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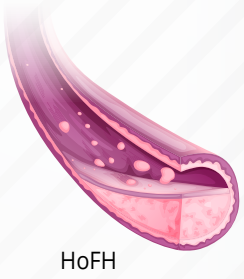
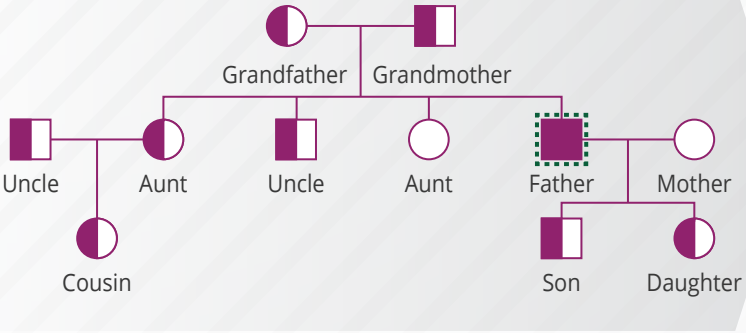
Spotlight on Homozygous Familial Hypercholesterolemia

Current treatment strategies and future innovations

Homozygous familial hypercholesterolemia: A genetic disorder





Homozygous familial hypercholesterolemia (HoFH) is an inherited genetic disorder and represents a rare and severe subtype of familial hypercholesterolemia

Characteristics[1]

Extremely high levels of low-density lipoprotein cholesterol (LDL-C) in blood since birth

Development of atherosclerotic cardiovascular disease (ASCVD) during childhood

Genetic causes (mutation)[1]

- Both alleles of LDL receptor (LDLR)
- Apolipoprotein B (ApoB)
- Proprotein convertase subtilisin/kexin type 9 (PCSK9)
- LDLR adapter protein 1 (LDLRAP1)

Criteria for diagnosis[2]

- Untreated LDL-C ~400 mg/dL
- Cutaneous or tendon xanthomas before 10 years
- Identification of bi-allelic mutations in *LDLR, APOB, PCSK9,* or *LDLRAP1* genes

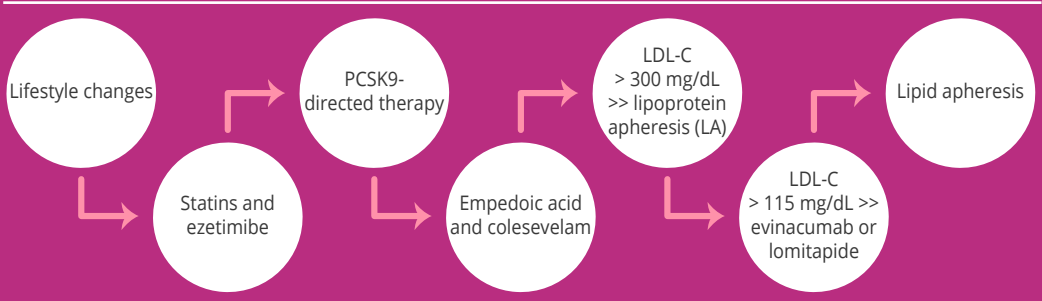
Treatment pathway and updated LDL-C goals[2]

Goals

Adults (>18 years): Target LDL-C levels of **<70** mg/dL

Children and adolescents: Target LDL-C levels of **<115** mg/dL

Pathway



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Current treatment strategies for HoFH[1,2]

- Effective lipid-lowering therapy (LLT) is the most widely used
- LDL-C is an effective predictor of disease progression
- Residual LDLR activity is the main determinant for achieving treatment goals
- Patients with HoFH exhibit variable responses due to diverse phenotypes and genotypes

Conventional LLT[1]

Statins and ezetimibe
- First-line therapy
- Mechanism of action is LDLR dependent
- ↓ ASCVD mortality in adults and children with HoFH

PCSK9 inhibitors

- ↑ Expression of LDLR ∞ ↑ LDL-C clearance

Alirocumab and evolocumab
- Humanised monoclonal antibodies (mAb)

Inclisiran
- Small interfering ribonucleic acid (siRNA)

Lerodalcibep
- Still in the research phase
- Small recombinant fusion protein of a PCSK9 binding domain and albumin

Pharmacological agents acting independently of LDLR[1,2]

Anti-ApoB therapies
- Lomitapide: Inhibits microsomal triglyceride-transfer protein
- Mipomersen: Antisense oligonucleotide inhibitor

Angiopoietin-like 3 (ANGPTL3) inhibitors
- Evinacumab
- RNA-based treatments targeting ANGPTL3 (vulpanorsen)

Interventions to lower LDL independent of LDLR[1]

LA
- Selectively remove the circulating ApoB-containing lipoproteins

Liver transplantation
- Curative treatment
- Severe complications

Potential of ANGPTL3 inhibitors in HoFH treatment[3,4,5]

ANGPTL3 is a circulating inhibitor of lipoprotein lipase (LPL) and endothelial lipase (EL)[3]

Produced only by the liver at low and constant rates[3]

Acts in coordination with ANGPTL4 and ANGPTL8 to control triglyceride breakdown[3]

ANGPTL3 inhibition leads to enhanced lipoprotein clearance[4]

Promising target to reduce ASCVD risk[3]

Evinacumab[5]

Evinacumab

- Fully humanised mAbs inhibiting circulating ANGPTL3
- ↓LPL and EL activities ∞ ↑Plasma LDL-C levels
- **Recommended dose**
  - 15 mg/kg via intravenous fusion for >1 hour
  - Once monthly
- Approved by the US Food and Drug Administration and the European Medicines Agency
- 46.3% reduction in LDL-C4

Advantages

- Long-term efficacy
- Safe
- Well-tolerated
- Independent of residual LDLR activity

Vupanorsen[3]

Vupanorsen

- Gal-NAc-conjugated antisense oligonucleotide targeting ANGPTL3 mRNA
- Specifically targets asialoglycoprotein receptor in hepatocytes
- Promising efficacy
- Associated with increasing liver steatosis
- Further studies needed

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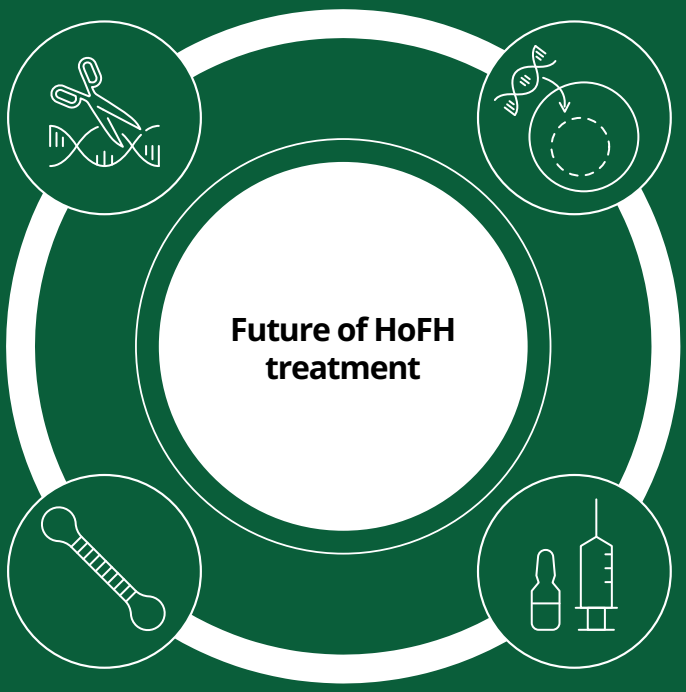
Future of HoFH treatment[1,2,3]

CRISPR-based genome editing[1,2]

- Modification of *ANGPTL3* and *PCSK9* genes ∞ ↓LDL-C levels

Gene transfer[1,2]

- Adenovirus-mediated gene transfer > Successful expression of LDLR in the liver ∞ ↓ LDL-C levels
- No adverse effects



siRNA ARO-ANG3[3]

- Undergoing clinical trials, ARO-ANG3 is an siRNA that targets ANGPTL3

Vaccine targeting ANGPTL3[3]

- Investigating a protein-based vaccine (E1-E2-E3) targeting ANGPTL3 for novel HoFH treatment

Key message

Advancements in the management of HoFH offer highly effective and diverse treatment options, from conventional therapies to cutting-edge innovations, which aim to improve LDL-C control, reduce ASCVD risk, and enhance the quality of life for patients with HoFH

References

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