DRUGS IN HYPERLIPIDEMIA

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DRUGS IN HYPERLIPIDEMIA

HYPERLIPIDEMIA: ↑levels of any or all LIPIDS &/or LIPOPROTEINS [LP] in blood.

LIPIDS such as**:** Triglycerides (TGs) & Cholesterols (C)

LIPOPROTEINS (LIPID TRANSPORTER) such as**:** Chylomicron (CM), VLDL, IDL, LDL, HDL.

Hyperlipoprotienemia Usually denotes as ↑in LDL unless specified other type

ATHEROGENIC (Apo-b): leading to or causing **atherogenesis** (forming atheromas, plaques in the inner lining of arteries)➔ **Non-HDL & Cholesterol**

ATHEROPROTECTIVE (Apo- A): (good and has no harm) **HDL & Cholesterol** (in normal range)

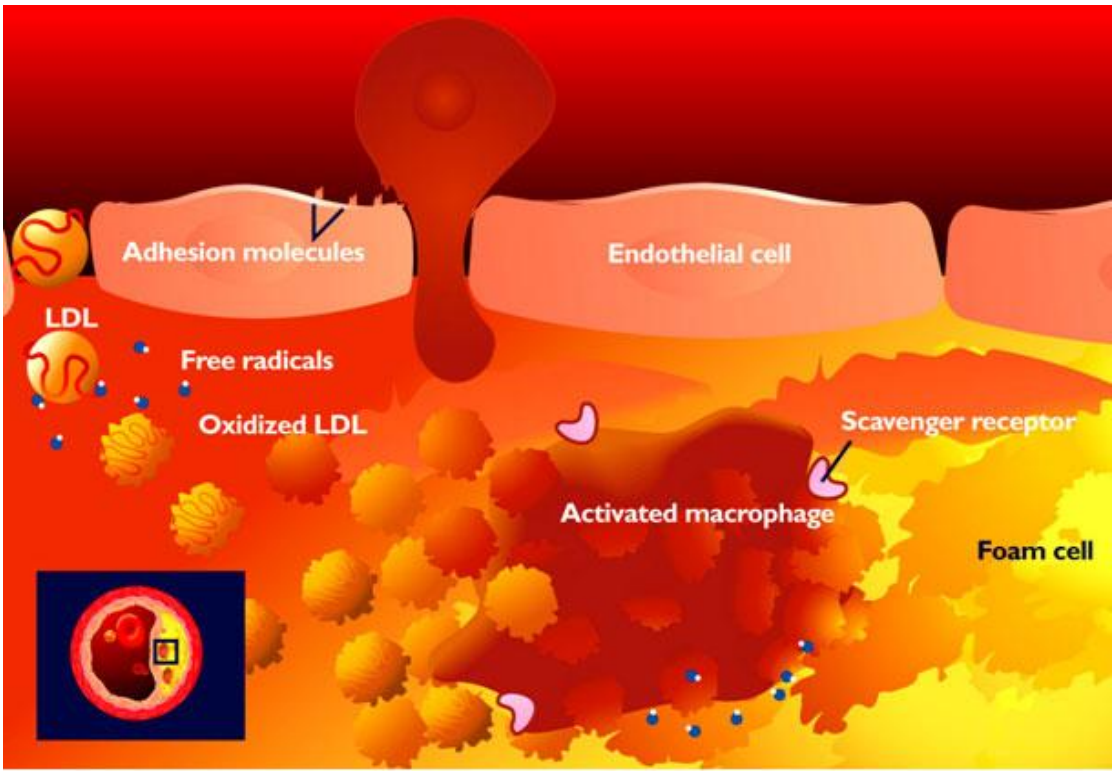
IMPORTANT!!

LProteinemia	↑LP	↑Lipids	Risk
Type I	CM	TGs	-
Type IIa	LDL	C	↑
Type IIb	LDL & VLDL	TG & C	↑
Type III	IDL	TGs & C	↑
Type IV	VLDL	TGs	↑
Type V	VLDL & CM	TGs & C	_

More about Atherogenesis:

When Cholesterol increases, the excessive amount will leak through permeable endothelium & accumulate & become modified (Oxedized-LDL which can produce inflammation in arteries in intimae**) this will produce MP (**methylprednisolone: a glucocorticoid used therapeutically primarily as an anti-inflammatory agent**) which will express SR-A (**class A scavenger receptors which play an important role in host defense and in many macrophage-associated pathological processes, including atherosclerosis**) so it and engulf (Ox-LDL) and trapped it inside,** here we have something called **Foam Cells.**

THIS PIC SHOWS THE MECHANISM



Begins as INFLAMMATORY REACTION triggered by;

Endothelial dysfunction + (Dyslipidemia) ←HYPERLIPIDEMIA is the most common form of it

Progress as FIBRO-PROLIFERATIVE DISORDER (characterized by accumulations of mesenchymal cells and connective tissue in critical locations, leading to organ dysfunction)

Switch into ATHERO-THROMBOTIC INSULT **at any stage of progression**

Morbidity & mortality outcomes prevented or decreased by CONTROLLING DYSLIPIDYMIA

THERAPEUTIC STRATEGIES FOT TREATMENT OF HYPERLIPIDEMIA

A - THERAPEUTIC LIFESTYLE CHANGES :

1. Healthy diet; optimal Quantitative & Qualitative fat content:

- Diet has <30% of calories as fat, <7% as saturated fat and <200mg cholesterol/day
- Avoid trans-fatty acids & acute increase in CHO intake
- Use better vegetable oils rich in unsaturated fatty acids: oleic acid, linoleic acid & linolenic acids. Diet should also contain plant stanols or sterols & soluble fibers.
- Eat food high in antioxidants vitamins

2.Regular exercise

3.Cessation of hazards habits; smoking, alcohol, …etc

4. Weight loss

Can achieve a fall in LDL-C of 8-15% … *but long-term compliance is a problem*

B – PHARMACOLOGICAL TRAETMENT (ANTIHYPERLIPIDEMIC AGENTS) :

According to the mode of action :

1-Inhibits cholesterol absorption in the intestine

Ezetimibe

2-Sequester bile acids in the intestine

Exchange resins

3-Inhibits synthesis of cholesterol

Inhibitors of hydroxymethylglutaryl coenzyme A reductase (HMG-COA Reductase)

4-Alter relative levels & patterns of different plasma LPs

Fibrates, Nicotinic acids

5-adjuvant agents

Omega-3-Fatty Acids, Stanols

Adjuvant therapy: Treatment that is given in addition to the primary (initial) treatment.

Adjuvant treatment is an addition designed to help reach the ultimate goal.

(TARGETING EXOGENOUS PATHWAY):

1-Inhibits cholesterol absorption in the intestine :

Class	Action	Example
1A	Selective C transporter inhibitor	Ezetimibe
1B	ACAT Inhibitors	Pactimibe (not effective)
1C	Selective C Efflux Agonist	Rexinoids (under investigation)

- ACAT: The enzyme which catalyses the intracellular formation of cholesteryl esters .

مهم اعالج الارتفاع في الكولستيرول حتى لو TGs مرتفع اكثر لان الكولستيرول اخطر

EZETIMIBE (Selective Cholesterol transporter inhibitor)

Mechanism :

Ezetimibe localizes at the brush border of the small intestine, where it inhibits the absorption of cholesterol from the intestine. Specifically, it appears to bind to a critical mediator of cholesterol absorption, the Niemann-Pick C1-Like 1 (NPC1L1) protein located on brush border. It also upregulate LDL-receptors on the surface of cells and an increased LDL-cholesterol uptake into cells, thus decreasing levels of LDL in the blood plasma.

brush border : is the name for the microvilli-covered surface of simple cuboidal epithelium and simple columnar epithelium cells in small intestine.

Pharmacological action :

- Decrease LDL 20%➔ 54% of intestinal cholesterol + phytosterol absorption are blocked
- Decrease TG 8% , increase HDL 1-4%
- No effect on steroids, lipid-soluble vitamins, bile acids.

Pharmacokinetics :

- Absorbed & conjugated in intestine to active glucuronide (> potent)
- Reaches peak blood level in 12–14 hours
- Its half-life is 22 hours
- Undergoes enterohepatic circulation (prolong action of drug)
- 80% of the drug is excreted in feces

N.B. Drug level increase if with statins & decrease if with cholystyramine

لما أعطي EZETIMIBE مع statins يحسن أداءه

ولما أعطيه معcholystyramine يقلل أداءه

Indications :

As monotherapy :

Pry prevention of low risk of CHD i.e. need modest ↓LDL

Statin-intolerant patients .

As combination therapy :

safe with statins; synergistic (In moderate/severe ↑ LDL).

If must decrease statin dose because of side effects

With other lipid : lowering drugs; As fibrates.

Adverse effects & interactions : Not common.

GIT disturbance, headache, fatigue, artheralgia & myalgia.

Seldom reversible impairment of hepatic function .

2- bile acid sequestrants :

cholestyramine, colestipol, colesevelam

Are polymeric cation exchange resins.

Mechanism :

Bind to bile acids [BA] preventing their enterohepatic recycling & increase fecal excretion (10 folds).

So in liver decrease BA will decrease C absorption & its increase hepatic breakdown

compensatory increase in LDL R that will increase hepatic C uptake & decrease plasma & tissue C & decrease LDL.

Liver tries to compensate by increase C synthesis but this is usually insufficient to overcome its raised catabolism

شرح مبسط : يرتبط الدواء بالـ bile acid ويمنعها من اكمال دورتها ويخرجها من الجسم ، تقوم الكبد بمحاولة تعويض هذا النقص عن طريق زيادة تصنيع الـ bile acid ولتصنيعه فإنها تحتاج كوليسترول ، تقوم الكبد باستهلاك الكوليسترول المخزن فيها وفي تزويد من LDLrعشان يزيد liver uptakeوبهذا تقل نسبة الكوليسترول الكلية في الجسم .

Pharmacological action :

- Decrease LDL 15-30%
- Increase HDL 3-5%
- increase TG & VLDL
- (initial & transient) but shoe marked increase in type IIb Hyperlipoproteinemia.

الدواء الذي يزيد TGs فلا اعطيه للناس الي عندهم زياده في TGs

Indications :

As Monotherapy;

- Seldom if statin is contraindicated & levels are not high

As combination;

- with statins in type 2A Hyperlipoproteinemia.
- Statins offsets the compensatory ↑ in C synthesis by resins & potentiate ↑ LDL R →synergism
- Pruritus due to biliary stasis or obstruction
- Digitalis poisoning

N.B. Resins must be taken in 2-3 doses with meals / lack effect if between meals

B. Other Indications

Pruritus due to biliary stasis or obstruction

Digitalis poisoning

Adverse effects :

↑ GIT bloating, diarrhea, constipation, dyspepsia

↓ absorption of fat soluble vitamins *(A, D, E, K)*

Dry flaking skin

Contraindications :

Biliary obstruction.

Diverticulitis

Chronic constipation.

Severe hypertriglyceridemia

Type IIb Hyperlipoproteinemia

Interactions :

Decrease absorption of some drugs; Digoxin, Thiazides, Frusemide, Propranolol,
L-thyroxin, Warfarin anticoagulant

N.B. So these drugs must be taken 1 hr before or 4 hrs after sequestrantes

TARGETING ENDOGENOUS PATHWAYS

Niacin(nicotinic) | Fibrates | Statins

Niacin (nicotinic acid):

Is known as Vit B_3. Its amide derivative nicotinamide has no lipid lowering effects

Mechanism

Bind to a specific receptors in adipose tissue (reverse effect of b-AR stimulation) → ↓ cAMP → ↓ PKA → -ve TGs breakdown → ↓FFA to liver → ↓TGs hepatic synthesis & VLDL formation

This eventually ↓LDL & ↑ HDL (CETP has a role???)

In plasma: ↑ LPL activity → ↑ VLDL & CMs clearance

Inhibits VLDL secretion and TGs synthesis from liver by binding to specific receptors in adipose tissue

And this will lead to decreases production of LDL and increase HDL

Pharmacological actions

- **↓LDL 5-25%**
- **↑ HDL 15-30%** اكثر دواء عندي يرفع HDL
- **↓ TG & VLDL 20-50%**
- **↓ LP(a)**
- **↓ Fibrinogen**
- **↑Tissue plasminogen activator**

Indications

Mono or in combination with fibrate, resin or statin

-Type IIa hypercholestrolemia

-Type IIb hypercholesterolemia & any combined hyperlipidemia

- Patient with hypertriglyceridemia & low HDL-C.

-Hyperchylomicronemia

ADRs

Sensation of warmth & flushing

I give him Aspirin to decrease flushing

(prostaglandin induced / -v by
aspirin ½ h before niacin)

Pruritus, rash, dry skin

Dyspepsia: nausea, vomiting, reactivation of peptic ulcer *(↓ if taken after meal).*

Reversible ↑ liver enzymes →hepatotoxicity.

Impairment of glucose tolerance → overt diabetes

↑ uric acid

Contraindications

Gout. **↑ uric acid**

Peptic ulcer.

Hepatotoxicity.

Diabetes mellitus **Impairment of glucose tolerance → overt diabetes**

FIBRATES

Peroxisome Proliferator Activator Receptor [PPARa]

Mechanism

Bind & activate PPARa R

Dimerize with RXR

Are ligands for nuclear transcription receptor called (PPAR-a)

Increase extracellular lipoprotein lipase activity in blood vessels of tissues

nicotinic acid&Fibrates كلهما يخفضون TGsويرفعون HDL

↓ **TGs in plasma**

↓ **VLDL Formation by liver**

Apo- A(1&2) ➢

↓

↑ **HDL**

↑ **RCT**

Drugs

Clofibrate (X)

↑*Gall stones/ Cancer*

Fenofibrate (F)

Bezafibrate not with us

Gemfibrozil (G)

Pharmacological actions

↓LDL 5-20%

↑ HDL 10-20% > (G)

↓ TG & VLDL 20-50%

↓ Fibrinogen

↓ Vascular inflammation > (G)

Improve glucose tolerance > (F)

يعني لو عند الشخص مرض السكر اعطيه F

N.B. Fenofibrate → uricosuric action → > if gout

Pharmacokinetics

	Gemfibrozil	Fenofibrate
Bioavailability	Nearly 100%	Less
Protein binding	95%, passes to placenta	99%
Metabolism	Hepatic (CYP3A4)	Glucuronidation
t ½	1.5 hours	20 hrs
Excretion	Renal 94% > unchanged Feces 6%	Renal 60% Feces 25%

Indications

As monotherapy; > (G)

Hypertriglcyredemia; Type IV lipoproteinemia

<u>As Combined therapy with statins ;</u> > (F)

1. Mixed dyslipidaemia; i.e type IIb & III lipoproteinemia

2. In ↓ HDL, ↑ TGs <u>±</u> [~LDL] + ↑ risk of atherothrombosis [Type 2 diabetes]

N.B. *(F) > (G) to combine specially with lipophylic statins for fear of interaction on CYT P450 → causing toxicity (myositis & rhabdomyolysis). Also the uricosuric action of (F) help in insulin resistance syndrome.*

As Combined therapy with other lipid lowering drugs ; in severe treatment-resistant dyslipidaemia.

ADRs

1. G.I.T upset, headache, fatigue, weight gain

2. Rash, urticaria, hair loss

مهم جدا هذا ADRS

3. Myalagia, myositis, rhabdomyolysis ➔ acute renal failure ➔ in alcoholics or in combination with lipophylic statins (each – ve metabolism of other) also in those with impaired renal function (elimination is ↑ & protein binding ↓)

Contrindications

Renal or hepatic impairment

Pregnant or nursing women

Gall-bladder disease & morbid obesity

In hypoalbuminaemia

In alcoholics

Interactions

They displace warfarin from their protein binding sites ➔ ↑ ◆ bleeding tendency ➔ anticoagulant dose must be adjusted.

They ↓ metabolism of lipophylic not hydrophilic statins ➔ ◆ toxicity ➔ myalgia, myositis, …….etc. Give lower doses

N.B. *Clofibrate > causing interactions. Also ➔ hypoglycemia when combined with sulphonylurea . Also > ADRS, that is why it is least used*

يطرد ارتباط warfarin مع البروتين فيزيد تركيزه بالدم ويزيد تاثيره الذي هو Bleeding

STATINS

HMGCoA Reductase INHIBITORS

Mechanism

One of the enzymes in cholesterol synthetic pathways that controls the rate limiting step of conversion to mevalonate

hepatic C synthesis➔ ↓ hepatic intracellular C

1. ↑synthesis of LDL receptors ➔↑ clearance of LDL

2. ↓ secretion of VLDL & ↑uptake of non-HDL-C

HDL يرفعون Fibrates+nicotinic acid

HDL لا يرفع statins بينما

Also by blocking cholesterol synthetic pathway it is also blocking signaling molecules responsible for progress of inflammation, vulnerability & athrothrombosis occuring 2^{ndry} to excess C accumulation

good effect on endothelial cell لها

PLEIOTROPIC ANTIATHEROGENIC effects

Improve endothelial function

↓vascular inflammation

↓platelet aggregability

↑ neovascularisation of ischaemic tissue

↑ circulating endothelial progenitor cells

Stabilization of atherosclerotic plaque

Antithrombotic actions

Enhanced fibrinolysis

Other effects

+ve osteoclast apoptosis

↑synthetic activity in osteoblasts

Immune suppression.

سوال مهم جدا مريض سكري عنده ارتفاع في TGs فانا اعطيه كاول دواء statinsحتى لو نسبه C ماكانت مرتفعه واعطي معه fibratesعلشان انقص TGs

Classification of STATINS

PRODRUGS	ACTIVE DRUGS

Pravastatin الدواءالوحيد الذي not metabolism in liver

Simvastatin / Lovastatin / Fluvastatin / Atorvastatin / Pravastatin / Rosuvastatin

Lipophylic **Hydrophilic**

Pharmacokinetics

Absorption varies (40-70%), fluvastatin almost completely ◆

Absorption enhanced if taken with food, except pravastatin ◆

All have high first-pass extraction by the liver, except pravastatin ◆

Metabolized variably; ◆

By CYP3A4 → Simvastatin, Lovastatin, Atorvastatin

By CYP2C9 ➔ Fluvastatin, Rosuvastatin

By sulphonation ➔ Pravastatin

Excreted in bile & 5–20% is excreted in urine, except pravastatin ◆ 80-90% urine

t½ ➔ Short 1-3 hrs ➔ Simvastatin, Lovastatin, Fluvastatin ◆

يوخذ بالليل لان تصنيع الكولستيرول يحدث بالليل

➔ 14 hrs ➔ Atorvastatin

➔ 19 hrs ➔ Rosuvastatin

يؤخذ في أي وقت

Indications

<u>As monotherapy;</u>

2ndry Prevention; All ischemic insults as transient ischemic attacks, stroke,

subtypes of ACSs up to AMI, …..etc.

Is given even from1st day of attack ➔ stabilize plaques + help to limit ischemic zone & to salvage preferential tissues

Must be pertained for life & lipid lowering must attain goals specified

Pry Prevention; Patients with hyperlipidemia and are at risk of developing any form of ischemic insults.

In Type IIa Hyperlipoprotinemia. If no control ➔ combine (sequestrants / ezatimibe, niacine,..) to ↓ C.

<u>As Combination therapy;</u>

1. Mixed dyslipidaemias; i.e type IIb & III lipoproteinemia, we add to fenofibrates or niacine if necessary

2. In diabetics even if there is only hypertriglyceridemia & low HDL alone without change in LDL because these patients possess atherogenic non-HDL dyslipidemia, usually with small dense LDL + evident endothelial dysfunction + increased thrombotic profile.

ADRs

↑serum transaminase → can progress to liver toxicity in patient with liver disease(or alcoholic).

Thus lab investigation recommended every 6 month → if levels ↑ 3 folds at any time, statin is stopped or dose adjusted.

↑ creatine kinase activity (index of muscle injury) → measured if myalgia or myositis develops → if ↑ 3-5 folds → we;

statin doses / change to less lipophylic statin / omit combination if with fibrates / search for a concomitant interaction as (amiodarone or verapamil) that could have ↓ statin clearance & ↑ its toxicity →so adjust doses or give alternative combinations

If severe elevation+blood in urine → Rhabdomyolysis →renal failure could be fatal →dialysis needed

Others; ↑lenticular opacity, insomnia, rash, GIT disturbance

Interactions

CYP3A4 , Drug inducers (Phenytoin, griseofulvin, barbiturates, rifampin, and thiazolidinediones) → ↓ efficacy & Drug inhibitors (e.g.macrolide antibiotics, cyclosporine, ketoconazole) ↑ toxicity of Simvastatin, Lovastatin, Atorvastatin

CYP2C9, Drug inhibitors (ketoconazole, metronidazole, sulfinpyrazone, amiodarone, and cimetidine) ↑ toxicity of fluvastatin & rosuvastatin

Adjuvants in hyperlipidemia

Omega-3-FA

B-Sitosterol

Omega -3-FA

found in fish oils containing highly unsaturated FA

Mechanism

↓ enzymes involved in TG synthesis

↑ beta-oxidation of FFA

↓ platelet function

And this will to decrease GTs

Prolongation of bleeding time

Reduction of plasma fibrinogen

Anti-inflammatory effects

These are some vascular protection

Indications

Approved as adjunctive for treatment of very high TGs

ADRs

Eructation, dyspepsia, altered taste

Can worsen glycemic control in diabetics

Can increase bleeding tendencies

β-Sitosterol

found in plants with structure similar to C

Mechanism &Pharmacological Effects

Compete with dietary & biliary C absorption➔ ↓ levels LDL levels ±10%

Indications

Given as food supplement before meal in hypecholestrolemia

ADRs

GIT ; nausea, vomiting, diarrhea, gases, constipation…

Impotence & ↓ sex drive

Avoided in pregnancy & breast feeding