Primary Biliary Cholangitis (PBC)

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ALASKA NATIVE
TRIBAL HEALTH
CONSORTIUM

What is PBC

- PBC is an autoimmune disorder where a persons immune system attacks their small bile ducts
- 90% of persons with PBC have an antibody in their blood called “anti-mitochondrial antibody (AMA) that is diagnostic for PBC when it is present
  - 10% of patients with this condition do not have this antibody and the diagnosis is made on liver biopsy
- Patients with PBC have evidence of damage bile ducts on liver biopsy that shows their bile ducts are under attack by white cells (lymphocytes) and the AMA which is poking holes in their bile ducts
- Bile from damage ducts leaks out and has a high electrical charge that damages (shocks) liver cells

What Happens to Persons who have PBC?

- PBC usually begins in persons who are in their late 20's or early 30 years of age
- These persons start with no symptoms but one of their liver enzymes is elevated, Alkaline Phosphatase (ALP)
- Over time the liver in persons with PBC slowly scars leading to cirrhosis in their late 40's or 50's and they present to their provider with liver disease
- If undiagnosed, PBC can lead to liver failure, liver cancer and the need to have a liver transplant

How Common is PBC in Alaska Native People

- PBC is considered a rare disease: world wide, the range or rates of PBC is as low as 2 per 100,000 persons to as high as 40/100,000 persons
- We found that in the Alaska Native (AN) population the rate is 43/100,000 persons. This is the highest rate reported in the world
- The male to female ratio in the AN population of PBC is 12:1
- PBC can run in families and most persons with PBC either have another or have family members with an autoimmune disease such a Rheumatoid Arthritis, Lupus, Sjogren's Syndrome or autoimmune thyroid disease.
- PBC is thought to be related to a predisposing immune genetic risk triggered by an environmental contaminant or infectious agent
  - Possible triggering agents include heavy meatal environmental contaminants or viruses

Treatment of PBC

- Only one medication is licensed for treatment of PBC: Ursodioxycholic acid or URSO (synthetic Bear bile)
- About 5% of human bile is URSO, the rest is human bile (cholic and chenodeoxycholic acid) and is made from cholesterol
- Human bile is highly electrically charged and when it leaks out after the AMA punches holes in the bile ducts it's high electrical charge damages liver cells, destroying them and leads to liver scarring
- URSO has no electrical charge and taking URSO increases the amount of this bile acid in humans bile to about 50% or half
- When URSO leaks out of the bile ducts, it coats liver cells protecting them from damage and also has anti-inflammatory properties

Response to Treatment of PBC with URSO

- One third of patients taking URSO have an excellent response with normal ALP levels
- One third have what is considered an adequate response defined by a 40% decrease in their ALP levels.
  - These patients experience improved survival than those not treated and some will outlive their disease
- One third have a poor response to URSO, can develop cirrhosis and are at risk of liver failure and liver cancer

A Study of Risk Factors in AN Persons with PBC

- We studied 65 Alaska Native persons with PBC who had a liver biopsy to identify risk factors for causes of death and overall survival in persons with PBC
- The Kaplan-Meier method approach was applied for comparison of survival curves,
- Cox proportional risk model was employed for the calculation of hazard ratios for the independent study variables.
- As of July 2020, 10 had died at an average age of 63 years, more than a decade younger than the average for the AN population.
- AN persons with PBC in whom URSO was unable to get their ALP below 135 U/L (normal level is 100 U/L) had significantly lower survival time independent of age at diagnoses, gender and liver biopsy score for amount of scaring at time of diagnosis

Conclusions

- AN People have the highest reported rate of PBC in the world
- ALP level in persons with PBC above 135 U/l is an independent risk factor for poor survival
- Medications are needed that can lower the level of ALP in AN persons with PBC below 135 U/L to improve survival time for those with this disease, allowing them to live a normal life span
- There is a medication that has shown good response and safety in phase 2 clinical trial and Dr. Barbour is working on participating in a phase 3 trial to offer a medicine to AN persons who failed URSO called Elafibranor that appears to be very effective and has a good safety profile
- Studies to search for triggers that can set of PBC in AN persons who are genetically susceptible such as environmental contaminants and viruses might be helpful in preventing PBC in at risk persons.