre-treatment levels within 2 to 4 weeks [7]. Specific recommendations exist for the management of children and adolescents with HoFH. The NLA Expert Panel on Familial Hypercholesterolemia recommends initial treatment for pediatric patients with statin therapy beginning at the age of 8 years, although patients with HoFH may require treatment at an earlier age [8]. The majority of pediatric patients with HoFH will require apheresis to achieve adequate control of LDL-C levels [8]. Actually LDL-apheresis is the standard treatment for patients with HoFH [9-11]. However, the decision to start LDL-apheresis is difficult because of the cost and practical considerations involved. Problems with insurance, venous access, and patient compliance must be observed for this procedure [12]. Recent new therapeutic strategies are involved to treat this rare disease. One of them, is the PCSK9 inhibitor. It is a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), a serine protease that binds LDL-R and promotes its degradation. PCSK9 gain-of-function represents a cause of FH, although rare [13]. On the other hand, more common loss-of-function mutations lead to very low LDL-C levels [14]. Gain-of-function and loss-of-function mutations in the gene for PCSK9 have been described. PCSK9 inhibition is considered an attractive target for therapy, especially in light of the fact that a large proportion of high-risk patients do not reach the target LDL-C levels, despite the maximal dosage tolerated of currently available lipid-lowering agents. Preliminary results of a study conducted by Amgen with AMG145 (evolocumab) showed a consistent reduction of LDL-C (mean -16.5% for monthly regimen and – 13.9% for bi-weekly regimen). This reduction was not however seen in the receptor-negative patients [15]. Mipomersen is another therapy. It is a second-generation antisense oligonucleotide, designed to inhibit apo-B100 protein synthesis [16]. Mipomersen binds to the mRNA sequences that encode apo-B100 and promote degradation of the apo-B mRNA by ribonuclease H. It specifically binds to the mRNA and blocks translation of the gene product. Decreasing the production of apo-B 100 reduces the production of very low density lipoprotein (VLDL) in the liver, which consequently reduces circulating levels of atherogenic VLDL remnants, intermediate density lipoproteins (IDL), LDL and lipoprotein (a) particles. Mipomersen has been granted orphan drug status by the Food and Drug Administration (FDA), which approved mipomersen in January 2013 for the treatment of HoFH [17]. Efficacy and safety of 200 mg/week of mipomersen has been assessed in patients with a clinical diagnosis or genetic confirmation of HoFH [18]. The mean reduction of LDL-C concentration was significantly greater with mipomersen (-24.7%) with a maximum reduction around to 17 weeks. A third of these patients have showed an increase in hepatic fat content from 9.6% to 24.8% [18]. Longer term studies will be needed to more fully evaluate the benefits and risks, particularly if use must be extended for patients with HoFH. Although recently approved by the FDA, in Europe The European Medicines Agency (EMA) has decided not to recommend approval for Isis and Genzyme as cholesterol-lowering drug mipomersen. Genzyme's group has requested a re-examination of the opinion. After considering the grounds for this request, the EMA re-examined the initial opinion, and has confirmed the refusal of the marketing authorization on 21 March 2013 because of safety concerns such as signs of liver toxicity and cardiovascular risks. Another drug currently evaluated as an adjunct to a low-fat diet and other lipid-lowering therapies for reducing LDL-C in patients with HoFH is the orphan drug lomitapide. Lomitapide (AEGR-733; BMS-201038) is a small molecule MTP- inhibitor [19], a protein located in the endoplasmic reticulum of enterocytes and hepatocytes and needed for the formation of chylomicron and VLDL particles. MTP is a chaperone that facilitates the apoB-containing lipoprotein assembly and secretion [20]. Inhibition of MTP represents a way to reduce LDL-C, apoB and TG concentrations. Lomitapide has been approved by FDA in December 2012 for the treatment of HoFH. A pilot trial with six patients with

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HoFH was conducted to examine the safety, tolerability, and effects on lipid levels during treatment with lomitapide. The reductions of LDL-C, ApoB, TC and TG from baseline, at this dose, were respectively (-50.9%, -55.6%,-58% and 65%) [19]. More recently Cuchel et al. [21] have observed in patients with HoFH a significative reduction to week 26 of LDL-C (-50%) from baseline at a median dose of lomitapide of 40 mg a day. The authors have also reported an increased hepatic fat accumulation from 1.0% to 8.6% at 26 weeks.

The patients with severe HoFH illustrate the natural history of atherosclerosis within a short timeframe. Lipid-lowering therapy has to start in early childhood. Apheresis is still the treatment of choice in HoFH in whom the maximal current therapy does not achieve adequate control. Regarding the approvals of lomitapide (and mipomersen) are been obtained for adult patients, however, children with HoFH represent a particularly important group to which the indication could eventually be extended since they often develop cardiovascular heart disease in the first decade their life [22]. In general the management of patients with rare diseases remains a continuous challenge.

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