Biology and Medicine

Monif, Biol Med (Aligarh) 2016, 8:2
DOI: 10.4172/0974-8369.1000270

Review Article Open Access

The *Mycobacterium avium* Subspecies Paratuberculosis Dilemma

Gilles R. G. Monif[1,2*]

[1]*Infectious Diseases Incorporated, 17121 Lakewood Drive, Bellevue, NE, United States of America*

[2]*College of Veterinary Medicine, University of Florida, Gainesville, FL, United States of America*

[*]**Corresponding author:** Gilles R. G. Monif, MD, Infectious Diseases Incorporated, 17121 Lakewood Drive, Bellevue, NE, United States of America, Tel: 001-402-618-0963; E-mail: gmonif@AOL.com

Received date: November 30, 2015; **Accepted date:** January 7, 2016; **Published date:** January 14, 2016

Abstract

The purpose of this paper is to present and update the longitudinal perspective of the *Mycobacterium avium* subspecies *paratuberculosis* dilemma as initially stated in Infectious Diseases Incorporated's 2012 White Paper.

In both wild and domestic herbivores, *Mycobacterium avium* subspecies *paratuberculosis* (MAP) produces chronic granulomatous enteritis (Johne's disease) that, if unchecked, is usually terminal.

Keywords: Crohn's disease; *Mycobacterium avium* subspecies *paratuberculosis*

List of Abbreviations

MAP: *Mycobacterium avium* subspecies *paratuberculosis;* DNA: Deoxyribonucleic Acid

Introduction

Crohn's disease is a chronic granulomatous disease of the human gastrointestinal tract [1]. The similarity of clinicopathogy of Johne's disease in herbivores and of Crohn's disease was the initial impetus for questioning a common etiology. Complementary receptor sites have been demonstrated throughout the bovine gastrointestinal tract [2]. Given MAP's ability to readily cross species lines, comparable receptor sites are presumed to exist throughout the gastrointestinal tracts of herbivores, omnivores, and primates. No difference exists in infectivity of MAP isolates obtained from cattle or humans with Crohn's disease [3]. The demonstration of MAP in the milk from herbivores consumed by humans opened a decade long controversy: is MAP a significant zoonotic pathogen for man?

According to the National Association for Colitis and Crohn's disease, Crohn's disease affects about one in every 1,600 individuals [4]. In 2001, the CDC's estimate of the number of Crohn's cases was approximately 200- 400,000. In 2010, the number of U.S. cases of Crohn's disease has been estimated to be in the neighborhood of 800,000. Current estimates place the number at one million and climbing. Along with the increase in the number of cases, there has been a significant shift in the demographics relating to individuals afflicted. The onset of disease is becoming more common in childhood and early adolescence. Data collected by the Institute of Health Information and Statistics of the Czech Republic demonstrated that, between 1995 and 2009, the incidence of Crohn's disease had increased five-fold in the general population and seven fold in its young population [5].

The purpose of this paper is to present and update the longitudinal perspective of the MAP dilemma initially stated in Infectious Diseases Incorporated's 2012 White Paper.

Infectious Disease Incorporate 2012 White Paper

1989: Chiodini published a review and comparison of the two disease entities Crohn's disease and Johne's disease, and put into question the possibility of a shared etiology [6].

1992: The United Nations Conference on Environment and Development issued The Rio Declaration on Food Safety. Principle 15 of the Rio Declaration stated: "In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full knowledge shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation" [7].

1994: The World Trade Organization published its Agreement on Sanitary and Phytosanity Measures. Article 5.7 allowed regulatory measures "where relevant scientific evidence is insufficient to demonstrate the safety of a product or commodity" [8].

1996: Chiodini and Rossiter summarized the isolation recovery of MAP from the feces of 26 out of 135 patients with Crohn's disease, but only one of 121 control individuals [9]. Millard et al. and others had demonstrated the presence of MAP in pasteurized milk [10,11]. The question of whether or not MAP organisms in milk were effectively killed by pasteurization became controversial as a result of a paper from USDA.

1997: Stabel et al. published data that demonstrated that MAP did not survive high-temperature, short-time pasteurization [12]. This study was challenged as having significant flaws [12].

1998: Grant et al. demonstrated that experimental high-temperature short-time pasteurization did not destroy all MAP organisms present in milk [13,14]. The question of whether or not MAP is present in the nation's milk supply was rendered mute by subsequent studies that demonstrate that MAP is present in milk taken from the shelves of

supermarkets [15-17]. MAP or its DNA can be demonstrated in cheeses and powdered milk [18-20].

1999: The National Institute of Allergy and Infectious Diseases (NIAID) published its research agenda in which it targeted an infectious cause of Crohn's disease [21]. This topic went unfunded.

2000: the Centers for Disease Control (CDC) reputedly requested funding to identify risk factors in animals for human disease. This request went unfunded. Naser et al. isolated MAP from the milk of two lactating women with Crohn's disease and none from samples from five normal control women [22]. The European Commission's Report of the Scientific Committee on Animal Health and Animal Welfare was completed [23]. In the conclusion of this comprehensive 76 page document were the statements that "The current available evidence is insufficient to confirm or disprove that *Mycobacterium avium* subspecies *paratuberculosis* is a causative agent of at least some cases of Crohn's disease in man" and that "There are sufficient grounds for concern to warrant increased and urgent research activity to resolve the issue". The report also contains the following statement; "The complete destruction of all viable MAP in milk pasteurized at 65 degrees for 30 minutes or 72 degrees for 15 seconds may not be assured. Viable map has been identified in pasteurized milk."

2001: The United Kingdom Food Standard Agency issued its report for food standards. The conclusion statement states "There is undoubtedly sufficient cause for concern (relative to MAP as being the cause of Crohn's disease) for further action to be taken urgently to determine what the available data means…… This question can be divided into two areas: What action should be taken to reduce exposure to MAP even though the causal link is not established; and what action can be taken to increase the knowledge base so that future decisions may be based upon more information [24]. The United States Congress held hearings concerning the potential threat Map constituted to the public health. In these hearings, the Food and Drug Administration (FDA) testified that the latest research showed conclusively that commercial pasteurization does indeed eliminate this hazard [25]. FDA based its testimony on a single highly controversial paper produced by USDA [12]. Stabel et al. had reported that Mycobacterium paratuberculosis did not survive high-temperature, short-time pasteurization. With FDA's assertion that milk did not constitute a public health hazard, Congress awarded stewardship of the zoonotic issue to FDA's sister agency, USDA.

2002: USDA-APHIS adopted portions of The National Milk Producers Federation Plan. USDA-APHIS funded implementation of the Uniform Program Standards for the Volunteer Bovine Johne's Disease Control Program [25] and instituted a five year Johne's Disease Prevention Dairy Herd Demonstration Program [26].

2003: Bull et al. demonstrated the presence of MAP in fresh ileocolonic mucosal biopsies [27]. Countering this observation was the observation that Map could be demonstrated in the stool of non-disease individuals.

2004: Naser et al. cultured MAP from 50% of patients with Crohn's disease, 22% of patients with ulcerative colitis and 0% of individuals without inflammatory bowel disease [28]. Ghadiali et al. documented that the human MAP isolates exhibited similar polymorphic locus patterns to animal MAP isolates, making it, more probable than not, that MAP isolates cultured from human beings could produce disease in susceptible animals and vice-versa [29].

2005: Sechi et al. using IS900 PCR on extracts of fresh intestinal mucosal biopsies, identified MAP DNA in 83.3% of the biopsies from patients with Crohn's Disease and 10.3% of control patients [30]. Autschback et al. confirmed the positive correlation between MAP and diseased gastrointestinal tissue from individuals afflicted with Crohn's disease [31]. Hruska et al. demonstrated that 49% of infant formula manufactured by seven different producers in seven different contained MAP DNA. [32,33].

2007: Scana et al. incriminated MAP as an etiological component of "irritable bowel syndrome" in humans [34]. The National Animal Health Monitor System identified that 31.2 pooled collections of milk obtained from 515 dairy farms contained MAP DNA [35].

2008: The American Academy of Microbiologists published its report on *Mycobacterium avium paratuberculosis*: Infrequent Human Pathogen or Public Health Threat [36]. The executive summary states, "the association of MAP and CD is no longer in question. The critical issue today is not whether MAP is associated with CD, but whether MAP causes CD or is only incidentally present."

2009: Three independent diagnostic laboratories (Michael T. Collins, Saleh A. Naser, and the Centers for Disease Control and Prevention) recovered MAP significantly more frequently from the blood of individuals with Crohn's disease than non-inflammatory bowel patients [37]. Their findings have been affirmed by other investigators [38,39].

Discussion

2015: The questions as to why the sudden emergence of a new disease entity and why a global Crohn's disease epidemic now have a plausible pathogenesis. The Hruska Postulate argues that Crohn's disease is an interaction of two immune mechanisms based upon the antigen profile of MAP [40]. In this new paradigm, if a newborn is infected before effective acquired immunity is in place, termination of mycobacterium replication challenges the host's inherent immunity to a point where the elicited pro-inflammatory response to MAP becomes fixed within in immunological memory. When an individual so infected is re-challenged by MAP, rather than exhibiting immune tolerance, the individual's immune system again elaborates a cascade of cytotoxic cytokines to the MAP inoculums challenge. Fixation of the pro-inflammatory response to by itself does not produce Crohn's disease. What it does create a population at risk for future development of Crohn's disease. What is required to convert potential into disease is repeated frequent re-exposure to MAP which is now widespread in the human food supply.

Once MAP is introduced into the pasture/production environment, its elimination is extra-ordinarily difficult [41]. Even if eradication could be achieved, the ultimate reservoir of infection can't be eradicated. The problem of MAP infection within dairy herds is here to stay and with it comes the need for a new public health paradigm that focuses on significantly reducing the amount of Map entering the human food chain through milk and milk-based products, particularly infant formula. With the widespread presence of MAP in the nation's food chain and the availability of complementary receptor site throughout the small intestines, human infection is, more probably than not, a function of diet and time [42]. The recovery of MAP from the tissues of individuals without inflammatory bowel diseases and the demonstration of MAP DNA in the blood of healthy individuals speaks to the prevalence of MAP infection within the general population.

Conflict of Interest

Since 2001, Infectious Diseases Incorporated (IDI) has been actively involved in research involving *Mycobacterium avium* subspecies *paratuberculosis*. IDI holds five patents dealing with the diagnosis and herd management of milk-producing animals.

References

1. Harris NB, Barletta RG (2001) Mycobacterium avium subsp. paratuberculosis in Veterinary Medicine. Clin Microbiol Rev 14: 489-512.
2. Schleig PM, Buergelt CD, Davis JK (2005) Attachment of Mycobacterium avium subspecies paratuberculosis to bovine intestinal organ cultures; method development and strain differences. Vet Microbiol 108: 271-279.
3. Allen AJ, Parks KT, Barrington GM (2011) Experimental infection of a bovine model with human isolates of Mycobacterium avium subspecies paratuberculosis. Vet Immun Immunopath 141: 258-266.
4. Crohn's Disease 2000 National Association for Colitis and Crohn's Disease (NACC).
5. Hruska K, Pavlik I (2010) Frequently asked questions on the links between mycobacterium and Crohn's disease. Lecture. International Conference on Gastrointestinal Microbiol Ecology, Kosice Slovakia.
6. Chiodini RJ (1989) Crohn's disease and the mycobacterioses: a review and comparison of two disease entities. Clin Microbiol Rev 2: 90-117.
7. United States Food and Drug Administration (US FDA) and the United States Department of Agriculture (USDA) (2000) United States Food Safety System Country Report. Annex II: Precaution in US food safety decision making. Washington, DC: US FDA/USDA.
8. Chiodini RJ, Rossiter CA (1996) Paratuberculosis: a potential zoonosis? Vet Clin North Am Food Anim Pract 12: 457-467.
9. World Trade Organization (WTO) (1994) The WTO agreement on the application of sanitary and phytosanitary measures (SPS Agreement). Geneva, Switzerland: WTO.
10. Millar D, Ford J, Sanderson J (1996) IS 900 PCR to detect Mycobacterium avium subspecies paratuberculosis in retail supplies of whole pasteurized milk in England and Wales. Appl Environ Microbiol 62: 3446-54.
11. Grant IR, Ball HJ, Neill SD, Rowe MT (1996) Inactivation of Mycobacterium paratuberculosis in cows' milk at pasteurization temperatures. Appl Environ Microbiol 62: 631-636.
12. Stabel JR, Steadham EM, Bolin CA (1997) Heat inactivation of Mycobacterium paratuberculosis in raw milk: are current pasteurization conditions effective? Appl Environ Microbiol 63: 4975-4977.
13. Grant IR (1998) Does Mycobacterium paratuberculosis survive current pasteurization conditions? Appl Environ Microbiol 64: 2760-2761.
14. Grant IR, Ball HJ, Rowe MT (1998) Effect of high-temperature, short-time (HTST) pasteurization on milk containing low numbers of Mycobacterium paratuberculosis. Lett Appl Microbiol 26: 166-170.
15. Grant IR, Ball HJ, Rowe MT (2002) Incidence of Mycobacterium paratuberculosis in bulk raw milk and commercially pasteurized cow's milk from approved dairy processing establishments in the United Kingdom. Appl Environ Biol 68: 2428-2435.
16. Ayele WY, Svastova P, Roubal P, Bartos M, Pavlik I (2005) Mycobacterium avium subspecies paratuberculosis cultured from locally and commercially pasteurized cow's milk in the Czech Republic. Appl Environ Microbiol 71: 1210-1214.
17. Ellingson JL, Anderson JL, Koziczkowski JJ, Radcliff RP, Sloan SJ, et al. (2005) Detection of viable Mycobacterium avium subsp. paratuberculosis in retail pasteurized whole milk by two culture methods and PCR. J Food Prot 68: 966-972.
18. Ayele WY, Svastova P, Roubal P, Bartos M, Pavlik I (2005) Mycobacterium avium subspecies paratuberculosis cultured from locally and commercially pasteurized cow's milk in the Czech Republic. Appl Environ Microbiol 71: 1210-1214.
19. Ikonomoplus J, Pavilk I, Bartos M (2005) Detection of Mycobacterium avium subspecies paratuberculosis in retail cheese from Greece and Czech Republic. Appl Environ Microbiol 71: 8935-9036.
20. Clark DL Jr, Anderson JL, Koziczkowski JJ, Ellingson JL (2006) Detection of Mycobacterium avium subspecies paratuberculosis genetic components in retail cheese curds purchased in Wisconsin and Minnesota by PCR. Mol Cell Probes 20: 197-202.
21. Hruska K, Kralik P, Pavlik I (2011) Mycobacterium avium subspecies paratuberculosis in powder milk: F57 competitive real time PCR. Veterinarni Medicina 56: 226-230.
22. http://www.niaid.nih.gov/dmid/crohns.htm.
23. Naser SA, Schwartz D, Shafran I (2000) Isolation of Mycobacterium avium subsp paratuberculosis from breast milk of Crohn's disease patients. Am J Gastroenterol 95: 1094-1095.
24. European Commission Report of the Scientific Committee on Animal Health and Animal Welfare: Possible links between Crohn's disease and paratuberculosis.
25. Rubery E (2001) A review of the evidence for a link between Mycobacterium avium subspecies paratuberculosis (MAP) and Crohn's disease (CD) in humans. A Report for the Food Standard Agency.
26. http://www.crohns.org/congress/index.htm
27. Uniform program standards for the Voluntary Johne's Disease Control Program (2010) United States Department of Agriculture, Animal and Plant Health Inspection Service. APIS 91-45-014.
28. Bull TJ, McMinn EJ, Sidi-Boumedine K, Skull A, Durkin D, et al. (2003) Detection and verification of Mycobacterium avium subsp. paratuberculosis in fresh ileocolonic mucosal biopsy specimens from individuals with and without Crohn's disease. J Clin Microbiol 41: 2915-2923.
29. Naser SA, Ghobrial G, Romero C, Valentine JF (2004) Culture of Mycobacterium avium subspecies paratuberculosis from the blood of patients with Crohn's disease. Lancet 364: 1039-1044.
30. Ghadiali AH, Strother M, Naser SA (2004) Mycobacterium avium subsp. paratuberculosis strains isolated from Crohn's disease patients and animal species exhibit similar polymorphic locus patterns. J Clin Microbiol 42: 5345-5348.
31. Sechi LA, Scanu AM, Molicotti P, Cannas S, Mura M, et al. (2005) Detection and Isolation of Mycobacterium avium subspecies paratuberculosis from intestinal mucosal biopsies of patients with and without Crohn's disease in Sardinia. Am J Gastroenterol 100: 1529-1536.
32. Autschbach F, Eisold S, Hinz U, Zinser S, Linnebacher M, et al. (2005) High prevalence of Mycobacterium avium subspecies paratuberculosis IS900 DNA in gut tissues from individuals with Crohn's disease. Gut 54: 944-949.
33. Hruska K, Bartos M, Kralik P, Pavlik I (2005) Mycobacteriumavium subspecies paratuberculosis in powdered infant milk: paratuberculosis in cattle – the public health problem to be solved. Veterinarni Medicina 50: 327-335.
34. Hruska K, Slama J, Kralik P, Pavlik I (2011) Mycobacterium avium subsp. paratuberculosis in powdered milk: F57 competitive real time PCR: Veterinarni Medicina 56: 226-230.
35. Scana AM, Bull TJ, Cannas S (2007) Mycobacteriumm avium subspecies paratuberculosis infection of irritable bowel syndrome and comparison with Crohn's disease and Johne's disease: common neural and immune pathogenicities. J Clin Microbiol 45: 3883-890.
36. http//nahms.aphis.usda.gov/dairy/dairyo7/dairy 7-Johnes. Pdf.2007.
37. Nacy C, Buckley M (2008) Mycobacterium avium paratuberculosis: Infrequent Human Pathogen or Public Health threat? Report from the American Academy of Microbiology.
38. Naser SA, Collins MT, Crawford JT, Valentine JF (2009) Culture of Mycobacterium avium subspecies paratuberculosis (MAP) from the blood of patients with Crohn's disease: A follow-up blind multi-center investigation. The Open Inflam J 2: 22-2.
39. Juste RA, Elguezabal N, Pavon A (2009) Association of Mycobacterium avium subspecies paratuberculosis DNA in blood and cellular and

humeral immune response in inflammatory bowel disease patents and controls. Intern J Infect Dis 13: 247-254 27.

40. Mendoza JL, San-Pedro A, Culebras E, Cíes R, Taxonera C, et al. (2010) High prevalence of viable Mycobacterium avium subspecies paratuberculosis in Crohn's disease. World J Gastroenterol 16: 4558-4563.
41. Monif GR (2015) The Hruska postulate of Crohn's disease. Med Hypotheses 85: 878-881.
42. Eisenberg SW, Nielen M, Santema W, Houwers DJ, Heederik D, et al. (2010) Detection of spatial and temporal spread of Mycobacterium avium subsp. paratuberculosis in the environment of a cattle farm through bio-aerosols. Vet Microbiol 143: 284-292.