Research and clinical challenges in paediatric inflammatory bowel disease

A. Bousvaros a,∗, 1, A. Morley-Fletcher b,1, L. Pensabene c,1, S. Cucchiara b,1

a Inflammatory Bowel Disease Center, Children’s Hospital Boston, Harvard Medical School, United States
b Department of Pediatrics, Pediatric Gastroenterology and Liver Unit, University of Rome, Italy
c Department of Pediatrics University “Magna Græcia”, Catanzaro, Italy

Received 23 July 2007; accepted 26 July 2007

Abstract

Inflammatory bowel disease in childhood has become the subject of intense scientific debate during the last two decades, when there has been a significant rise in its incidence. There is a commonly agreed view that the disorder in children has peculiarities both in terms of underlying mechanisms and clinical management. This review highlights the emerging pathophysiologic concepts and clinical issues in paediatric inflammatory bowel disease and their effects on the management of children with this disorder are discussed. Particular emphasis is given to the link between the improvement of the research in the pathogenetic mechanisms and the development of novel therapeutic strategies able to promote a change in the natural course of the disorder.

© 2007 Published by Elsevier Ltd on behalf of Editrice Gastroenterologica Italiana S.r.l.

Keywords: Biological therapy; Children; Genetics; Immunology; Inflammatory bowel disease; Microbiology

1. Introduction

Paediatric inflammatory bowel disease (IBD) has become a topic of major interest over the past 20 years. A detailed document published by the Crohn’s and Colitis Foundation of America in 2006 entitled “Challenges in Pediatric Inflammatory Bowel Disease” nicely summarized the progress that has been made in the study of this field to date, and many of the high-priority questions that need to be answered in the future [1]. In summary, while our therapy has improved, our understanding of the pathogenesis remains limited. On the positive side, a number of new therapeutic interventions have been developed that have consistently improved the quality of life of children with this serious chronic illness. Specifically, the early introduction of immunomodulator drugs, the proper use of enteral nutrition and the utilization of tumour necrosis factor inhibitors in patients who have failed immunomodulators have resulted in improved quality of life and improved growth for children with Crohn’s disease (CD) and ulcerative colitis (UC) [2,3]. Unfortunately, our understanding of the basic biology and pathophysiology of this condition remains suboptimal, and therefore we have no current interventions that prevent the disease. There is a markedly increasing prevalence of IBD throughout the modernized world, with two recent epidemiological paediatric studies from Wisconsin and from Sweden indicating an overall incidence rate of 7.05/100.000 and 7.4/100.000, respectively [4,5]. While some of this reported increase may be due to improved methods of case ascertainment, our technology to diagnose IBD (endoscopy, colonoscopy and radiography) has not changed significantly in the last 15 years. Therefore it is highly likely that the findings of these epidemiological reports represent a true increase in the incidence of paediatric IBD.

In order to prevent IBD in the future and to improve the management of the disorder in paediatrics we need to better understand its cause. We now realize that the development of the research over the last decade has led to novel therapeutic strategies that target specific immunological pathways in

* Corresponding author at: Children’s Hospital Boston Inflammatory Bowel Disease Center, 300 Longwood Ave, Boston, MA 02115, United States. Tel.: +1 617 355 2962; fax: +1 617 730 0494.
E-mail address: athos.bousvaros@childrens.harvard.edu (A. Bousvaros).

1 These authors contributed equally to this work.
the intestinal mucosa, whereas traditional mainstay of IBD therapy consisted of non-specific, immunosuppressive and anti-inflammatory drugs.

In this review we present emerging pathophysiologic concepts and clinical issues in pediatric IBD and we discuss their effects on the management of children with this disorder.

It is now understood that mutations or polymorphisms of many different human genes can predispose patients to the development of CD or UC. The same is true of genetically altered animal models of IBD. Recent research has focused on the paradigm of gene–microbe interactions [6]. Such interactions may result in an activated mucosal immune system, with an unregulated, uncontrolled immune response directed against the affected tissue (the bowel). The gene mutations thus far identified in IBD seem to influence the innate immune system, which regulates the body’s response to commensal bacteria [7]. The next 20 years of inflammatory bowel disease research will no doubt continue to elucidate additional genes that contribute risk of developing this condition, combined with the potential of environmental triggers that may set off the diagnosis. This review will summarize some of the important progress that has been made in this area.

2. Genetic risk

Numerous papers from the 1990s have demonstrated that mutations in the innate and adaptive immune systems of mice and rats may predispose these animals to develop inflammatory bowel disease. Animal models of inflammatory bowel disease are well described and summarized elsewhere. They include the HLA-B27 transgenic rat (which develops a profound arthritis and colitis), the IL-10 knockout mouse, the IL-2 knockout mouse, the TCR alpha beta knockout mouse and the Samp/yit murine model [8,9]. While all of these mice have different genetic mutations that affect immunoregulation, they all have one important thing in common: these mice generally do not develop inflammatory bowel disease in a germ-free environment. However, when exposed to enteric microflora or a non-germ-free diet, colitis will promptly develop. Elegant studies recently performed by Drs. Sandra Kim and Balfour Sartor utilizing the IL-10 knockout have elucidated how gene–microbe interactions determine phenotype. Mutant mice with a deleted IL-10 gene do not develop IBD in a germ-free environment. However, when infected with a strain of Escherichia coli, they develop a right-sided colitis (caecal inflammation, similar to Crohn’s disease), and when infected with a strain of enterococcus, they develop left-sided colitis (UC-like disease) [10]. This finding offers an explanation as to why Crohn’s disease and ulcerative colitis run in the same kindreds. One gene may predispose an individual to develop IBD, but colonization of the intestine to different microbes may determine which specific IBD phenotype an individual will develop.

In the human, whole genome scanning and genetic linkage studies have demonstrated a number of genes that correlate with inflammatory bowel disease. The best described of these genes is the NOD2 gene, a gene that encodes an intracellular protein which binds microbial antigens (e.g. muramyl dipeptide). In adults, this gene can be identified in approximately 25% of patients with Crohn’s disease, and correlates primarily with primarily distal small bowel and fibrostenosing disease. There does not appear to be an increased prevalence of NOD2 mutations in children compared to adults [11].

A second gene that has been recently identified in patients with inflammatory bowel disease is the interleukin-23 receptor gene. Mutations in this gene were first identified primarily through whole genome scanning [12]. Recently, Dubinsky et al. evaluated DNA from children (151 Crohn’s disease and 52 ulcerative colitis trios), and genotyped them for mutation in the IL-23 receptor (R381Q), which appears to confer protection against Crohn’s disease [13]. The investigators confirmed that this particular allele was negatively associated with inflammatory bowel disease, thus confirming in children what has already been shown in adults. Additional genes that have been investigated include the multi-drug resistance 1 (MDR1) gene, Toll-like receptor genes and the IBD-5 (OCTN) genetic locus [14,15]. While the association between these genes and IBD may be less strong than with NOD2 and IL23R, they are useful candidate genes that warrant further study.

3. Microbiology

While genetic research in inflammatory bowel disease is well underway, the utilization of similar technology to study the intestinal microbiome remains in its infancy. The intestine is populated by approximately 400 different species of bacteria, and intestinal colonization is thought to be largely complete by 1 year of life. Once microbial flora have been established, they may be quite difficult to modify [16].

Those who study intestinal microbiology and its relationship to inflammatory bowel disease have one of two primary alternative hypotheses. The first hypothesis suggests that the human host who develops inflammatory bowel disease is exquisitely predisposed to develop inflammation whenever there are subtle alterations in the intestinal microenvironment. Therefore, while humans are all colonized with the same bacterial species, different shifts in those bacteria might produce a slightly different pattern of pro-inflammatory peptides (for example, muramyl dipeptide, flagellin or lipopolysaccharide). Therefore, minor changes in the intestinal microenvironment might be enough to set up a pattern of uncontrolled inflammation in the genetically predisposed host [17].

An alternative hypothesis, however, is that a group of microbes that have yet to be defined have developed some sort of mutation that predisposes them to pathogenicity. For example, in the past 20 years, staphylococcus has become more virulent, and there are now community-acquired strains that have both a methicillin-resistance gene and Panton-Valentin
leukocidin, a virulence factor that enables the staphylococcus to resist phagocytosis by leucocytes [18,19]. The emergence of this virulent strain of staphylococcus has resulted in epidemics of community-acquired methicillin-resistant Staphylococcal cellulitis and impetigo across the United States. It is therefore possible that some strain of bacteria has in some way mutated, developed similar virulence factors, and now it is attacking genetically susceptible hosts. If that were to be the case, we may in the future identify such a strain of bacteria in patients either with ulcerative colitis or Crohn’s disease. In support of this hypothesis, a recent paper by Kotlwoski et al. has demonstrated a high prevalence of a particular strain of E. coli that may adhere preferentially to enterocytes [20].

Emerging molecular technology is now allowing investigators to better characterize the intestinal microbiome. This has always been difficult to do because of the large number of organisms and strains in the faeces and the very difficult, labour-intensive process of individually culturing each of these strains. With the development, however, of fluorescence in situ hybridization, 16-S ribosomal RNA techniques and denaturing gradient gel electrophoresis, investigators will be better able to characterize the microenvironment of the intestine [21]. More recently, investigators have started developing gene chips that may give a more qualitative and quantitative assessment of the entire intestinal microbiome. While these techniques have yet to be fully applied to the study of inflammatory bowel disease, there is no question that these techniques will be utilized more frequently in the future.

4. Immunology

Ultimately, whatever the gene–microbe interaction is in patients with IBD, the end result is a poorly controlled immune response. The lack of immune regulation in patients with inflammatory bowel disease and other autoimmune disease has been a major focus of study for investigators for the past 20 years. It has been known that the lamina propria of patients with both Crohn’s disease and ulcerative colitis contains large numbers of activated T-cells that produce increased demands for interleukin-2, and also express activated interleukin-2 receptors. Many different cytokines have been identified in the pathogenesis of these conditions, but it is unclear if there is one cytokine that functions as a primary regulator of these diseases. Recent interest has focused on interleukin-12 and -23 in Crohn’s disease and interleukin-13 in ulcerative colitis [22–24].

One of the major questions in paediatric inflammatory bowel disease is whether or not inflammatory bowel disease can be prevented by promoting the proliferation of regulatory cells (CD4 CD25 positive T-cells). Such cells typically express the Fox-P3 gene [25]. Mutations in this gene produce a clinical syndrome characterized by multiple autoimmune manifestations, including polyendocrinopathy and enteropathy. This syndrome has been termed IPEX syndrome, and the autoimmune enteropathy associated with this syndrome can be treated with immunosuppressive therapy [26,27]. Ultimately, however, the best treatment for some patients with this condition may be bone marrow transplantation as patients with IPEX are at risk for developing life-threatening autoimmune disease over time.

Additional mutations in children that either induce inflammation or inhibit regulation of the immune response can also cause atypical inflammatory bowel disease in early infancy. Conditions associated with this kind of process include chronic granulomatous disease (which histologically can mimic Crohn’s disease), the Crohn’s disease subtype associated with glycogen storage disease 1B, the inflammatory bowel disease associated with NF kappa beta essential modifier (NEMO) mutation and the IBD associated with Hermansky-Pudlak syndrome. Once again, these children with rare diseases confirm the conjecture that inflammatory bowel disease is not one gene causing one phenotype, but rather many genetic mutations causing many different phenotypes [28].

Can the immune system be modified in early childhood in order to prevent inflammatory bowel disease in later childhood? While the answer to this question is unknown, studies utilizing probiotics in children with atopic dermatitis and allergy suggest that this may indeed be the case. In 2001 a group led by Dr. Erika Isolauri randomized infants at risk for food allergy to receive the probiotic lactobacillus GG. Their pregnant mothers were treated with probiotics in the last portion of the third trimester, and the infants subsequently received probiotics for several weeks. After 1 year of follow-up the prevalence of allergy in the probiotic-treated group was approximately 20% as compared to 40% for the group treated with placebo [29]. Subsequent follow-up studies by Dr. Erika Isolauri’s and Dr. Susan Prescott’s groups have also suggested that probiotics might not only help prevent atopic dermatitis but may also lessen the severity of atopic dermatitis, once it starts [30]. Dr. Prescott’s studies evaluated active eczema utilizing a clinical scoring system, and noted a moderate but statistically significant decrease in eczema severity in children treated with probiotics.

As of this time, there is no one probiotic that has been shown to definitively modify inflammatory bowel disease or prevent it once it starts. A randomized controlled trial of probiotics in the prevention of IBD in family members of patients—such a study would be difficult to conduct, and require large numbers of patients and long-term follow-up. If the evidence that probiotics have beneficial effects on the immune system continues to mount, the feasibility of such a study should be more carefully examined.

5. Utilizing surrogate markers to identify high-risk phenotypes of IBD

A number of children with inflammatory bowel disease develop serious complications of their illness. It has
been estimated that approximately 30% of Crohn’s disease and/or ulcerative colitis patients will require bowel resection over the first 5 years of their disease. Surgical complications may include abdominal abscesses or strictures (in Crohn’s disease) or medically refractory colitis requiring colectomy (in ulcerative colitis and indeterminate colitis). In addition, a subset of patients who have been operated on will develop either chronic pouchitis after colectomy surgery or recurrence of their Crohn’s disease at the anastomotic segment (in Crohn’s disease).

One major research problem that translates between basic research and clinical research is the ability to identify surrogate markers of paediatric inflammatory bowel disease that will either predict response to therapy or a higher-risk population. Recently, Dubinsky and colleagues have started to better delineate such markers through their study of inflammatory bowel disease serologies. The investigators have identified that patients who have antibodies to *Saccharomyces cerevisiae* (both IgG and IgA) have a higher risk of surgery (primarily ileocaecal resection) and are at high risk for either perforating or fibrostenosing disease. Similarly, patients with antineutrophil cytoplasmic antibodies who have Crohn’s disease tend to have an ulcerative colitis-like picture, and can be highly refractory to medical therapy. The serology appears to be an independent predictor of the need for surgery, even after adjusting for age, sex and genotyping [31]. Therefore, it is possible that in the future, serologies could be utilized to find a high-risk genotype and serotype that would warrant more aggressive (step-down) therapy in the future. The main difficulty with these studies, however, is that they cannot be generalized to the individual patient. Even if serotypes could prove that 40% of patients with this particular serotype would require surgery within 3–5 years, it is unclear whether it is appropriate to treat the remaining 60% with a high-risk medication such as infliximab in order to prevent surgery in the 40% who will ultimately require surgery. Ultimately, however, studies of serology may be similar to studies of leukaemia that have identified high-risk groups who warrant more aggressive therapy.

6. Pathogenesis of growth failure in inflammatory bowel disease

One of the main complications of inflammatory bowel disease (particularly Crohn’s disease in children) is the development of growth failure and permanent height stunting. Children with Crohn’s disease often are markedly shorter than their counterparts despite medical therapy, and the stunting can have permanent effects in terms of well-being, self-esteem and employment later in life [32].

There is an increasing amount of work being conducted with regards to pathogenesis of growth failure in children with inflammatory bowel disease. It is now recognized that interleukine-6 may affect signal transduction at the level of the hepatocyte period. Growth hormone produced by the pituitary gland typically travels through the bloodstream to the liver with very complex signal transduction pathway involving JAK and STAT proteins, insulin-like growth factor-1 is produced. It is now recognized that at least in vitro, cytokines such as interleukin-6 and tumour necrosis alpha may decrease IGF-1 production by inhibiting such signal transduction [33]. Of note, corticosteroids also suppress growth but by a different mechanism, that of suppressing bone remodelling. Further research into this area is essential to better characterize what, if any, corticosteroids have less of an effect on bone remodelling. In addition, better characterization of the growth hormone JAK/STAT/IGF-1 pathway may allow for more targeted treatment designed to improve growth in children with Crohn’s disease. For right now, however, the primary mechanism of improving growth in this condition involves avoiding the use of corticosteroids, utilizing enteral nutrition aggressively and also utilizing steroid-sparing therapy with immunomodulators and biologics. The role of surgery in these patients remains highly beneficial, as resection of a limited portion of active disease may allow significant growth.

7. Implications for future treatments

Since IBD cannot be cured, the traditional therapeutic goals have been to achieve and maintain clinical remission and to attain the highest available quality of life. Recently there has been a growing view that intestinal mucosal healing should be the primary therapeutic objective in IBD: this challenges the concept of clinical remission because clinical indexes of IBD are subjective and seem to correlate poorly with inflammation as detected by endoscopy [34]. Indeed, clinical remission may coexist with mild-to-moderate degrees of mucosal inflammation and has been associated with a high degree of relapse [35]. There is evidence that infliximab, the most commonly used biological agents for IBD, is able to promote mucosal healing that seems to be associated with a reduction both in the hospitalization rate and need for surgery [36]. These observations suggest the concept that healing of mucosal lesions could modify the natural history of IBD, i.e. carrying a lower risk of developing perforating disease (fistulas and abscesses) and/or fibrostenosis.

Currently, several arguments limit the use of biological agents as first-line therapy for adult and paediatric subjects, despite some immunological views tend to encourage the early introduction of disease-modifying drugs in patients with a short-lasting and recently diagnosed IBD [37]. The inability of numerous patients to respond to traditional therapy seems to justify a top-down approach with biologics as a first-line treatment, either alone or in association with immunomodulators. Preliminary data in adults make this approach appealing [38]; however, current data...
on the long-term efficacy, risks and costs following the reversal of the traditional therapeutic pyramid are scanty. A recent report on serious adverse events with infliximab, through a post-marketing experience with the recently available FDA adverse event reporting system (AERS), indicates that lymphoma and serious infections are reported 6.9 and 2.9 times more often, respectively, with infliximab than would be expected [39]. The potential risk of lymphoma in IBD patients treated with immunomodulators such as azathioprine or 6-MP has been discussed with conflicting results. A recent meta-analysis suggests an approximately fourfold increase of the risk of lymphoma in IBD patients receiving azathioprine/6-MP [40]. However, it is widely agreed that the actual risk of lymphoma in IBD patients remains largely unknown and since most available data result from observational studies it cannot be excluded that an increased risk of lymphoma is associated with the severity of the underlying disease rather than with the immunoregulatory therapy. In any case, it is clear that clinicians should carefully balance the potential benefits of these drugs against the potential risk for malignancies and infections.

A troublesome concern on the use of infliximab has recently been reported: the occurrence of an unusual but aggressive and commonly fatal form of malignancy, an hepatosplenic T-cell lymphoma (HSTCL), in 11 young adults or adolescents with IBD treated with infliximab (10 with CD, 1 with indeterminate colitis) [41] (Centocor, data on file). All of these patients had received azathioprine or 6-MP concomitantly with infliximab; thus, the exclusive role of infliximab in the occurrence of HSTCL cannot be established. The association of this rare peripheral mature T-cell NHL in IBD patients seems to be remarkable. The expected incidence of NHL in paediatrics is roughly 800 cases per year in the USA: while over half are aggressive mature B-cell phenotype and approximately 30% have a precursor T-cell phenotype, mature T-cell NHLs are very rare (<5% of all NHLs in children) [42]. It has been suggested that one case of HSTCL per year should be expected in the paediatric age in the USA. Description of these cases of HSTCL seems to have induced a generalized immune dysregulation occurs, a combined approach in order to neutralize different path-ways sequentially or concomitantly will be an attractive choice.

8. Conclusions

The fundamental basis of IBD is a genetic predisposition leading to an over-reactivity of the mucosal immune system to normal constituents of the mucosal microflora or environmental triggers. Based on extensive research over the last decade there have been tremendous advances in understanding IBD and its pathophysiologic mechanisms, enabling in turn the development of powerful therapies with new ambitious goals such as mucosal healing and slowing or interrupting progression of IBD from an early “juvenile” course to the adulthood form of the disease. Novel therapeutic agents now consist of monoclonal antibodies, small molecule inhibitors, peptides and vaccines. Despite these advances IBD is still difficult to treat and only few patients benefit deeply from the new therapies. The comprehension that multiple variables contribute to the mechanisms of IBD and that different pathway abnormalities are present in diverse clusters of patients will lead to identify target pathogenetic steps for tailored therapeutic interventions, along the continuum of events underlying intestinal inflammation. Interestingly, as the role of genetic mutations is fully understood, early therapeutic approach can be aimed at preventing the disease in predisposed individual, i.e. gene therapy or modulation of intestinal microbiota through antibi-otic or probiotic strategies. In the early or induction phases of the disease development, approaches aimed at blocking single therapeutic steps will likely be successful (i.e. neu-tralizing distinct adhesion molecules, Th1 or Th2 cytokine blockade). Finally, in the late stages of the disease, when a generalized immune dysregulation occurs, a combined therapeutic approach in order to neutralize different pathways sequentially or concomitantly will be an attractive choice.
Practice points

- To emphasize that the inflammatory bowel disease (IBD) occurring in childhood has peculiar specificities as compared to the disorder in adulthood.
- To highlight the principal topics in the mechanisms underlying the disorders as well as in its clinical management.

Research agenda

- To delineate the priorities of the research in the field of paediatric IBD during the next years.
- To make a link between the advancement in the knowledge of the pathogenetic mechanisms and the improvement in the clinical management of the patients.

Conflict of interest statement

Dr. Bousvaros served as a consultant to Abbott Pharmaceuticals and UCB pharmaceuticals in the past year.

Acknowledgement

Dr. Bousvaros was funded in part by the Wolpow family fund and the MacInnes friends and family fund.

References


Please cite this article in press as: Bousvaros A, et al., Research and clinical challenges in paediatric inflammatory bowel disease, Dig Liver Dis (2007), doi:10.1016/j.dld.2007.07.168


