



Crohn's Disease: A Curable Disease Held Hostage?

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Clinical Opinion

Permanent remissions have been attained in Crohn's disease. Nevertheless, the current focus of therapy remains sclerosed with the prevailing drug therapy through which but temporary remissions are attainable. FDA's reliance on clinical validation must through comparative, placebo controlled, double-blinded studies has created an impediment to acceptance of divergent alternated therapies as being within the standard of care. In so doing, FDA has basically has surrendered the therapeutic dialogue of Crohn's disease to those who can pay from such studies.

The current standard of care of Crohn's disease evolved from trial-and-error therapeutic attempts to address the signs and symptoms of disease. The prevailing standard of care is based on "evidence-based" data, demonstrating that the current drugs of choice produce a statistically significant improvement of disease over placebo or alternative therapy. For over two decades, disruption of the effect or arm of the immune response has been the foundation of Crohn's disease therapy. Despite not having produced cures in over a decade of clinical use, biologics have attained the status of drugs-of-choice foe Crohn's disease.

The rush to disease plication has overshadowed the clinical observations that two divergent therapeutic approaches (diet and anti-tuberculosis drugs) have produced occasional permanent remissions. These isolated instances of permanent remission induction have been glossed over by their failure to constitute being "evidence-based" data. For the Food and Drug Administration (FDA) and other government agencies to accept a clinical therapeutic outcome, the data needs to be "evidence-based" derived from primarily comparative, double-blinded, placebo-controlled studies.

In 2015, a pathogenesis for Crohn's disease was introduced that put into focus the shared mechanism by which dietary manipulation and selected anti-mycobacterial therapy had achieved long-term remissions/cures [1]. The Hruska Postulate proposed the thesis that, in the absence of functional acquired immunity, a newborn infected by Mycobacterium Avium Subspecies Paratuberculosis (MAP) could be so challenged to abort mycobacterium replication that its inherent immune system became fixed within immunological memory. Owing to the loss of immunological tolerance, every time the baby's immune system encountered MAP. It would again respond by elaborating pro-inflammatory cytokines directed at MAP at its points of mucosal attachment to the gastrointestinal mucosa and its antigen processing. The expanded Hruska Postulate states abortion of the immune-mediated aspect of Crohn's disease is contingent on the destruction of the sustaining MAP immune template [2].

A major factor complicating attempts to construct meaningful comparative therapeutic groups for clinical trials is the degree to which the gastrointestinal microbiota has altered gastrointestinal structure and function [3-4]. Once mucosal integrity is lost, the microbiota of the gastrointestinal tract becomes a superimposed disease process. The failure to address the resultant polymicrobial infection is responsible for the permanent sequel of Crohn's disease: strictures, bowel-to-bowel fistulae, perianal fistula bowel perforation, sepsis, etc. Once in place, the resultant alterations of structure and function create therapeutic subgroups which necessitated added therapy. The unaddressed question is, not the occurrence of permanent remissions, how do diet or selected anti-microbial drugs induce cures?

That diet could be a therapeutic modality has long been inferred. Before the introduction of biologics, diet had long been used in front line therapy for Crohn's disease in Japan. In the United States selected pediatric gastroenterologists' using dietary manipulations have documented a beneficial effect, but not cure [5-7].

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In isolated instances, individuals afflicted with Crohn's disease have achieved permanent remission by rigid adherence to what are variations of basically vegetarian-like regimens. Chiba et al. [8] reported that 94% of Crohn's afflicted individuals who remained on a semi-vegetarian diet maintained their clinical remission whereas 33% who returned to a regular diet relapsed. Much of this clinical response has been attributed to reducing the volume of antigen challenges by exclusion of foods potentially adulterated by MAP [2,8]. Left unanswered had been why. A veterinary experiment-in-nature demonstrated that dietary targeting to enhance host immunity produced the mass destruction of MAP with terminal Johne's disease (due to the replication of MAP) [9]. In Crohn's disease, the diarrhea and loss of absorption areas cause significant loss of key vitamins and minerals vital to the integrity of host immunity [10]. The cures achieved through dietary manipulation, reduction of antigen challenges, anabolic diet enhancement and enhancement of host immunity speak to a potential mechanism by which individuals have achieved self-cure without pharmaceutical intervention [11].

The explanation as to why selected anti-mycobacterial drugs have achieved permanent remissions is less obvious [12-14]. Unlike Johne's disease in domestic animals, Crohn's disease is not due to organism replication. MAP can't be identified with special stains nor isolated from disease tissue. Prior attempts to cure Crohn's disease using anti-tuberculosis drugs largely failed. Why selected anti-MAP therapy has produced individual cures is due to their ability, not to destroy MAP as such, but to destroy MAP that exists in its cell-wall free state. The MAPs that drive the dysfunctional immune response exist as cell wall free versions of itself. The prior failures of prior anti-tuberculosis drugs are largely attributable to their mechanism of action being directed against mycobacterium cell wall. To destroy MAP in its spheroblastic form, drug therapy must be able to disrupt MAP's RNA metabolism.

Given the number of years required to assess outcome, the subset of patient groups based upon degree of documented tissue damage required, age, immune status, diet, etc., make conducting a comparative, placebo-controlled, double blinded comparative study against a given biologic a near impossibility that no one will pay for.

Unless FDA begins to accept small clinical trials, whose endpoint is either failure or success without continued drug therapy over a prolonged period of time to be "evidence-based", the therapy of Crohn's disease will continue to reside with those that can pay the bill for the creation of "evidenced-based" data. Without FDA validation, physicians attempting innovative therapies face loss of liability protection afforded by the "standard of care".

Currently, the will to cure Crohn's disease appears subordinate to FDA's inflexibility and the elephant in the room. In 2018, the maker of the principle biologic used in the therapy of Crohn's disease made a reputed 19.94 billion dollars. The 2018 American College of Gastroenterology's Clinical Guideline states "Despite the recent advances in the treatment of patients with CD, there still remains a

large group of patients who do not respond adequately to our current medication armamentarium." We will certainly expand our medical treatment war chest and uncover effective biologics with different mechanisms of action to treat our patient. If the initial biologic drug fails, the patient will be able to switch to another agent and even combination biologics may become a reality [15]. The Guideline further states that the standard of care is "rigid" and "rarely violated". Chronic diseases function as a revenue enhancer for both healthcare provider and the pharmaceutical industry.

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