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Inflammatory Bowel Disease 2018: Consistency and Controversy

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Abstract

Recent research has reckoned the human digestive tract as the arena where inflammatory processes are continuously waxing and waning. A driving force for this inflammatory lingering has been identified with the huge indwelling microbiome population, which, notably, becomes easily upset by lifestyle changes influencing diet composition. Thus, the microbiome may act as the element linking gut inflammation with individual life habits, allowing to imagine a continuum of inflammation intensity corresponding to the strength of the perturbing event playing at any time. If this mind frame may please basic researchers, it is of poor help to clinicians seeking sharply designed drugs for demarcated conditions. It may be anticipated that this clash between basic science and real-world medicine will affect future medical practice well beyond the limits of gastroenterology.

Keywords: Inflammatory bowel disease; Microbiome; Anti-TNF therapy

Introduction

The Inflammatory Bowel Diseases (IBDs) were reported as serendipitous observations between the end of the 19th century and the first 40 years of the 20th century [1,2]. Traditionally, it is agreed that the first patient to be described with an Ulcerative Colitis (UC) was a lady from London [1], whose hitherto unrecognized colonic lesions were labeled in 1859 as "morbid appearances"; instead, a granulomatous fistulizing lesion of the digestive tract was first identified in the 1930's in a patient series from the New York City Mount Sinai Hospital, and named Crohn's disease after the principal author of the relevant paper [2]. The label Inflammatory Bowel Disease was later to become the world-wide umbrella identification for this disease type. The hypothesis of an infectious etiology prevailed initially: Crohn's was supposed to hide a Tubercle-like disease, based on some morbid anatomy similarities supposed to be shared with the mycobacterium infection [3]; UC was supposed to harbor an infectious agent, in analogy with rheumatism, a hypothesis that initially led to the release of "combo drugs" containing anti-inflammatory moieties (5aminosalicylic acid, ASA), and a sulpha fraction (sulphapyridine) [4].

Brief Modern History

The prognosis of IBD remained ominous with a death risk exceeding 30% in the first year [5], and this outlook was not meant to change until the mid-50's. By this time, failure to firmly identify an etiologic agent, and the evidence that IBD can often present with a bulk of inflammatory extra-intestinal manifestations [6], all contributed to reinforce the impression that IBD could in fact be the result of a (days) immune reaction.

The keystone cortisone trials of the 50's [7] showed robustly that the IBDs are inflammatory conditions wherein the anti-inflammatory action of the corticosteroids can quench the disorder in most of the cases [8].

Today's Issues

Today IBD is a world problem, with the US Centers for Disease Control guessing that some 1.6 million IBD patients live in North America. IBD concepts have now been impacted by two main pieces of knowledge:

(1) The discovery and characterization of the microbiome [9].

(2) The repositioning of the IBDs as dysfunctions of a barrier organ acting in parallel with the barriers of the skin and lungs [10].

Briefly, the gut, skin, and lungs systems are now functionally perceived as "sheaths" dividing our inner milieu from the outer domains: inner specificity gets insured by the full function of the barriers (epithelia or mucosae with a reactive lymphoid tissue underneath) to check the invasiveness of the "outside". In the gut, the huge microbiome [10,11] bacteria species [11], is an inside prolongation of the outside: the balance between it and the gut mucosa is the pre-requisite for the persistence of a controlled inflammation that is compatible with life.

Updated Thoughts

By some, microbiome colonies are now understood as sensors of feeding changes, which in turn spy life's variables including income levels, individual's employment chances, nightshifts, free time, mood stressors, and tens of other variables [12]. Thus, swings of the states of the controlled inflammation alluded to above, may be thought to reflect the alarm state of the system, with mostly ample swings reflecting mostly stressful changing drifts hitting the microbiome under the input of changes from the surroundings [13]. If one then figures out a specific clinical situation corresponding to any inflammatory degree of the underlying "sensors", it is not difficult to accept the existence of a "continuum" extending from conditions formerly known as "functional" (The irritable bowel syndrome, IBS, for example) through mildly inflammatory states (Lymphocytic Colitis), up to full blown IBD [14].

Treatment Arsenal

The IBD arsenal nowadays includes traditional, new, and "breaking out" drugs. Traditional molecules include the anti-inflammatory mesalamine derivatives [15], and various steroid formulations [16]. Thiopurines continue to be the traditional IBD maintenance molecules [17]. The undecapeptide Cyclosporin [18] and the anti-TNF monoclonals [19] represent the new remedies for the acute IBD presentations. The very new strategy designed to inhibit the bulk of the immune responses promoted by activation of the Janus Kinases, is the design that pivots on the molecule "Tofacitinib", a JAK inhibitor that is active on a number of pro-inflammatory cytokines [20].

Therapeutic Advancement and Indication Consistency

The new hints delineated above raise interesting issues of indication consistency.

- 1. The current drift towards figuring out a pathogenetic continuum across the various gut inflammation forms, whereby IBS is assimilated to IBD, (see above) may conflict with the desire to identify personalized weapons for precise medicine to address firmly defined disease entities [21].
- 2. With the introduction of Tofacitinib, two inhomogeneous strategies seem to coexist and be recommended for UC: hit one target (anti-TNF designs) or multiple steps along the inflammation pathway (anti-JAK Tofacitinib) : which is the correct project?

Conclusion

IBD continues to make a challenge. While scientists are getting close to the concept of the human digestive tract as a "cosmic" theater where inflammation seems to be a way to go by with evolution, pharmaceutical firms compete to release ever more potent inflammation killers, disregarding all theoretical coherence. Only future perhaps can tell which policy carries the payback [22].

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