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The medications used in treating nonalcoholic fatty liver disease: clinical pharmacology insights

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Abstract— Nonalcoholic fatty liver disease (NAFLD) is becoming a leading cause of chronic liver injury and its end-stage may require liver transplantation. The NAFLD affects approximately one-fourth of the population and is common in both developed and developing countries. The changes caused by COVID-19 pandemic can show an upward trend in hepatic disease incidence & sequels. Weight reduction via life-style and bariatric interventions are considered lines of NAFLD treatment. The complex pathogenesis of NAFLD gives a chance for several novel agents in treatment. The drugs can target any of the pathways including energy balance & metabolism and/or cellular stress &steatoheptitis, as well as apoptotic & fibrotic changes. Several pharmacological agents including AramcholSemaglutide, Obeticholic Acid, Dapagliflozin, Pemafibrate, Saroglitazar, Emricasan, and Cenicriviroc are in advanced phases of clinical trials for NAFLD. The present work presents a summarized the marketed medications like Metformin, Pioglitazone, α-Tocopherol, Omega-3 fatty acids, and Ursodeoxycholic acid that are employed in the treatment of NAFLD with emphasis on their pharmacokinetics (bioavailability, distribution, biotransformation, and elimination), precautions during therapy, and adverse effects.Presently, the clinical outcomes of the pharmacological agents remain poor and future work is required to get established effective novel medications to optimize the therapeutic regimens for NAFLD.

Key word: Clinical pharmacology, NAFLD, nonalcoholic, bioavailability, half-life, elimination

1.Introduction

Nonalcoholic fatty liver disease (NAFLD), the most common chronic liver disease, affects up to 25-30% of the general population worldwide. With modernization of life style, NAFLD remains an important cause of end-stage liver injury. Moreover, the changes caused by COVID-19 pandemic including unhealthy eating/drinking habits, lack of outdoor physical activity and reduced the visits hepatology-care can show an upward trend in NAFLD incidence and/or severity. NAFLD-related cirrhosis becomes the leading indication for liver transplantation in developed countries[1-3] Despite the above mentioned high prevalence, its clinical presentation is low because early stages of NAFLD are usually asymptomatic. Indeed, NAFLD includes a wide spectrum of liver injuries that range from simple steatosis through nonalcoholic steatohepatitis (NASH) to liver cirrhosis or even hepatocellular cancer (HCC). The NAFLD is presented with other comorbidity (e.g. Type 2 DM, obesity) in a subset of patients making a careful diagnosis necessary. [4-5]

The factors underlying development of NAFLD are not yet completely recognized. The most important factors include weight gain, sedentary lifestyle, (low physical activity and excess caloric intake), endocrine disorders (diabetes, thyroid or polycystic ovary disorders), aging, hyperuricemia, genetics, and stress.[6-8] Additionally, whether insulin resistance is a causative factor or a consequence of NAFLD is a debatable issue. There are several potential and emerging targets for treatment of NAFLD including inflammatory

mediators such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), glucagon-like peptide-1 (GLP-1), peroxisome proliferator-activated receptor (PPAR), farnesoid X receptor (FXR) and uric acid.[9,10] Such variable mediators or targets might be the cause of absence of a satisfying solitary medical therapy. The complex pattern and heterogeneity of NAFLD pathogenesis offer an opportunity to investigate multiple new pharmacological compounds as potential therapeutic options. The pharmacological agents act on multiple targets including energy balance & metabolism (e.g. Metformin, pioglitazone, Dapagliflozin), hepatocyte lipotoxicity&steatoheptitis (e.g. Aramchol, vitamin-E, Resmetirom), and fibrotic/cirrhotic changes (e.g. Obetichlolic acid, cenicriviroc, Selonsertib). The present work presents a summarized review of the marketed medications in use for treating of NAFLD with a special emphasis on the pharmacokinetics (bioavailability, distribution, biotransformation, and elimination), precautions during therapy, and adverse effects of these medications

2.Treatment employed for NAFLD patients

In almost all guidelines, there is no consensus regarding the optimum pharmacotherapy for NAFLD. Moreover, a plethora of reviews presented the present and potential pharmacological agents.[11-14] However, still there is a shortage in the data addressing the clinical pharmacology of such therapies. Hence, the present review presents the pharmacological data of the medications currently or potentially used in treatment of NAFLD.

Both pharmacological and non-pharmacological treatments are considered for some patients (Table 1). It is worthy to note that weight loss through lifestyle modification, diet (low carbohydrate ketogenic diets or high-protein Mediterranean diet) and physical exercise represents the gold standard in treatment of NAFLD patients. In case of insufficient response to life style modification there is satisfying pharmacological intervention. The multiplicity of the pathogenesis of NAFLD that include oxidative stress, insulin resistance, and inflammation suggests that the combination therapy would be essential in tailoring the therapeutic strategy.[12-16]

Table 1: Therapeutic management for NAFLD in recent guidelines:

Line of therapy	Effect	Guidance statement
Life-style modification (Caloric restriction, Increase physical activity)	Weight reduction that decrease hepatic steatosis and histologic improvement of NASH	Weight loss of 3%-5% of BW appears necessary to improve steatosis, but a greater loss (7%-10%) is needed to improve the majority of histopathology
Pharmacological **Vitamin E** (800 IU /day)	Vitamin E improves liver histology in non-diabetic adults with biopsy-proven NASH.	May be considered for this patient population. Risks and benefits should be discussed with each patient before starting therapy.
Pioglitazone (30 -45 mg/day)	Pioglitazone improves liver histology in NASH	May be used to treat in patients with and without T2DM. Risks and benefits should be discussed with each patient before starting therapy.

Metformin (500-1000 mg/day)	Improves serum aminotransferases and IR, but it does not significantly improve liver histology	Metformin in such doses is not recommended for treating NASH in adult patients.
GLP-1 analogues 3 mg Liraglutide SC once-daily	associated with greater resolution of SH and less progression of fibrosis	It is premature to consider GLP-1 agonists to specifically treat liver disease in patients with NAFLD or NASH
Bariatric Surgery	Sustained weight loss after bariatric surgery is beneficial to patients with comorbidities.	Foregut bariatric surgery considered in otherwise eligible obese individuals with NAFLD or NASH.

3.Clinical pharmacology of the NAFLD medications

The medications used currently for NAFLD patients are almost repositioned/repurposed previously-marketed drugs for metabolic disorders. Clinical pharmacology of the medications used for treatment of NAFLD is shown in (Table 2).

Table 2: Clinical pharmacology of medications used for NAFLD:

Drug	Oral Bio-availability	VD/F	Half-life	Elimination and clearance
Metformin	50-60%	300–1000 L	About 5h	Mainly in urine (90%) CL: 510±120 ml/min
Pioglitazone	60-80%	0.6 L/kg	About 7h	Mainly in feces, 15-30% Renal
α-tocopherol	Variable 9-28%	Variable 2-13 L/kg	Variable 15-60 hours	Mainly in feces
Omega 3 FA	Variable 44-89%	82 L	79 hours	mainly oxidized in the liver, excreted in milk
UDCA	Incomplete 30-60%	2.5L	3.5-5.8 days	Primarily in feces, 1% Renal

3.1.Metformin

Metformin, a biguanide introduced to medical therapy as an insulin sensitizer several decades ago, is still a first-line drug for type 2 diabetes mellitus. Metformin, acts mainly by suppressing excessive hepatic glucose production, through the reduction in gluconeogenesis. Metformin does not stimulate endogenous insulin secretion, rather, it improves insulin signaling, decreases fatty acid and triglycerides synthesis, and increases fatty acid β-oxidation. Metformin results in the phosphorylation and activation of AMP-activated protein kinase (AMPK) in the liver leading to its diverse biological effects. Studies have shown improved insulin resistance and liver function (serum aminotransferases) with metformin but without significant improvement in liver histology in patients with NAFLD or NASH.[17-19]

Metformin is well absorbed after oral administration; usually from long-acting formulations. The intestinal absorption of metformin may be primarily mediated by plasma membrane monoamine transporter expressed on the luminal side of enterocyte. The drug is widely distributed to body tissues including the intestine, liver, and kidney by organic cation transporters. Metformin is not bound to serum proteins and has a half-life of approximately 3-5 hours. Metformin is not metabolized, and is excreted in urine as the active compound by active tubular secretion in the kidney as it is the principal route of elimination. Adverse effects of metformin include the commonly gastrointestinal symptoms (anorexia, nausea, vomiting, abdominal discomfort, and diarrhea), and vitamin B12 malabsorption.[20, 21] Due to its accumulation when high doses are used, metformin may increase the risk of lactic acidosis. It is advised to temporarily hold metformin therapy during radiologic contrast procedure and to avoid its use in critical patients such as shock, or cardiac failure. Metformin can be used cautiously by dose adjustment with moderate renal impairment and is contraindicated if the GFR is less than 30 mL/min in severe renal impairment. There is a large inter-individual variability on its therapeutic levels as measured by differences in trough steady-state metformin plasma concentration that may be related to methodological and/or conceptual differences.[22-24]

3.2.Pioglitazone

Pioglitazone, a thiazolidinedione (TZD) derivative for type 2 diabetes mellitus, acts as an agonist at the peroxisome proliferator activated receptor gamma (PPAR-γ) increasing the transcription of insulin responsive genes and thus increases insulin sensitivity. Consequently, pioglitazone contributes to the regulation of carbohydrate and fat metabolism showing improvement of glycemic control, HbA1c, fasting glucose levels and lipid profile.[25] Several studies have reported that pioglitazone is beneficial for NAFLD patients with and without T2DM via improved insulin sensitivity and aminotransferases, steatosis, inflammation, and ballooning.[26-28]

Pioglitazone is well absorbed with a peak plasma concentration is reached after two hours from oral ingestion. Pioglitazone may be taken once daily; the usual starting dosage is 15–30 mg/d, and the maximum is 45 mg/d. Food may delay the uptake of pioglitazone, but the total bioavailability is not affected. Absorption is decreased with the concomitant use of bile acid sequestrants. Pioglitazone is highly bound to plasma proteins (approximately 97%) with a small volume of distribution. Pioglitazone is metabolized by CYP2C8 and CYP3A4 to active metabolites.[29,30] Pioglitazone and its metabolites are excreted to some extent (15-30%) via urine, and the remainders are excreted into bile and feces. The bioavailability of numerous other drugs also degraded by these enzymes may be affected by pioglitazone therapy, including estrogen-containing oral contraceptives; additional methods of contraception are advised. Adverse effects of pioglitazone may include fluid retention, weight gain and macular edema. Animal studies have reported increased risk of bladder tumor with pioglitazone use, however, analysis of human population studies failed to find an association with bladder cancer.[31-33]

3.3.Vitamin E

Vitamin E refers to a group of 8 tocochromanols (4 tocopherols and 4 tocotrienols) with some bio-discrimination in their pharmacokinetic profile. Vitamin E preparations are formulated primarily from synthetic dl- α-tocopherol that has the high oral bioavailability. Vitamin E (alpha-tocopherol) is a lipid soluble vitamin with actions related to its antioxidant properties and plays an important role in the suppression of free radical-induced lipid peroxidation. As a free radical scavenger, vitamin E protects

membrane-bound polyunsaturated fatty acids and other oxygen-sensitive substances from oxidation.[34] Oxidative stress is a key mechanism of hepatocellular injury and disease progression in patients with NAFLD. Vitamin E is an antioxidant and has been evaluated as a treatment for NASH. Vitamin E administered at a daily dose of 800 IU/day improves liver histology in nondiabetic adults with biopsy-proven NASH and therefore may be considered for this patient population.[35-38]
Vitamin E is usually administered orally and its absorption from the gastrointestinal tract is low depending upon biliary and pancreatic secretions, micelle formation and uptake into enterocytes and chylomicron secretion. After reaching the circulation, the absorbed vitamin E is bound to plasma beta-lipoproteins and is widely distributed, particularly in fat tissues. Alpha-tocopherol undergoes recirculation from the liver to the plasma contributing to its long half-life. The plasma half-life of alpha-tocopherol is 48 to 60 hours, while the synthetic form has a half-life of approximately 15 hours.Cholestatic jaundice was reported after IV use α-tocopheryl acetate in premature infants. Vitamin E is mainly cleared from the body via fecal elimination with small amount excreted unchanged in the bile or appear in the urine.[39-41]

3.4.Glucagon-like peptide-1 agonists

Agonists at GLP-1 receptor (Liraglutide, Semaglutide) have been reported to enhance insulin secretion in a glucose-dependent manner, suppress the abnormal high postprandial glucagon secretion resulting in decreased hepatic glucose production, increased satiety, slowed gastric emptying, and promoted weight loss. Liraglutide has a half-life of approximately 12 hours, permitting once-daily dosing.[42,43] The role of GLP-1 agonists in patients with NAFLD and NASH was investigated and trials to date have shown that liraglutide administered subcutaneously once-daily for 48 weeks was associated with greater resolution of SH and less progression of fibrosis.[44-45] The therapy with liraglutide is associated with weight loss, but adverse effects most frequent are nausea & vomiting and a risk of pancreatitis. Semaglutide, GLP-1 receptor agonist recently approved for the management of obesity. It has been shown that treatment with semaglutide resulted in a significantly higher percentage of patients with NASH resolution than placebo. [47]

3.5.Omega-3 fatty acids

Omega-3 polyunsaturated fatty acids (PUFAs) are essential fatty acids that are commonly found in marine sources.Supplementations containing high doses of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as the active ingredients are often administrated for patients with hypertriglyceridemia.[48]
Omega-3 fatty acids have been investigated in large studies in patients with NASH/NAFLD, however a combination of EPA & DHA failed to show significant therapeutic benefit. Therapy with omega-3 fatty acids is limited to be indicated in NASH/NAFLD with hypertriglyceridemia.[49,50] Common adverse effects of omega-3 fatty acids include abdominal pain, nausea, bloating, and diarrhea.

3.6.Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA), a naturally occurring bile acid, decreases cholesterol content of bile by reducing hepatic cholesterol secretion and is used for dissolution of small cholesterol gallstones in symptomatic inoperable patients. After oral administration, it is absorbed, conjugated in the liver and excreted in the bile. Conjugated UDCA undergoes extensive enterohepatic recirculation. The serum half-life is approximately 100 hours. Therapy with UDCA rarely induces serious adverse effects and its bile salt-induced diarrhea is uncommon.[51] Due to its hepatoprotective properties, UDCA has been studied in several trials in patients with NASH/NAFLD. Early studies revealed an improvement in aminotransferases levels and hepatic steatosis but a subsequent randomized controlled trials showed no improvement in liver histology or aminotransferase. Thus, UDCA is not recommended as a monotherapy but is part of a drug combination regimen in some trials on NAFLD in progress.[52-54]

3.7.Statins

Statins, inhibitors of 3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, interrupt the conversion of HMG-CoA to mevalonate, the rate-limiting step in the de novo cholesterol biosynthesis thus

lowering of LDL-C. The therapeutic benefit of statins can be via correction of the dyslipidemia in NASH patients to reduce cardiovascular risk. While statins may be used in patients with NASH cirrhosis, they should be avoided in patients with decompensated cirrhosis.[5, 55,56]

4.Newer therapies and challenges

Given the increasing number of drugs with different mechanisms of actions is undergoing clinical trials for NAFLD, the disease progression, and other comorbidity (DM, renal and other organ pathologies) it becomes challenging to determine pharmacokinetics (absorption, distribution, metabolism, and excretion) for such newly introduced drugs in such clinical situations. Moreover, the impact of NAFLD itself on the intestinal absorption, the hepatic CYP enzymes and/or the renal transporters may add complexity that requires a lot of work to define unbiased pharmacokinetic parameters. So, the relationship between NAFLD and its medication is reciprocal and complex. Attempts have been reported suggesting a consensus on pharmacokinetic screening or 3D human liver spheroids to help choice during development of new drug candidates for NASH.[57, 58]

Table 3: Medications inadvanced phases of clinical trials for NAFLD

Agent	Group	References
Semaglutide	glucagon-like peptide-1 (GLP-1) receptor agonist	[47]
Obeticholic Acid	farnesoid X receptor (FXR) agonist	[62,63]
Pemafibrate	selective PPARα modulator	[64,65]
Saroglitazar	acts as a dual PPAR agonist at the subtypes α (alpha) and γ (gamma) of the peroxisome proliferator-activated receptor (PPAR).	[66]
Elafibranor	PPARa and PPARd modulator	[67]
Emricasan	pan-caspase inhibitor	[68]
Selonsertib	an inhibitor of MAP3 kinase 5 (also known as apoptosis signal-regulating kinase 1 [ASK-1])	[69]
Dapagliflozin Ipragliflozin, Luseogliflozin	sodium–glucose cotransporter 2 (SGLT2) inhibitors	[70-72]
Cenicriviroc	inhibits macrophage accumulation in the liver and	[73]

	ameliorates fibrosis	
Aramchol	modulator of stearoylcoenzyme A desaturase-1 (SCD1)	[74]
Resmetirom	thyroid hormone receptor-beta (THRβ) agonist	[75]

In parallel to the clinical trials employing previous medications for beneficial effects against NAFLD, there is accumulating data making advances in basic science regarding the signaling pathways induced by lipid overload that cause hepatocyte injury and contribute to the pathogenesis of NASH. Current therapeutic strategies are outlined and include antiapoptotic agents, inhibitors of vesicle release & pathogenic cargoes sorting, inhibitors of macrophage chemotaxis, proinflammatory polarization & activation and other targets.[59-61]

Some pharmacological agents (Table 3) are evaluated in phase-3 trials targeting multiple emerging targets mediating the hepatocellular injury in NASH for example ligands at the farnesoid X receptor (e.g. Obeticholic Acid)[62,63]; PPAR ligands[14] including (selective PPARα modulator (e.g. Pemafibrate)[64,65] a dual PPARα/γ agonist (e.g. Saroglitazar),[66] a dual agonist of PPAR α/δ receptors (e.g. Elafibranor)),[67] ; the pan-caspase inhibitor Emricasan,[68] ; the apoptosis signaling kinase 1 inhibitor (e.g. Selonsertib),[69] sodium–glucose cotransporter 2 (SGLT2) inhibitors (Dapagliflozin, Ipragliflozin, Luseogliflozin)[70-72] and cenicriviroc; a dual antagonist of chemokine receptor types 2 (CCR2) and 5 (CCR5).[73]

The newer therapies for NAFLD including Aramchol a modulator of stearoylcoenzyme A desaturase-1 (SCD1) [74], Resmetirom a thyroid hormone receptor-beta (THRβ) agonist [75]and modulators of gut microbata like Probiotics are also being evaluated in NAFLD patients [76-77] A role for the intestinal hypoxia-inducible transcription factor 2-alpha (HIF-2α) in development of NALFD has been suggested making the HIF-2α inhibitors a potential therapeutic option for NAFLD.[78]

5.Conclusion and perspectives

After modernization of life, NAFLD has become the most frequent chronic liver disease with an increasing health burden due to association with the obesity epidemic in populations worldwide. In the past decade, there was a plethora of studies that increased understanding of molecular mechanisms and pathogenesis of NAFLD and suggested several potential medications. The newer therapies which target different pathways of NAFLD are promising and include Dapagliflozin, Obeticholic Acid, Semaglutide, Aramchol, Saroglitazar, Emricasan, Cenicriviroc, and Pemafibrate. However moving from bench-side to bed-side failed to establish and effective therapy and scanty of the suggested medications is approved for NAFLD treatment. Effective management employs a team of healthcare providers (GPs, hepatologists, dieticians, physiotherapist and/or bariatric surgeons) making benefits from the multidisciplinary clinic models. Further work is needed to get established effective novel medications along with treatment algorithms in order to optimize the therapeutic regimens for specific NASH/NAFLD patient stage.

6.Declaration of interest

The author declares that they have no conflict of interest.

7.Acknowledgment

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