Obeticholic Acid, a Farnesoid X Receptor agonist, reduces bile acid synthesis in patients with Primary Bile Acid Diarrhea.

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OCA therapy in PBAD patients increased FGF19, on the first and last days of OCA therapy BA sequestrants were discontinued throughout a 6-week run-in period. There was a strong correlation between % reduction in 6h total BA AUC response (34.5 to 20.9 µmol/l, p = 0.02) and 6h peak BA response (7.5 to 4.0 µmol/l, p = 0.02) were both significantly lower. The reduction in fasting bile acids was not statistically significant. An inverse correlation was found between the change in fasting FGF19 and % change in 6h BA AUC response (r = -0.65, p = 0.02), so that reductions in BA response were associated with increases in fasting FGF19. There was a strong correlation between % reduction in 6h total BA AUC with the reduction in number of stools per week (r = 0.78, p = 0.004).

RESULTS

- OCA treatment for 2w led to a significant reduction in median fasting C4 (16 to 3 ng/ml, p = 0.03), indicating that the rate limiting step of new BA synthesis was inhibited.
- The % change in fasting C4 was significantly associated with the change in FGF19 6h response (r = -0.62, p = 0.05), indicating that an increase in FGF19 correlated with a reduction in fasting C4. This was also associated with the reduction in urgency score (r = 0.66, p = 0.04).
- The total BA 6h AUC response (34.5 to 20.9 µmol/l, p = 0.02) and 6h peak BA response (7.5 to 4.0 µmol/l, p = 0.02) were both significantly lower.
- The reduction in fasting bile acids was not statistically significant.
- An inverse correlation was found between the change in fasting FGF19 and % change in 6h BA AUC response (r = -0.65, p = 0.02), so that reductions in BA response were associated with increases in fasting FGF19.
- There was a strong correlation between % reduction in 6h total BA AUC with the reduction in number of stools per week (r = 0.78, p = 0.004).

CONCLUSIONS

- OCA therapy in PBAD patients increased FGF19, associated with reduction in BA synthesis, as measured by C4 and BA response, and to improvement in clinical symptoms.
- Stimulation of FGF19 and inhibition of BA synthesis by OCA is rational therapy in this patient group and further trials are warranted.

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REFERENCES