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Hypolipidemic Drugs

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ABSTRACT
The management of lipid disorders is a work in progression on account of continuous research leading to regular new developments.So much so that the optimal target blood concentration of various components also remains unsettled.The expanding panoply of available drugs has made the therapeutic approach complicated and demanding.Hence,the treating physician needs to have thorough knowledge of all therapeutic options to choose the best option for his patient.This article intends to present the up-to-date information regarding the pharmacological agents available and the various recommended strategies,emphasising on drug compliance for prolonged periods and the salutary outcome of a systematic plan with regular followup.

Keywords:dyslipidemia,statin,pcsk9 inhibitor

I. INTRODUCTION

Atherosclerotic cardiovascular disease is the commonest cause of mortality worldwide.[1]The disease burden showed a consistent fall from the 1970s onwards in sync with the widespread use of multiple effective therapeutic agents.The impressive results encouraged the scientific community to anticipate further improvements in the future.This optimism prompted the American Heart Association set a daunting target of a 20% decrease in mortality of stroke and CVD by 2020.[2] Worringly,the trend started to plateau and subsequently changed direction especially in middle-aged Americans.This was likely the net result of multiple reasons including increasing geriatric burden, rise in metabolic illnesses like diabetes and obesity,poor drug compliance and nonuniform availability of health services.Presently,more than 100 million Americans are afflicted by some form of CVD placing it as an important cause of death and disability among both men and women.While the age adjusted increase in CVD is falling,coronary artery disease,stroke,hypertension and heart failure continue to be a significant burden.By straining the health care infrastructure,the COVID pandemic has worsened the problem.Soberingly,75% of CVD deaths occur in low and middle income countries with 27% of deaths in India related to CVD.[3]

Evidently,reining in the CVD problem is an urgent necessity.The ideal cardiovascular health (CVH) score mooted by the AHA is a summative assessment of 7 factors that positively influence CVD namely food,exercise,body mass index,smoking,blood sugar,blood pressure and total cholesterol. Less than 1% of US adults fulfill the criteria in all 7 fields and this number is progressively falling over last 2 decades.More than half of all patients discontinue statin after 1 year and only one-fifth continue the drug at the end of 5 years.[4]Thus,understanding the impediments and use of tangible parameters are vital to achieving the objectives.One of the most impactful and extensively researched field is the pharmacotherapy of dyslipidemia because dyslipidemia,as identified from raised LDL-C is the main reason for genesis and perpetuation of atherosclerosis.

LIPID ANALYSIS

An essential element of hypolipidemic therapy is estimation of blood lipid concentration.Fixing the desirable target level,periodic review to gauge treatment efficacy and analysis of the risk conferred in each individual patient are all equally important.In a standard biochemical laboratory,the commonly measured components in a lipid profile assay are total cholesterol,low density lipoprotein(LDL-C),high density lipoprotein(HDL-C),very low-density lipoprotein(VLDL) and triglycerides(TG).The most widely studied LDL-C is usually deduced from the Friedwald formula.The dominant opinion is that nonfasting sample is acceptable in most situations other than extremely fat rich diet in last 8 hours or evaluation for a family history of ASCVD.

The risk estimate of atherosclerotic cardiovascular disease is measured by multiple factors e.g. pooled cohort equation.(PCE).[5]This score summarises information from multiple study populations of age group 40-75 years to furnish an estimate of future (10 year) adverse events encompassing myocardial infarction and stroke.The SCORE system (and lately SCORE2) is recommended by the European society for the same purpose.Based on the PCE,four categories have been created for primary prevention(<5%,5 to 7.5%,7.5 to 20 and >20%).While the highest risk

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warrants statin therapy,the lower categories demand risk factor modification and optional statin therapy.

HYPOLIPIDEMIC DRUGS

STATINS:

The lynchpin of management of dyslipidemia,statins are widely recommended to ameliorate cardiovascular risk.All guidelines on blood cholesterol endorse statin as first line drugs for established ASCVD,familial hypercholesterolemia,40-75 year old diabetics with LDL>70 mg/dl or nondiabetics with ASCVD risk>7.5%They retard activity of HMG CoA reductase which is responsible for converting HMG-CoA to mevalonic acid,a rate limiting step in cholesterol production.Higher blood glucose promotes HMG CoA reductase activity,thus allowing it to be modulated by insulin and glucagon.The multifarious effects of statins include promotion of endothelial function,suppression of inflammation, anticoagulant and immunomodulatory function.Endothelial function is promoted by antioxidant activity preventing free radical damage,promotion of eNOS activity and folate pathway modulation.Statins regulate cytokine synthesis.The magnitude of LDL-C reduction is dose related with LDL-C fall> 50% achieved by atorvastatin 40-80 mg,rosuvastatin 20 mg or statin-ezetimibe (40/10 mg). A low bioavailability and multiple side effects like muscle pain,joint pain,intracerebral hemorrhage and amnesia are its drawbacks.Statin induced myopathy is diagnosed by muscle pain or debility associated with 10 fold rise in CK.Rhabdomyolysis is an extreme form entailing 40 times rise in CK with myocyte death manifesting as myoglobinuria and sudden renal impairment.Coenzyme Q levels fall by upto 50%.[6]

Newer studies focusing on use of statins for primary prevention in the elderly include STAREE and PREVENTABLE.A cohort study indicated that risk of ASCVD is related to initial LDL-C but maximum in 70-100 year age group underlining that number needed to treat will be lowest in this group.[7]

EZETIMIBE:

A small molecule inhibitor of NPC1L1 protein,it prevents absorption of cholesterol from the small intestine ,thus preventing its transport to liver and hence,promoting LDL receptor expression on hepatocytes. It also inhibits aminopeptidase N and may also downregulate macrophage recruitment, reduce oxidative damage and plaque size.It is slotted under class II of hypolipidemic dru,reducing LDL-C by 20-25%.It is second line for patients not reaching target on statin and first line for statinintolerant patients.

BEMPEDOIC ACID

A new drug that retards cholesterol synthesis by suppression of the enzyme ATP citrate lyase(ACLY).This enzyme acts upstream of HMG CoA reductase and causes citrate to change to acetyl CoA. Reduced cholesterol synthesis stimulates LDL receptor expression which in turn raises LDL uptake and reduces LDLc concentration.This effect is also mediated by the drug's inhibition of AMP kinase. It is a prodrug that is converted to active form by a liver specific enzyme very long chain acyl CoA synthetase-1.Absence of this enzyme in muscle explains lack of muscle toxicity.Liver uptake of the drug is via a receptor distinct from statin uptake and hence,noncompetitve.The statin plus bempedoic acid combination is as efficacious as high dose statin alone but without the myotoxicity.It was approved by USFDA in 2020 in heterozygous familial hypercholesterolemia or known ASCVD.[8]

Its anti-inflammatory effect has been proven in multiple studies.It has been shown to reduce hsCRP by 24.3% and also inhibit prostaglandin synthesis by inactivating ACLY.The CLEAR group of trials established reduction of LDL-C by about 30% alongwith nonHDL-C,total cholesterol and apo B levels.A meta analysis has concluded that it causes a 17% (not significant) reduction in cardiovascular endpoints.The CLEAR Outcomes trial aims to focus on cardiovascular effects of the drug in 14000 odd high CV risk statin intolerant patients.[9]Bempedoic acid has been shown to cause rise in blood urea,creatinine and uric acid but fall in hemoglobin..A mild fall in triglycerides is hypothesised to result in a lower occurrence of new onset DM.Bempedoic acid-ezetimibe combination reduces LDL-C by almost 40% even without statin use whereas with PCSK-9 inhibitor,the drug caused asn additional 30% reduction over 2 months.

PCSK9 INHIBITORS:

Proprotein convertase subtilisin/kexin type 9(PCSK9), synthesised in the hepatocytes attach to the LDL receptor on its membrane and promotes its breakdown,thus raising circulating LDL.PCSK9 inhibitors act by blocking of PCSK9/LDLR complex formation (peptides, adnectins, monoclonal antibodies), suppression of PCSK9 expression(small molecules like berberine, oleanolic acid;antisense nucleotides; siRNA) or interference with PCSK9 secretion (sortilin, sec24a).The monoclonal antibodies attach to

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PCSK9 and hence, prevenr breakdown of LDL receptors. Both alirocumab and evolocumab have been shown to improve LDL-C,reduce total cholesterol,increase HDL and lipoprotein(a).They improve atheroma burden in coronary artery and CV outcome. Evolucumab in the FOURIER trial decreased CV risk by 15% and LDL-C level by upto 75% whereas alirocumab caused a reduction of upto 50%[10].ODYSSEY OUTCOMES documented a fall in CV risk by 15%.Both drugs caused a fall in MI and stroke but not cardiovascular mortality.Present guidelines dictate use of these agents in high risk patients if combination of statin and ezetimibe is unable to reduce LDL<70 mg/dl.Both drugs are administered subcutaneous at 2 to 4 week intervals.No adverse effects other than injection site reaction have been reported.

Inclisiran is the first-in-class siRNA that particularly attaches to PCSK9 Mrna preventing translation of the protein.It causes sustained fall in PCSK9 and LDL-C for upto 6 months.A long hallife of drug gives it a headstart over mAbs.The phase III RCT ORION-1 revealed that a maximum of 2 injections(at 6 monthly intervals) can drastically reduce LDL with favorable safety profile.The drug was approved in 2020 for primary hypercholesterolemia.The phase3 ongoing trial ORION 4 is expected to elucidate its cardiovascular effects.[11]A lab study found that lipid containing nanoparticles with ALN-PCS decreased PCSK9 Mrna and protein levels by 70% and correspondingly, LDL by 60%.The comparision of cardiovascular studies of PCSK9 inhibiting antibodies or inclisiran showed equal efficacy.

Vaccination against PCSK9 can be a more effective option than mAbs as it is cost effective and obviates repeated injections.The vaccine promotes development of antibodies that show ameliorative effect upto 2 to 4 years.The vaccine has also been shown to be anti-inflammatory by decreasing circulating inflammatory markers and growth factor.A phase 1 safety trial of the vaccine has been completed.A nanoliposomal anti-PCSK9 vaccine has shown encouraging results in animals.Another composite single dose vaccine against multiple target proteins like PCSK9,ApoB and CETP has shown salutary effects on blood parameters of interest.[12]

Small molecules against PCSK9 are a viable option due to simple and inexpensive production coupled with better safety profile.P-4 and its newer nano formulation P-21 impairs attachment of LDL and PCSK9 reducing LDL-C level and also doubles HDL-C after 2 weeks of oral therapy.

TRIGLYERIDE REDUCTION

Multiples lines of research have established a tenuous causative relationship between raised TG and ASCVD.TG containing lipoproteins ,rather than TG itself ,can promote plaque synthesis.n-3 fatty acids are recommended in high risk patients alongwith statins when TG level is between 135500 mg/dl.Fibrates are PPAR-αagonists that diminish ASCVD risk in those with background raised TG.Pemafibrate is the first selective PPARα agonist with manifold selectivity as compared to PPARγ and delta.Pemafibrate causes about 40 to 50% fall in TG which is comparable to fenofibrate but with lesser side effects.PROMINENT,a phase3 cardiovascular outcome trial was terminated early in 2022 due to futility.[13]The results of 2 ongoing studies on patients with TG of 500 to 2000 mg/dl are expected to clarify the picture further.

OMEGA-3 FATTY ACIDS

Recommended for severe hypertriglyceridemia, here is no evidence to support its use for protection against ASCVD in patients on statins. REDUCE-IT concluded a substantial fall in cardiovascular risk by 25% but EVAPORATE reduced plaque volume by about 20%.Cardiovascular event reduction was absent in STRENGTH. The incongruous result is possibly due to a change in comparator oil(mineral oil vs corn oil).

APO C3 INHIBITOR

An important modulator of TG metabolism,it inhibits lipoprotein lipase that degrades TG in VLDL and chylomicron.Plasma apoC3 appears to be a risk factor for CVD.Loss of function mutations in APOC3 reduces CVD risk by almost half. Volanesorsen is an antisense oligonucleotide (ASO) against apoc3RNA.In the APPROACH trial,an encouraging 75% of patients achieved TG<750 mg/dl whereas in COMPASS,the fall was about 870 mg/dl. Volanesorsen was approved by EU for treatment of adults with FCS.[14]

ANGPTL3 INHIBITOR

ANGPTL3(with ANGPTL4 AND ANGPTL8) reduces LPL activity in a coordinated manner and hence,control plasma TG.Evinacumab, an antibody against ANGPTL3,in the ECLIPSE HoFH study reduced LDL and plasma TG by 50%.Vupanorsen,an ASO against ANGPTL3 mRNA, revealed a fall in ANGPTL3,TG,LDL and VLDL levels.ANGPTL4 and ANGPTL8 inhibitors have caused dose dependent fall in TG,LDL and apoB.[15]

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Lp(a) LOWERING DRUGS

Lp(a) concentration is associated with coronary artery disease,stroke and aortic valve disease.Patients with established ASCVD and Lp(a) > 60 mg/dl upon receiving apharesis accrued a fall in CV events by 70-80%.IONIS-APO(a) Rx,an apo(a) inhibitor ,reduces Lp(a) upto 90%.A phase III trial(HORIZON) is ongoing.

HDL TARGETING AGENTS

Niacin and CETP inhibitors which increase HDL substantially showed no reduction in ASCVD risk.The apoA1 peptide is the largest structural component of HDL.HDL mimetics containing apo A1 products showed dismal results(MILANO-PILOT and CARAT).A phase III trial of CSL-112,a new form of apoA1,in ACS patients is ongoing.[16]

TARGETED THERAPIES:

Enhancement of the bioavailability and efficacy of statins is being attempted by multiple novel drug formulations such as nanoparticles (polymeric or lipid based or chitosan based).Polylactic-co-glycolic acid nanoparticles use enabled reduction of dose by 66%.These particles slowed development of hypertension and multiplication of pulmonary myocytes.The biopolymer chitosan itself may decrease cholesterol but principally, it forms a layer on liposome to increase stability and improve drug release.Cerium oxide based nanoparticles can prevent oxidative damage by neutralising free radicals.In addition to the hypolipidemic effect, they reduce insulin and triglyceride levels and also provide antioxidant activity.Drug mounted on lipid base nanoparticles improved oral bioavailability translating into greater magnitude change in total cholesterol and its components. Parenteral formulations of HDL nanoparticles are able to release the drug within the atheroma. Use of nanoemulsions and nanoliposomes markedly enhanced circulating drug levels. Nanotransfersomal carriers absorbed through transdermal route have shown,in rats,satisfactory therapeutic effects but bypassing the liver and preventing hepatotoxicity. Selfnanoemulsifying drug delivery system (SNEDDS) of statins raises manifold the drug absorption, bioavailability and hence, therapeutic efficacy.[17]

II. CONCLUSION

Inspite of the burgeoning number of molecules available for hypolipidemic therapy,a substantial unmet need of a safe,low-cost and long acting agent persists.30 odd years of first line use notwithstanding,impediments like statin intolerance or suboptimal response remain.The speed of research in pharma cotherapeutics is paralleled by evidence of improving outcomes with progressively lower LDL-C thresholds and the future holds great hope for conquering the atherosclerosis conundrum.

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