Understanding Therapeutic Concepts in Crohn's Disease

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ABSTRACT: For more than a decade, the therapeutic focus for Crohn's disease has remained fixed at temporary arrestment of symptomology. The Centers for Disease Control and Prevention (CDC) lists Crohn's disease as a disease entity without current cure. Biologics in combination with antibiotics can frequently achieve remissions. Without ongoing drug administration, these remissions tend to be of limited duration. Conceptual advancements in understanding the pathogenesis of Crohn's disease have identified treatment approaches, the focus of which goes beyond temporary remission. Concepts derived from Infectious Diseases Inc.'s 17 years of research with *Mycobacterium avium* subspecies *paratuberculosis* delineate how new knowledge can be integrated to achieve more sustained remissions.

KEYWORDS: Crohn's disease, *M avium* subspecies *paratuberculosis*, pathogenesis, therapy

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Pathogenesis of Crohn's Disease

Only now is it becoming evident that the gross pathology is the consequence of not 1, but rather 2 co-functioning disease mechanisms: first an immune-mediated process and the second due to polymicrobial infection.[1,2]

The ability of immunomodulators, steroids, and biologics to abort symptomology has demonstrated that the disruption of the immune system's effector arm can achieve time-limited remissions that are contingent on continued drug administration. The mechanism by which the immune-mediated process is created is attributed to autoimmunity until 2015.[2] Strong circumstantial scientific data argue that an ongoing pro-inflammatory cytokine cascade is the consequence of arrestment of immunologic tolerance to *Mycobacterium avium* subspecies *paratuberculosis*' (MAP) antigenic array. For the pro-inflammatory response to MAP to be fixed within immunologic memory, human MAP infection must occur in the absence of functional acquired immunity.[3–5] Oral ingestion of MAP results in cytotoxic cytokines attacking MAP at its sites of mucosal attachment and antigen processing.[6] Over time, sustained antigen challenges by dead or alive organisms leads to focal loss of mucosal integrity and creates an open access to the underlying tissues for the gastrointestinal microbiota.

Restoration of Mucosal Integrity

The correlation between restoration of mucosal integrity and arrestment of symptomology documented one of the therapeutic touchpoints for the potential curing of Crohn's disease. Re-epithelialization of the lining mucosa is the critical step in attaining therapeutic control. Closure of an open portal of infection enhances the ability of embedded local immunity to curtail residual submucosal infection.

The speed with which re-epithelialization is attained can be influenced by reducing the frequency of MAP antigen challenges. Exclusion of milk and milk-based products potentially adulterated by either living or dead MAP is central to achieving this objective. In the lay literature, dietary manipulation/exclusions have been responsible for individual sustained remission to date. The inability to totally exclude from diet all potentially MAP adulterated foods argues for therapy with a biologic until epithelial closure is documented. If epithelial reconstitution is achieved quickly, host immunity can often re-establish governance over residual microbial presence that is not addressed by antibiotics. Once healing is documented, the potential adverse effect of biologics on infectious disease agents, the containment of which is governed by cell-mediated immunity, argues for their discontinuation.

Antibacterial Therapy

What has been poorly appreciated is that the clinical spectrum of Crohn's disease is the composite of 2 inter-related disease processes. Stricture formation, submucosal fibrosis, loop-to-loop fistula, and bowel perforations are not the consequence of the immune-mediated disease component. Once focal mucosal integrity is lost, the intra-luminal gastrointestinal microbiota has open sustained access to the lamina propria and submucosa. The invading gastrointestinal microbiota constitutes a polymicrobial infection. The mechanism by which polymicrobial infections produce divergent patterns of disease has been termed the anaerobic progression.[7] Submucosal infection dominated by the *Enterobacteriaceae* results in healing by fibrosis; that dominated by obligatory anaerobic bacteria accounts for bowel penetrations and loop-to-loop-fistula. Based on polymicrobial infections of the female genital tract, antibiotic therapy must be comprehensive for the 4 major categories of the Gainesville Classification.[8,9] If antibacterial therapy is not comprehensive, bacteria for which the spectrums of susceptibility are not addressed will re-align themselves within the anaerobic progression. As long as the gastrointestinal microbiota has open access portal, antibiotic administration has the

potential to select for antibiotic resistance among the bacteria that have continued open portal access.

Anti-MAP Therapy

Selected anti-MAP drug therapy regimens have only indirect impact on fecal-derived polymicrobial infection. Only a few anti-MAP regimens have been shown to positively affect the clinical course of Crohn's disease.[10,11] The heterogeneity of tissue damage and the failure to match for dietary manipulation have undermined interpretation of meta-analysis. The ability to create a match for degree of pathology, age and double-blinded, placebo control study with sufficient number to attain statistical significance is beyond attainment. What one is left with are individual case studies of sustained remissions with the addition of anti-MAP therapy.[12]

For anti-mycobacterium therapy to induce sustained remission, drug selection should include compounds and/or antibiotics that impacted the ribosomal function. Demonstration of MAP DNA within diseased tissue, the reticuloendothelial system, and white blood cells of afflicted individuals is argued to represent the spheroblastic form of MAP. Lacking cell walls, destruction of spheroblasts requires that the drug's mechanisms of action disrupt ribosomal function. It is argued that these MAP spheroblasts constitute MAP template that sustains the dysfunctional, pro-inflammatory immune process within Crohn's disease.

Translation of Objectives to an IDI Theoretical Pediatric Protocol

The inability of the autoimmunity paradigm to address the specifics embedded in natural history of Crohn's disease and the ability of the Hruska Postulate to achieve a hand-and-glove fit leave the Hruska Postulate as the last theory standing.[2,13,14] Not having been validated by double-blinded, placebo-controlled comparative studies, the Infectious Diseases Inc.'s (IDI) Pediatric Research Protocol is presented as a data-based interpretation of the Hruska Postulate.[2]

Principle I: Rapid Commitment to a Presumptive Diagnosis in Pediatric Cases of Crohn's Disease

Rational. Mucosal/lamina propria damage is increased the longer the tissue destructive process has been in place. As there is no definitive diagnostic test for Crohn's disease, a combination of clinical evidence of prolonged gastrointestinal dysfunction, laboratory evidence of inflammation, and exclusion of enteric pathogens in the pediatric age groupings warrants serious consideration of a presumptive diagnosis of Crohn's disease.

Principle II: Reduction of Antigen Challenges by MAP Adulterated Foods

Rational. MAP's presence in milk, powdered milk, and milk-based products has become so pervasive that total exclusion is advocated. The antigenic array of either killed or live MAP will elicit a pro-inflammatory response that can contribute to the ongoing process. The positive results achieved with selected diets have been achieved. That exclusion diets have efficacy is underlined by the positive results produced by the specific carbohydrate diet (SCD).[15–17] The SCD diet is both one of exclusion and inclusion. The sole use of SCD can achieve symptomatic relief without complete mucosal healing.[18] Exclusion diets with dietary immune system enhancement stand, at very least, as a low-cost adjunct to therapy.

Principle III: Administration of Aggressive Antibiotic Coverage

Rational. Antibiotic selection is predicated by an understanding of a process termed anaerobic progression.[7] The underpinnings for therapy are derived from studies on the vaginal flora.[19] In women, given access to the vaginal microbiological flora, tissue damage initiated by *Neisseria gonorrhoeae* puts into motion the anaerobic progress that is a coning down of complex bacterial to a final obligatory anaerobe.[8,9,20] The resultant tissue damage resulted in ectopic pregnancies, secondary infertility, tubo-ovarian abscesses, and septic deaths. In men, *N. gonorrhoeae* functions in a primarily aerobic environment. As a consequence, late sequelae in men are limited to strictures due primarily to the *Enterobacteriaceae*. This application of knowledge of the anaerobic progression and its clinical validation caused the Centers for Disease Control and Prevention to radically alter its therapeutic recommendations for women. In Obstetrics and Gynecology, antibiotic selection for women with acute pelvic inflammatory disease became lockdown coverage for the 4 categories of the Gainesville Classification.[21]

The combination of ciprofloxacin and metronidazole provides reasonable theoretical, but not lockdown, coverage for categories 1, 3, and 4 of the Gainesville Classification. Coverage for *Enterococci* is wanting. This latter coverage becomes progressively more important the longer the microbiota resides with the underlying submucosal tissues. With prolonged non-closure and antibiotic administration, selection of resistant strains is a theoretical concern.[22]

Once obligatory anaerobic infection within the muscularis layer of the small bowel attains relative protection from antibiotics by early abscess formation, the mechanism is in place for future loop-to-loop fistula or bowel penetration.

Principle IV: Re-establish Mucosal Integrity as Quickly as Possible

Rational. In total, 80% of the body's immune system resides within the gastrointestinal tract. The ability of biologics to achieve clinical remissions without concomitant antibiotic administration reflects the ability of local host immunity within the lamina propria to handle a fairly substantial bacterial challenge. Disruption of the pro-inflammatory response allows for the mucosal regeneration to re-establish mucosal integrity. Increased re-establishment of mucosal integrity warrants use of short-term use of a biologic in conjunction with dietary enhancement

of cellular immunity. In an animal model, specific targeting of cellular immunity can result in the destruction of MAP.

Principle V: Destruction of the MAP Template

Rational. The dysfunctional cytotoxic cytokine cascade is elicited by the representation of MAP antigen array. Once clinical remission has been attained, permanent termination of the immune-mediated mechanism requires destruction of MAP template. The quick method is the use of anti-MAP compounds, the mechanism of action of which is disruption of ribosomal function. The longer way is the incorporation of dietary enhancement cellular immunity into exclusion.[23] The inclusion of Vitamin D is deemed essential. Vitamin D acts directly on the gene that encodes an antimicrobial peptide as well as the NOD2 gene. Addition of the probiotic Lactobacillus GG is a secondary consideration.

Risk/Benefit Analysis of Advocated Therapy

Dietary exclusion of foods known to be potentially adulterated by MAP is risk free. Dietary supplementation that targets enhancement of cell-mediated immunity is risk free.

Complete coverage of the bacterial groupings within the anaerobic progression introduces augmented potential of added adverse drug reaction. Nevertheless, the risk outweighs the failure to do so which opens the afflicted individual to consequences of withheld, inappropriate, and/or prematurely terminated antibiotic coverage.

Summary

Therapy requires understanding the events that combine to produce disease and using strategic intervention points. Basically, repeating what has been done to date therapeutically and expecting a different outcome has a definition. Attention to details now makes attainment of a cure for Crohn's disease a very real possibility.[24]

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Author Contributions

GRM is the Investigative Author.

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