Diagnosis and Treatment of Primary Sclerosing Cholangitis in Children

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Primary Sclerosing Cholangitis (PSC) In Children

• PSC is chronic inflammatory disease of the biliary tree leading to biliary strictures and cirrhosis.

• 80% to 90% associated with inflammatory bowel disease, esp. ulcerative colitis.*

• Cause is unknown but positive immune markers (ANA, pANCA, ASMA, AMA) suggest immune mechanisms. **


Primary Sclerosing Cholangitis

• Children with PSC usually have inflammatory bowel disease, esp. in colon, & may be mild.* **

• Children with IBD often have PSC with minimal elevation of LFTs.***

• Rarely PSC associated with other conditions (immunodeficiency, histiocytosis X, cystic fibrosis, Alagille’s syndrome, celiac disease, reticulum sarcoma, and sickle cell disease).

**Boonstra et al: Inflamm Bowel Dis, 2012

Overlap Syndromes of Autoimmune Liver Diseases*

• Primary sclerosing cholangitis**
  – Genome-wide association

• Autoimmune hepatitis

• Immunoglobulin G4-related sclerosing cholangitis

• Primary biliary cirrhosis

*Czaja: Dig Dis Sci: 2012
**Ellinghaus et al: Hepatology 2012

Diagnosis of Primary Sclerosing Cholangitis

• MRCP (or ERCP)* **
  – narrowing & irregularity of intra- and extra-hepatic bile ducts; beading of intrahepatic duct

• Liver biopsy
  – Periportal hepatitis, bile duct inflammation & necrosis, lamellar (onion skin) fibrosis, & biliary cirrhosis

*Dave et al: Radiology 256:387, 2010

Limited Effectiveness of Treatments for Primary Sclerosing Cholangitis

• Immunosuppressive drugs
  – Corticosteroids
  – Cyclosporine
  – Methotrexate

• Ursodeoxycholic acid
  – Ineffective*
  – Increase risk in UC of colorectal cancer**

*Triantos CK: Aliment Pharmacol Ther 34:901,2011
Long Term Outcome of Primary Sclerosing Cholangitis

• Often leads to cirrhosis of the biliary tree, portal hypertension, and liver failure.
• Approximately 6,000 adults and children have had liver transplants for PSC.
• Risk of recurrence of PSC after liver transplant is common as high as 40% in adults.
• Long term risk for PSC is cholangiocarcinoma as high as 20% of adults.

Pediatric Liver Transplantation for PSC: SPLIT Registry*

• 79 patients or 2.6% SPLIT patients
• 60% inflammatory bowel disease
• 9.8% recurrence of PSC after transplant at mean 18.7 ± 13.8 mos
• Similar survival as age matched non-PSC


Cholangiocarcinoma in Primary Sclerosing Cholangitis*

• 2-3% of all cancers.
• 1.5 times more common in males
• 10% of patients PSA (9-23%)
• 40% PSC have incidentally at autopsy
• Early detection with serum carbohydrate antigen 19-9.

*Abbas: J Gastrointestinal Caner 40:19, 2009

Oral Vancomycin: Treatment of PSC in Children with IBD*

• 1st case was 15 yr. old male with PSC, UC, and C. difficile infection.
• He had resolution of PSC on oral vancomycin.
• He had recurrence of PSC off oral vancomycin after C. difficile had been cleared.
• PSC resolved again on oral vancomycin.
• 2 cases with Crohn disease & PSC without C. difficile PSC responded to oral vancomycin.


Oral Vancomycin Treatment of Primary Sclerosing Cholangitis*

• Normal or improved liver blood test and biliary pathology (liver biopsy, imaging).
• Improvement of IBD and pre-treatment positive immune markers are negative.
• Often recurrence of IBD and PSC after oral vancomycin is discontinued.

Vancomycin: Bactericidal Antibiotic*

- Exerts its effects by binding to the precursor units of bacterial cell walls, inhibiting their synthesis.
- Alters gram positive bacterial wall permeability.
- Gram negative organisms are not sensitive to vancomycin because it does not bind to the bacterial wall.


Possible Mechanisms Oral Vancomycin Treats PSC

- Since oral vancomycin is not absorbed, likely its effect is in the intestine.
- Bactericidal effect on gram-positive organisms which trigger release of cytokines like TNF-α
- Vancomycin down-regulates the TNF-α mRNA accumulation in monocytes.

Long-term Treatment of PSC in Children with Oral Vancomycin*

- 14 children (age 2-17 yrs; male:female 2.3:1)
- All with IBD (11 with UC; 3 with Crohn disease; 13 had colitis)
- Stool culture negative; 1 with C. difficile.
- Oral vancomycin dosing 50 mg/kg/d divided into t.i.d. dosing upto 1500 mg/day.


Autoimmune Markers Response to Oral Vancomycin Treatment of PSC*

- 12 had autoimmune markers (ANA 5; 3 ASMA; 11 p-ANCA; 1 ASCA).
- Markers before & on 3 mos of vancomycin.
  Before Tx On Tx
  – ANA 4 0
  – ASMA 4 0
  – p-ANCA 4 0

More recent 9 Children on Oral Vancomycin for PSC and IBD*

- Age: 2 to 16 yrs of age with average 9 yrs.
- 6 males; 3 females
- All have ulcerative colitis and PSC
- Treated with oral vancomycin 50 mg/kg/d up to 1500 mg divide 3 times per day.


Effect of Oral Vancomycin on PSC and IBD in 9 Children*

- Colitis: 4 - resolution of colitis on biopsies
  3 - minimal inflammation on biopsies
  2 - asymptomatic without biopsies
- PSC: 5 - normal liver biopsies
  3 - fibrosis without inflammation
  1 - much reduced inflammation
- Anti-inflammatory effects on blood T lymphocytes and cytokines


Effect of Oral Vancomycin on Blood Liver Test (GGT) for 9 Children with PSC*

Effect of Oral Vancomycin on White Blood Cell Count (WBC) for 9 Children with PSC*

Plasma cytokines and growth factors tested for biomarkers

- Luminex 35 plex
- Molecules tested:
  ENA78, EOTAXIN, FGFb, G-CSF, GM-CSF, GRO ALPHA, IFN-G, IL-10, IL-12P40, IL-12-P70, IL-13, IL-15, IL-17, IL-17F, IL-1a, IL-1B, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IP10, LEPFTIN, MCP-3, MIG, MIP1a, MIP-1B, NGF, PDGFBB, RANTES, TGF-b, TNF-A, TNF-B, VEGF

Longitudinal changes in cytokine production patterns from Th1 (TNFα), Th2 (IL-4, IL-13), and Treg (TGFβ) subtype cells before and 3 months post OV administration in children with PSC+IBD (n=6);

Composite data of A) CD4+CD25hiCD127lo and (B) CD4+FoxP3+ Treg levels in pediatric PSC+IBD patients before and after OVT administration in pediatric PSC+IBD patients.

Preliminary Data:
Patient A Regulatory T cell Analysis*

- Patient A: on OVT for >1yr
- Removed from therapy and experienced disease recurrence


HYPOTHESIS

- Oral-vancomycin might alter the gut microbiota composition and preferentially induce local T cells to adopt a regulatory T cell phenotype.
- Induction of regulatory T cells in the gut tissue might affect the inflammatory status of nearby tissues such as the biliary tree.

Oral Vancomycin Treatment for Primary Sclerosing Cholangitis

- 33 children with PSC have been treated with oral vancomycin.
- In those without cirrhosis, LFTs, liver biopsies and imaging normalized and those with cirrhosis had improvement.
- Most had recurrence of disease within 12 months when oral vancomycin was stopped.
- On therapy, most autoimmune antibodies (ANA, ASMA, p-ANCA, ASCA) decreased or became negative.
- Most had remission on IBD on therapy.
- None had side effects on therapy.

Questions to be Answered by Current Oral Vancomycin for PSC & IBD Study

- Do adults respond to vancomycin like children?
- What is the most effective dose of vancomycin and is it detectable in the blood?
- Is the quality life (Harvey Bradshaw test) improved on therapy?
- Will changes in the immunology and microbiota determine how vancomycin produces its effect?