The effects of Obeticholic Acid, a Farnesoid X Receptor agonist, in patients with chronic diarrhea secondary to Crohn’s ileal disease.

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BACKGROUND

- Chronic diarrhea is a frequent result of excess fecal bile acid (BA) loss though this is often unrecognized.(1)
- Secondary bile acid diarrhea (SBAD) is common in Crohn’s disease with ileal inflammation and/or resection.
- Bile acid malabsorption can result from reduced expression of bile acid transporters in ileal disease, but this also alters Fibroblast Growth Factor 19 (FGF19) secretion.(2,3)
- The normal ileum produces FGF19 in response to BA absorption and farnesoid X receptor (FXR) activation.
- FGF19 synthesis is stimulated by the natural farnesoid X receptor (FXR) agonist chenodeoxycholic acid.
- Obeticholic acid (OCA) is a semi-synthetic FXR agonist with 100-times greater potency.(4)
- FGF19 acts as a hormonal regulator of hepatic BA synthesis.

AIMS

- To investigate the effects of OCA therapy in patients with secondary Bad to Crohn’s, and in idiopathic diarrhea controls.

METHODS

- 32 patients were recruited to this pilot trial by Nov. 2013. The final total was 35 (April 2014).
- 10 primary BAD patients (7F:3M, median age 41y, SeHCAT 7d retention <10%, median 4.8%), have been presented separately.
- 8 SBAD patients (6F:2M, median age 45, ileal resection 0-46 cm, median 22.5cm, and/or SeHCAT <11% (Western General Hospital, Edinburgh).
- The final total was 10 and updated data are also shown as here.
- 7 idiopathic diarrhea controls (2F:5M, SeHCAT 16-35%, median 25%).
- Patients received OCA 25mg daily for 2w after a 2w run-in period. BA sequestrants were discontinued.
- Symptoms were recorded. A stool index was calculated from frequency, stool form and loperamide use. Urgency, pain & bloating scores were also recorded for the 6w period.

RESULTS

- In the SBAD group, 7 out of 8 patients showed beneficial but variable changes in stool form and stool index [median changes p = 0.04 and 0.03 on final cohort of 10 pts.]
- Pain frequency [-64%, p = 0.03] and severity [-71%, p = 0.04] both improved.
- Increases in FGF19 fasting and post-prandial were relatively small in the SBAD group overall, except in 2 patients.
- FGF19 values were associated with improvements in urgency [r = -0.58, p = 0.05] and % reductions in C4 [r = -0.61, p = 0.03].
- Median BA post-prandial AUC was significantly reduced [p = 0.04].

- By contrast, in the diarrhea controls, there were no significant changes in clinical symptoms or FGF19. BA responses were reduced (p = 0.03) and significant relationships between FGF19 and BA responses were found.

- On the first and last days of OCA therapy, blood samples were assayed for FGF19 and total BA levels. Samples were collected fasting and for 6h response after OCA and meals to provide area-under-the- curve (AUC). Standardized meals were provided at 8am and 12 noon.
- Fasting levels of 7dOH-4-cholesten-3-one (C4) were assayed by HPLC (Western General Hospital, Edinburgh).
- Fasting and 6h AUC total BA levels were measured by standard colorimetric method (Clinical Chemistry, Imperial College Healthcare NHS Trust).
- Statistical analyses were performed with Winstat. Non-parametric comparisons (Wilcoxon paired tests) and correlations (Spearman rank) were used.

- Ideal resection length in SBAD was related to the change in stool frequency (r = 0.78, p = 0.01), index (r = 0.63, p = 0.05) and urgency (r = 0.68, p = 0.03) so that those with the smallest resections had the greatest improvements.
- The % reductions in post-prandial BA AUC response [r = 0.63, p = 0.03], fasting and peak values, and in fasting C4 [r = 0.71, p = 0.01] were greater in those with shorter resections.
- Post-hoc analysis of the 7[10] patients with an ileal resection length < 45cm showed significant changes in stool frequency (p = 0.03), stool form (p = 0.02) and index (p = 0.02). This group also had significant changes in FGF19 (p = 0.03) and C4 (p = 0.02).

CONCLUSIONS

- This pilot study has shown that OCA produces clinical benefit in many Crohn’s patients with secondary bile acid diarrhea.
- Patients with shorter resections had greater improvements.
- No significant clinical changes were found in idiopathic diarrhea controls.
- Further trials in Crohn’s patients are warranted.

ACKNOWLEDGMENTS & CORRESPONDENCE

L and JN were supported by the Bhandar Research and Education Trust.
Obeticholic acid was donated by Intercept Pharmaceuticals.
Disclosures: JS is employed by Intercept Pharmaceuticals, JW has received consulting, speaking and teaching fees from GE Healthcare, Intercept, Novartis, NGBLS, Sanofi and Pendellapharm.
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