Inhibition Of Stearoyl Coenzyme A Desaturase (SCD1) Activity By Aramchol Reduces Liver Fat And Presents A New Therapeutic Option In NAFLD And NASH

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Abstract

We evaluated the effects of Aramchol (Fig.1), a Fatty Acid Bile Acid Conjugate, and a direct,liver SCD1 inhibitor on experimental NAFLD. Its safety and tolerability and PK were tested in animals and humans.

In animals on a high fat diet (HFD) Aramchol prevented the development of NAFLD (not shown) and consistently reduced liver fat (Fig.2) and SCD1 activity (Fig.3) in pre-established NAFLD. Liver fat (triglycerides) was reduced even while the animals were eating a high fat diet. The rapidity of the fat reduction was inversely proportional to fat concentration in the treatment diet (Fig.2). The HFD increased while Aramchol markedly decreased SCD1 activity in the liver (Fig.3). Aramchol did not affect the mRNA of SCD1 or other lipogenic genes . Doses of Aramchol up to 1000mg/kg/day were well tolerated for 28 days in rats and dogs in two different CROs.

Aramchol with a formulation producing 3 times higher blood levels was well tolerated (500mg/kg/d) in 2 species for 3 months (Table). In a Phase I study in 41 human volunteers single oral doses of 30-900 mg/day were well tolerated and absorbed (Fig.4). Four day repeated daily doses of 30 or 300 mg given to moderately obese and hypercholesterolemic volunteers (mimicking NAFLD) were also well tolerated (Text, Phase I). Deletion or suppression of the SCD1 gene in animals was conflictingly reported to be pro or anti atherogenic and to cause weight loss in animals, associated with a skin lesion. However, in 8 studies in animals the effect of Aramchol was modestly anti-atherogenic (not shown) and there was no weight loss or skin lesion. A Phase IIA study is pending.

Methods

Liver fat was measured chemically (Folch). SCD1 activity was measured by the production of [14C] Palmitoleic acid from [14C] Palmitic . Toxicity/safety in animals and humans was evaluated by standard methods. Aramchol blood levels were measured by MS.

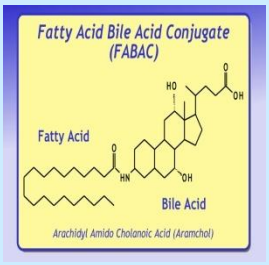

Fig1 Scheme Aramchol

Results

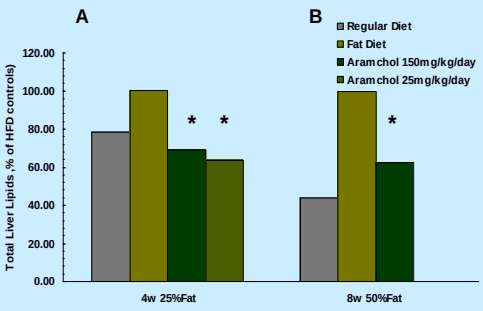

Fig2 A:Liver fat in C57Bl6/J mice after 4 weeks on a 25% High Fat Diet (HFD)without (yellow) or with (green) oral Aramchol (2 doses). B:Same as A, mice fed a 50% HFD for 8 weeks without or with oral Aramchol.

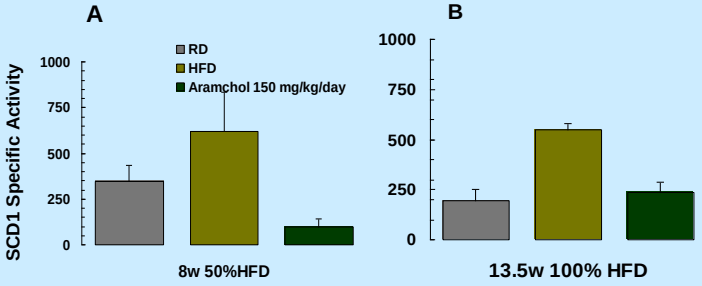

Fig3 SCD1 activity in mouse livers after A:8 weeks of RD (white),50% HFD only (yellow) or with oral Aramchol supplementation (green).B:Mice treated 13.5 weeks with RD,100%HFD only or with oral Aramchol supplementation (green).

Table : **Toxicity/ Safety tests**

Species/CRO	Dose (mg/kg/d)	Duration (w)	NOAEL mg/kg/d)*
Dogs, Holland	100-1000	4	1000
Rats India	250-1000	4	1000
Dogs Canada **	50-500 **	13	500
Rats Canada **	50-500 **	13	500
Human, Estim.	0.5-2		

* NOAEL - No Observed Adverse Effects Level
** New Formulation, Blood Levels 3x Higher

OTHERS: The mRNA levels of SCD1,LXRs, PPARs,CPRs,DGATs,etc. Were unchanged in the livers of mice treated with Aramchol up to 3 ½ month.

Phase I study - Humans

Protocol

41 healthy human volunteers were studied:
16 received single, escalating, oral doses of Aramchol 30,100,300 or 900 mg/day or Placebo (Part A).
25 received 4 day repeated oral doses of 30 or 300 mg/day of Aramchol or Placebo.(PartB).
The latter were moderately obese and hypercholesterolemic.
Clinical and laboratory monitoring, Aramchol PK and minimal Pharmacodynamic tests were performed.

Results

All subjects completed the study. No Serious Adverse Effects were observed.
Mild ,transient,possibly Adverse effects were observed at similar frequencies in the Placebo and Aramchol groups. The same applied to laboratory tests.
Aramchol blood levels were dose proportional ,suitable for once a day dosing. The Monitoring group found "Aramchol safe and tolerable at the doses tested".

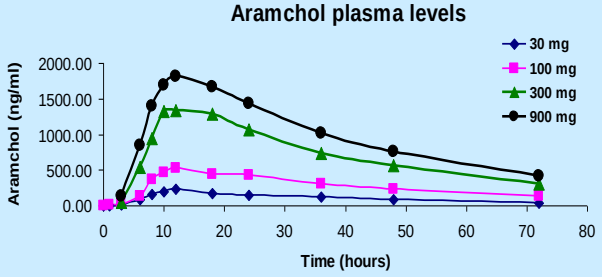

Fig4 Aramchol Plasma Levels (ng/ml) in human volunteers after single oral doses of 30,100,300 or 900 mg Aramchol. Six subjects per dose group.

Conclusions

Aramchol inhibition of SCD1 consistently reduced liver triglyceride content in animal models of NAFLD and NASH.
It was well absorbed, tolerated and safe in animals and humans.
It is about to be tested in a Phase IIA study in patients with NAFLD and NASH.

References

1. Gilat T, et al. Prevention of diet induced fatty liver in experimental animals by the oral administration of a fatty acid bile acid conjugate (FABAC) Hepatology 2003;38:436-442.
2.. Leikin-Frenkel A, et al. Treatment of pre-established diet induced Fatty Liver by oral Fatty Acid Bile Acid Conjugates(FABACs) in Rodents. European J.Gastroenterology & Hepatology 2008; 20:1205-1213.