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MINIREVIEWS

Inflammatory bowel diseases: Current problems and future tasks

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Abstract

Current knowledge on inflammatory bowel disease (IBD) is mainly endorsed by controlled trials and epidemiologic studies. Yet, we seldom look at the messages from real-world practice. Among a patient population followed since 2008, we looked at an unselected sample of 64 IBD patients [26 Crohn's disease (CD) and 38 ulcerative colitis (UC)] who had been seen as out-patients in the last year. Inducing remission, mesalamines (86% for UC/69% for CD/33%-16% as MMX formulation) prevailed as prescriptions; steroids (55%/19% for UC/CD) ranked second. Prescription of third-party drugs (antibiotics, NSAIDs, biologics) and adherence, were issues in the maintenance. 34% of CD, and 23% of UC patients showed accompanying immunologic diseases: CD-associated familiar psoriasis (4:9) ranked first. Main Message. The association between IBD (CD mainly) and psoriasis, now found in our practice, matches current basic science gathering IBD together with psoriasis (and perhaps chronic respiratory disease) under the comprehensive term "barrier organ disease" wherein an epithelial surface with sensor systems rules contacts between outer antigens and a reactive underneath tissue, with the balance between inflammation and quiescence kept at any time by mucosal permeability. IBD is thus viewed as a polyfactorial/polygenic/syndromic disorder, embedded into a galaxy of immune conditions offering multiple points of attack. This mindset of splitting the IBDs into pathogenic categories may allow overcoming the uniformly targeting of a single cytokine by biological drugs, in favor of demarcating the boundaries between different disease-subtype-specific indications, and paving the way to future personalized strategies.

Key words: Inflammatory bowel disease; Immunopharmacology; Barrier organs; Future trends in inflammatory bowel disease; Microbiome

Core tip: Long after their description, ulcerative colitis and Crohn's disease (IBD) are still treated but not cured. This somber spell has now begun to be broken by genetic discoveries and by the study of the human microbiome. The former have uncovered hundreds of genetic variants lending support to the clinical hint that IBD is a syndrome encompassing discrete polymorphisms of the immune response pathways, each requiring a personalized approach. The latter has shown the microbiome to be a cell universe which, if disrupted, can provoke IBD together with a myriad of disturbances apparently unrelated with the gut. A frame of mind seeing the IBDS as embedded into a plethora of genetically linked immune disturbances must fuel IBD research from now on.

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STUDY SETTING AND SCOPE OF THE ANALYSIS

Supported by the Italian Health System, in 2008 Grad-

Table 1 Contains patients' demographics and disease characteristics

	UC (38, 24 m)		CD(26, 16 m)
Age, yr	Extension	Age, yr	Extension
18-80	Proctitis, 12	16-73	Ileo-colonic 15
	Sub-total, 11		Colitis, 5
	Left, 8		Universal, 4
	Pancolitis, 6		Ileitis, 2
	IPAA, 1		

UC: Ulcerative colitis; CD: Crohn's Disease; IPAA: Ileo-pouch anal anastomosis.

Table 2 Gives the frequencies of use of the main drugs *n* (%)

Ulcerative colitis	Crohn's disease
Mesalamines 33 (86)	18 (69)
Steroids 21 (55)	5 (19)
Thiopurines 14 (36)	8 (30)
Biologics 1(2.6)	1 (3.8)

Table 3 Illustrates the distribution of the main extra-intestinal affections

	n	Familial	Personal
Ulcerative colitis			
Psoriasis	2	0	2
Inflammatory bowel disease	3	3	0
Asthma	2	1	1
Rheumatoid Arthritis	2	0	2
Crohn's disease			
Psoriasis	4	3	1
Inflammatory bowel disease	3	3	0
Asthma	1	1	0
Rheumatoid Arthritis	1	1	0

enigo Hospital has launched an out-patient service mainly devoted to patients with inflammatory bowel disease (IBD). An interim analysis of the activities of this service has already appeared in 2010[1]. Eversince its establishment, the service has mostly been conducted by one of us (GCA), enrolling some 200 IBD patients. The scope of the present analysis was to reappraise the data under the light of modern achievements (for example the concept of "barrier organ disease"); to gain more insight into the drawbacks and the limits of traditional therapy with special regard to factors countering maintenance of remission; then, to cast a glimpse into the future of treatment approaches for IBD. We deliberately meant to not loose adherence to our daily clinical experience in this out-patient setting, when either dissecting actual difficulties or visualizing future therapeutic scenarios (personalized treatment for example). At a time when the literature is being "flooded" by a number of large epidemiologic and population studies, we chose to present the limits and the peculiarities of a study that pivots on the narrow environment of an outpatient office conducted by one physician.

STUDY POPULATION

Sixty-four IBD patients, gathered in the most recent interim analysis between 6.6.2012 and 04-24-2013 included 26 Crohn's affections (CD) and 38 ulcerative colitis (UC) cases, corresponding to some 6 IBD patients per month; overall analysis in the previous 31 months had yielded 119 IBD patients. Changes in the core storage system beginning 2010 have imposed a discontinuity in the data collection modalities, a fault that is now mended (Tables 1-3).

Managing chronic remission: open questions

Both medical and budget issues make the maintenance of remission of IBD a crucial challenge. The relevant literature has particularly expanded on UC[2]. A variegated list of factors may provoke loss of IBD remission, and we ourselves had the chance to face some of the conditions in our real-world practice. (1) lack of adherence to prescriptions, mostly mesalamine and thiopurine medications. Among the 64 patients in this report, the adherence rate for mesalamines and thiopurines was found to attain 90% and 94%, ranking high with regard to literature data[2]; (2) unavailability of a non-replaceable drug; we had to face this event for a few patients, who, owing to their intolerance of azathioprine, were prescribed 6-mercaptopurine, at a moment when the latter had become unavailable in our country (see below); (3) toxicity of a pivotal drug (mesalamine, azathioprine). Noteworthy, based on the results of an English survey which was able to reveal only 11 alleged cases of renal damage per million prescriptions, mesalamine is listed among the most tolerated drugs[3]. Our own present series included a rare case of mesalamine-induced cholestasis[4,5] which responded to patient's transitioning to balsalazide. As described in various publications[6,7], we faced a rather common azathioprine toxicity. In a population of 42 UC patients and 37 subjects with CD (females mostly) we recently found an 11% of gastric intolerance to azathioprine. Transition to 6-MP was tolerated in 6 cases which acquired disease control[8]; (4) undermining of remission because of the introduction of third party drugs: antibiotics and NSAIDs are mostly recognized as capable to reactivate IBD or induce it de-novo. Indeed, analysis of our office experience has gathered convincing evidence of a role for antibiotics and/or non-steroid anti-inflammatory drugs (NSAIDs) in active episodes of IBD, requiring the consideration of prescribing physicians[9]. A specific attention must be devoted to the Crohn's-like colitis[10] that is not rarely found as an accompaniment to immune-mediated diseases from rheumatoid arthritis to multiple sclerosis: its inciting factors have been recognized in anti-tumor necrosis factor (TNF) formulations and/or rituximab[11], the impact matching the rising prescription rate of these drugs. In our opinion, these observation are an indicator of the pathophysiologic and genetic commonalities linking the IBDs with their surrounding galaxy of immune disorders of which psoriasis is just the most obvious instance; and (5) the issue of

the ancillary symptoms in IBD. Likewise any other individual, IBD patients may present with bowel abnormalities being due to a plethora of factors from irritable bowel syndrome to celiac disease. Such situations must be borne in mind, in order to avoid prescribing IBD drugs for the wrong indication (so-called over-treatment)[12].

EXOGENOUS AND ENDOGENOUS FACTORING

Among variables factoring in the management of IBD, smoking is obviously the most studied, with a detrimental action being demonstrated for CD[13], and a protective one for UC[14].Sometimes overlooked in clinical practice, passive smoking must by contrast be given adequate consideration. The causative role of NSAIDs and antibiotics has already been touched on.

Genomic instability is gaining crucial importance among endogenous factors in IBD management, with excessive frequency of hematologic or immune-allergic disorders in the patient or among his/her relatives.

PROGNOSIS

The anticipation that the IBDs that are followed in an out-patient environment might be benign is sometimes contradicted by data. Beginning 2008, for example, in our series we recorded at least three fatalities, including one hematologic malignancy, and two cases of septicemia. One drop-out patient was reported with colonic malignancy from another hospital.

WRAPPING UP SUMMARY

This data were gathered from a random sample of 64 IBD patients (38 UC, 26 CD), who were followed in the last year at an out-patient unit with a 5-year service history. Proctitis was common among the UC patients; mesalamines were the most prescribed drugs, with the MMX formulation attaining 16% in CD and 33% in UC; beclomethasone prescriptions were prominent among steroids, ranking to 12 prescriptions including 9 of local formulations; remission maintenance was a significant challenge, pivoting over two main aspects: the control of third-party drugs, and maintenance of adherence.

At least two patients on biologics presented with superimposed immune disorders: a young female receiving adalimumab for diffuse CD developed psoriasis of the sculp; a young male with juvenile rheumatoid arthritis received three different anti-TNF formulations and developed UC on each of the three[15]; switched finally to certolizumab presented with psoriasis of the elbows.

The tables hint to an association between psoriasis and rheumatoid arthritis. Such clinical evidence in our opinion launches a few messages of a theoretical and clinical impact, and in the lines to follow we shall try to gain more insight into this matter.

Modern understanding of the anatomy of the gut and of the pathophysiology of its associated immune system all convey a concept of the IBDs as disorders pivoting on a disrupted balance between the gut mucosal immune tissue and luminal antigens, with gut microbiota as one crucially causative variable in favoring or countering the rise of an inflammatory response; the underlying dogmatic view supporting this reasoning is that while the mucosal immune system has evolved following a tolerization tune, the submucosal lymphoid tissue is highly reactive and can mount a significant inflammatory response should any antigen breach the mucosal barrier.

IBD is now thought to best be described using a concept of a "contextualized syndrome"[16]. The basis of this concept is double: (1) a uniform curative strategy for the IBDs is yet far from reach; and (2) though often presenting with obvious clinical commonalities, in fact the IBDs do hide distinct serological or genetic subtypes that are best accounted for by a process of splitting rather than one of lumping up[17].

The frequent observation of a co-morbidity between IBD and psoriasis, such as that observed in our office, served as one of the triggers for this frame of mind. A part of the scientific community has thus begun to conceive IBD as an archetype of "barrier organ diseases" whereby the essential ingredients are a mucosal surface endowed with sensor molecules of the outer environment (see the NOD system for example), and an underneath lymphoid tissue, this mixing being ruled in the background by an abundant metagenomic microbiota load (see below).

At least three systems with similar characteristics have nowadays been defined in human beings: the gut (chiefly the colon); the skin; and respiratory epithelia. It is not by chance that clinical experience has long highlighted that disorders of these three districts might be co-morbid. Our case series recorded hereby emphasize a coincidence between CD and psoriasis, but others have written about chronic obstructive pulmonary disease and IBD[18]. It is worth noting that the concept of barrier organ has been pioneered in 2005 by the brilliant work of Stefan Schreiber[19]; the Italian research has recently contributed to this field by a comprehensive dermatologic review[20] and by a gastroenterologic paper from our own[21]. As to the state of the art, it seems uneasy to identify a morphological or molecular marker to distinguish those IBDs that associate with psoriasis from those which do not. A few years ago, a North-European group focused their attention on polymorphisms of the Il23 receptor (IL23R) in both IBD and psoriasis, thus perhaps envisaging a genetic link between the two disorders[22].

Interest in the issue of the systemic positioning of IBD has been fostered by the increasingly frequent observation of ancillary immune diseases arising in patients on biologic treatments: development of IBD in rheumatic subjects receiving etanercept[23], presentation with IBD of hematologic patients treated with rituximab[24], and observation of psoriasis in cases of IBD prescribed adalimumab[25]. The bulk of these observations implies the existence of a galaxy of immune-inflammatory con-

ditions (of which IBD is just one component) spanning from the gut to skin, lungs, and joints. The link between these conditions might be represented by anatomic/physiologic commonalities (barrier organ diseases) or a generic genetic instability perhaps sustained by polymorphisms of STAT transducers[26].

This scenario recommends that the IBDs no longer be conceived as one nosographic entity. The bulk of the following observations: (1) NOD receptor polymorphism might drive CD phenotypes; (2) there is a link between serologic subtypes and clinical presentations; and (3) some CD presentations do depend on ethnic factors, All of these data contribute to build up a vision of IBD like a non-dichotomic collection of different (though linked) entities that are best described using the definition of "syndrome"[16].

The implications of this changed frame of mind cannot be ignored. If it is understood that the entity "IBD" contains in fact multiple distinct syndromes along a clinical-serologic-genetic axis, then this must somehow be reflected in differentiated clinical interventions. Such a cutting-edge frame of mind can now hardly fit the widespread recommendation and use of biologic approaches[27], which target one cytokine in an homogenized-pragmatic attempt to interfere with the common downstream pathways in the mechanisms of IBD.

A GLIMPSE INTO FUTURE TARGETS TO STUDY AND TREAT THE IBDs

Attempts to ensure "sealing" of the gut mucosa with the scope to limit contacts between the immunogenic luminal content and the lymphoid tissue underneath. Partial results of an approach using phosphatidylcholine have already been published[28].

Triggered by the classic evidence that germ-free animals do not develop IBD, investigators could not neglect the colonic microbiota, which constitutes a heavier meta genoma than somatic cells themselves. Various attempts to modify the amount and composition of colic metagenoma have thus proliferated: (1) oral administration of pro-biotic lysates[29]; (2) fecal transplants[30]; and (3) diet modifications[31].

The data from the bulk of these studies is conveying the message that a quantitative or qualitative change of gut microbiota colonization (dysbiosis) might associate with a plethora of (auto)immune and (auto)inflammatory disorders[32], with a particular emphasis on rheumatoid arthritis (RA)[33]. Relevant cutting-edge results[34] are now showing that Prevotella Copri (an in-habitant species of the microbiome) might train T-lymphocytes to secrete IL-17, a key mediator in the pathogenesis of RA. To this end, attention is concentrating on the recent claim that NOD receptors on colonic epithelial cells (whether tolerant or reactive against colonic flora at birth) might drive the metagenomic phenotype of the newborn: rather a breakthrough, in view of the ability of colonic species to condition a whole array of affections, from IBD itself to hepatic steatosis[35].

Research directed to identify and change factors in the genesis of IBD, such as life style and diet composition[36].

Along a totally different line, the results have been published of attempts at unraveling genetic IBD surrogates, that though mimicking IBD, might atypically respond according to the signal conveyed by the hidden gene: Behcet mimicking IBD[37] and familial mediterranean fever are instructive example[38].

CONCLUSION

Though generated in a limited environment, the analysis of the data from our office has led to general considerations. The IBDs can no longer be considered as autonomous entities, but rather as poly-organic and poly-genic syndromes wherein a critical mass of polymorphic genetic information and environmental factors must interact for full-blown disease to develop[39]. Visualizing the IBDs like archetypes disorders of the immunological interaction between the "in" and the "out" (together with skin and pulmonary epithelia disorders) to make the umbrella label of "barrier organ disease" seems particularly seminal. This novel positioning of IBD might at first sight increase the degree of complexity, but on the other hand can favor novel therapeutic approaches and pave the way towards the conception of a personalized therapy.

Though apparently stable in the Western World, IBD has two formidable avenues to run. Firstly, Far East populations seem no longer to be immune from the IBDs, and in the next few years may witness an epidemic explosion of these disease[40]; secondly, populations that immigrate to countries with a higher hygiene standard seem to be particularly prone to develop IBD[41]. For certain countries, such challenges are not an issue of tomorrow, but are already here today.

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