MYCOBACTERIUM AVIUM SUBSPECIES *PARATUBERCULOSIS*: AN INFECTIOUS CAUSE OF CROHN'S DISEASE?

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Crohn's disease is a chronic inflammatory intestinal disease of unknown etiology that is often considered as a dysregulated immune response. Current therapies for Crohn's disease target inflammation by blocking pro-inflammatory signaling, which often provides symptomatic improvement but is not curative [1]. Genome wide association studies of genetic susceptibilities have shown Crohn's disease susceptibility genes are linked to cell functions that control infection by intracellular pathogens, such as *NOD2*, *SLC11A1*, and *ATG16L1* [2]. *Mycobacterium avium* subspecies *paratuberculosis* (MAP) is an obligate intracellular pathogen that causes Johne's disease in ruminants [3]. Johne's disease was described in 1895, by the German veterinarian Heinrich Albert Johne, and has histology and course similar to Crohn's disease. In 1912, before the description of Crohn's disease as 'regional ileitis' by Burrill Crohn in 1932, a possible link between MAP and human disease was made by the Scottish surgeon Thomas Kennedy Dalziel, who noted that the clinical and gross appearances of the intestine in his patients were similar to cattle with Johne's disease. MAP is now known to be widespread in the environment as a contaminant of both drinking water and human food, especially in meat and dairy products [4].

What evidence supports a causative role for MAP infection in Crohn's disease?

Viable MAP has been cultured from peripheral blood mononuclear cells of humans and is seven times more likely to be detected in Crohn's disease patients. Numerous studies have reported detecting MAP DNA in tissues and peripheral blood of Crohn's patients. However, MAP has not been detected in, or isolated from, all Crohn's patients or by all laboratories, possibly because of technical limitations in culturing MAP and recovering the organisms from host tissues. MAP has also been detected in non-IBD subjects, consistent with the ubiquitous environmental exposure of humans to MAP. Even in the natural bovine host, only approximately 10-15% of animals develop Johne's disease despite most in a herd being MAP positive.

Factors that possibly influence the outcome of MAP exposure include the infectious dose, health and age of the host at time of exposure, and virulence factors of infecting MAP strain. This is similar to other chronic diseases in humans such as with *Mycobacterium tuberculosis* or *Helicobacter pylori,* which cause clinical disease in only a small proportion of the infected population. For example, when *H. pylori* was first cultured and proposed as the cause of gastritis and the gastritis-associated diseases peptic ulcer and gastric cancer, the association was generally not believed to be causative because *H. pylori* infections were ubiquitous and often found in otherwise apparently healthy individuals. The tide turned when it was shown that curing *H. pylori* infection healed gastritis and led to cures of up to then incurable peptic ulcer disease. More recently, its etiology in gastric cancer has also been confirmed.

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This field is poised to learn the results of a large clinical trial testing the hypothesis that MAP infection is etiologically linked to Crohn's disease. Redhill Biopharma is near the end of a Phase III double-blind placebo controlled clinical trial in which anti-MAP therapy (a fixed-dose combination of clarithromycin, rifabutin, and clofazimine) is being compared to standard therapy plus a placebo for inducing remission in Crohn's patients. All subjects have been enrolled and results of the data analyses are expected within the next three months, followed later by the one year follow-up data.

What are the public health implications if the study is positive?

MAP is thought to spread to humans from the environment, or more often from infected animals via direct and indirect contact especially by foodborne routes, as MAP can survive a range of standard cooking or processing temperatures. The Centers for Disease Control (CDC) and the United States Department of Agricultural Research (USDA), public health regulatory agencies guided by research- and science-based prevention and control of foodborne illnesses, have not yet classified MAP as a zoonotic infection. As such, MAP-infected animals have not been excluded from production of human food products and viable MAP has been reported in retail food products including baby formula, ice cream, yogurt, meat, cheese, and in municipal water systems. Confirmation of MAP as a cause of Crohn's disease will necessitate eliminating foodborne exposures to MAP. Such efforts are already underway in Ireland [5], which is one of the largest suppliers of milk for infant formula.

What are the effects on MAP research?

There is a need for improved and more rapid tests for the presence of MAP infection in humans. Treatment success will prompt study of different anti-MAP therapies or co-therapies such as specific antimicrobials, anti-MAP vaccines, mycobacterial phage therapies, etc. Nonetheless, the results from the recent trial suggest that, if confirmed, we are likely at the end of the beginning or the beginning of the end of Crohn's disease.

REFERENCES

1. Gajendran M, Loganathan P, Catinella AP, Hashash JG. A comprehensive review and update on Crohn's disease. Dis Mon. 2018.64:20-57.
2. Verstockt B, Smith KG, Lee JC. Genome-wide association studies in Crohn's disease: Past, present and future. Clin Transl Immunology. 2018.7:e1001.
3. McNees AL, Markesich D, Zayyani NR, Graham DY. Mycobacterium paratuberculosis as a cause of Crohn's disease. Expert Rev Gastroenterol Hepatol. 2015.9:1523-1534.
4. Waddell L, Rajic A, Stark K, McEwen SA. Mycobacterium avium ssp. paratuberculosis detection in animals, food, water and other sources or vehicles of human exposure: A scoping review of the existing evidence. Prev Vet Med. 2016.132:32-48.
5. Graham DA, Lynch M, Coughlan S et al. Development and review of the voluntary phase of a national BVD eradication programme in Ireland. Vet Rec.2014.174:67.