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Inflammatory bowel disease: review and future view

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1. ABSTRACT

Inflammatory bowel disease (IBD) is chronic problem that cause an inflammation of the intestines. Significant progress has been made in recent years to the field of IBD epidemiology, pathogenesis and treatment and a number of new insights have been created. Also, there is an increasing interest in the discovery of different new aspects related diagnosis and treatment. In this review we will highlight few points related to current situation of inflammatory bowel disease and some areas of progress in different fields.

2. INTRODUCTION

Ulcerative colitis and Crohn's disease are heterogeneous chronic inflammatory disorders of the intestine. IBD represents an important public health problem because it affects mostly young people at an age when they are most active in their private and professional lives and a management challenge because of its unpredictable relapsing nature (1).Significant progress has been made in recent years to the field of IBD epidemiology, pathogenesis and treatment and a number of new insights have been created. There is an increasing interest in the discovery of new inflammatory bowel disease (IBD) biomarkers able to predict the future patterns of disease and to help in diagnosis, treatment, and prognosis (2). Also, history of gastrointestinal endoscopy is one of striking technical advances; from the first rigid instrument developed by Kussmaul in Germany, or the semiflexible instruments designed by Rudolf Schindler in Chicago, to the current video endoscopes, a more accurate visualization of the gastrointestinal tract offers increasing knowledge of gastrointestinal disease and better therapeutic possibilities (3).

Curative treatment is still needed. As such, management has focused largely on ameliorating symptoms, and reducing hospitalization and the need for surgical treatment. It has been hypothesized that complete healing of the intestinal mucosa in inflammatory bowel diseases should result in reduced disease complications, reduced hospitalization and reduced surgical treatment (4). Diet is one of the most frequently discussed points and interrelationships between IBD and diet are complex and are an area of great interest and confusion among both physicians and patients (5). The interaction of food and the GI mucosal immune system is an important factor in intestinal inflammation. Patients with UC demonstrate increased mucosal eosinophils and IgE in relation to certain foods (6). Results from clinical trials of biologic anti-TNF drugs performed in the late 1990s confirmed the biological relevance of TNF function in the pathogenesis of chronic noninfectious inflammation of joints, skin and gut, which collectively affects 2–3% of

the population (7). Current therapies ranging from anti-inflammatory drugs to immunosuppressive regimens, remain inadequate. Advances in our understanding of the cell populations involved in the pathogenetic processes and recent findings on the regenerative, trophic and immunoregulatory potential of stem cells open new paths in IBD therapy (8).

Researchers have developed a novel approach for delivering small bits of genetic material into the body to improve the treatment of inflammatory bowel diseases. Delivering short strands of RNA into cells has become a popular research area because of its potential therapeutic applications, but how to deliver them into targeted cells in a living organism has been an obstacle (9).

3. EPIDEMIOLOGY

During the last few decades the incidence of IBD has changed in many ways. Incidence rates of traditionally high incidence areas such as Western Europe is relatively stable or even decreasing,(10) while diseases have become more prevalent in previously low incidence areas, such as Asia and Eastern Europe (11). An almost two-fold variation has also been reported from the United Kingdom, with Kyle finding the incidence of Crohn's disease continuing to rise in north-east Scotland at 98/ million/year in 1985–87, while in the Cardiff area incidence was declining with the figure for 1986–90 being 62/million/year and 56/million/year for 1991–95 (12). IBD is more common in the Northern than the Southern part of the world, and it is more common among Caucasian compared with non-caucasian populations. The highest incidence rates have been recorded in North America and North and West Europe, while lower rates have been reported in South America, Africa and Asia (13). In Asia, several studies have indicated a rising trend of the incidence and prevalence of IBD although only few data are available on the true epidemiology of IBD in Asia (14). Up to our knowledge no data available about incidence and prevalence of IBD in north Africa and middle east.

4. DIAGNOSIS

Many aspects of the inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC) bear challenges for the physicians treating this disorder: its diagnosis, prognosis, assessment of disease activity and severity, as well as the outcome of therapy. For each of these aspects, there is no single standard or 'golden' test or exam. Instead, physicians apply a combination of symptoms, clinical examination, laboratory indices, radiology and endoscopy with histology (15).We will discuss the existing IBD biomarkers, focusing on the new reported serum biomarker; their diagnostic and prognostic utilities, capsule endoscopy as diagnostic tool under focus of research.

4.1. New biomarkers

Serologic testing has been used with increasing frequency as a diagnostic tool and proposed as a screening measure for IBD (16) . Chronic inflammation in the intestinal tract with IBD may result in a change in immune response toward microbial flora. Antibodies against such microorganisms or against self-antigens have been detected in IBD populations. Markers include immunoglobulin A (IgA) and immunoglobulin G (IgG) antibodies against the yeast *Saccharomyces cerevisiae* ([ASCA] IgA and IgG), perinuclear cytoplasmic immunofluorescent antibody deoxyribonuclease (p-ANCA), and antibodies to outer membrane porin of *Escherichia coli* (anti-OmpC). These antibodies were initially studied in the adult populations. ASCA and p-ANCA are the most widely used markers, whereas anti-OMPC has been more recently studied (17).The test or marker of inflammation that should be carried out should be decided individually taking into account its convenience, together with cost issues, availability and accuracy, as well as specific qualities (specificity, correlation with severity of inflammation). In the management of patients with IBD, several markers measuring inflammation will be monitored and carried out together (15). There is an increasing interest in the discovery of new inflammatory bowel disease (IBD) biomarkers able to predict the future patterns of disease and to help in diagnosis, treatment, and prognosis (2).

Since 2007, several independent studies on New anti-glycan antibodies: ACCA, ALCA and AMCA have been reported, and their clinical utility has been validated . Glycan, a generic term for all molecules bearing glycosidic bonds, includes mono-, oligo- and ploy-saccharides or carbohydrates (18) Recently, new serological biomarkers for IBD have been accurately reviewed by Li et al, including a new contribution from proteomics studies (2,19). Proteomics can be used to identify and test novel proteins (or pattern of proteins) as diagnostic biomarkers in IBD. Different proteomics approaches have been applied to in vitro models of IBD (colonic epithelial cells (20). A large-scale proteomic study using LC and MS is performed to evaluate the response of the mammalian Caco-2 cell culture line to the enteropathogenic Escherichia coli. More than 2000 proteins were identified and the 13% of them were found differently expressed in the presence or absence of the pathogen, thus generating novel testable hypotheses about the role of this enteric human pathogen in the disease (2,21). Subproteomic may serve as a new approach to study new markers and to provide insight into the etiopathogenesis of the disease itself. While current serological IBD biomarkers are useful, but their clinical utility has been limited. New technologies, demonstrate the significant potential for identifying previously unrecognized IBD biomarkers. Future direction is predicted to be, in addition to the continuation of ongoing efforts in developing novel biomarkers using conventional and new technologies, the integration of multiple biomarkers with extensive bioinformatics analysis/modeling.

This will be the key to eventually developing specific "endpoint-oriented" serological

biomarker kits. These may include, but not be limited to, individual biomarker sets that are specific for one or more of the following: (1) differentiating CD *vs* UC *vs* normal *vs* other non-IBD gut diseases that share some similar clinical presentations (such as abdominal pain and diarrhea in infectious colitis or IBS); (2) predicting IBD risk (before disease onset; subclinical biomarkers) and disease course (risk of complication and surgery); (3) predicting therapeutic efficacy even before initiation of specific medication(s); and (4) monitoring therapeutic efficacy and predicting relapse. One can envision that such kits will rely on "integrated algorithms", rather than absolute differences, to enhance the accuracy of diagnosis and/or prognosis of IBD (18).

4.2. Capsule endoscopy

Endoscopic assessment of the small bowel has remained a challenge, because its length and tortuosity determines a major difficulty for its exploration with flexible endoscopes. Sonde and push enteroscopes provided a significant advance in this field (22). A prospective study compared Capsule Endoscopy (CE), computed tomography (CT) enterography, ileoscopy, and single contrast small bowel follow-through (SBFT) in 17 patients with known or suspected CD. Findings revealed small bowel lesions in 71% via CE, 65% via ileoscopy, 53% via CT enterography, and 24% via SBFT (23). Other studies established that CE has an incremental diagnostic yield of 25%-40% over other methods, such as barium studies or CT scanning (24), other well designed papers have limited the role of CE in comparisons with other procedures as CT enterography, ileocolonoscopy or small bowel follow-through (25).

Capsule endoscopy (CE) was initially marketed in 2001, and, to date, has been the greatest advance in the field of small bowel exploration. The procedure provides state-of-the-art imaging of the small intestine (26). CE may determine medical response to therapy at the level of mucosal healing. One study reported a case of ileal mucosal healing detected with CE in a CD patient 16 months after starting therapy with azathioprine and mesalamine . Given that isolated CD of the small bowel may be difficult to follow with other imaging modalities, CE may provide the opportunity to monitor both the onset and degree of improvement with the use of medical therapy (26,27). Major advantage of CE is that being comparable to other radiographic methods in the assessment of activity in patients with established Crohn's disease, it offers of no radiation exposure (24). Another controversial issue is the position of CE in the diagnostic algorithm of suspected Crohn's disease. Although, as mentioned above, it is widely accepted to perform it after ileocolonoscopy and a small bowel radiographic method, in view of the results of the Mayo Clinic trial (25,26), the authors recommend the performance of CT-enterography after ileocolonoscopy but before CE. Indeed, they had a similar sensitivity but a higher specificity rate for CT enterography compared to CE. In the discussion, they finally state that the algorithm ought to be adapted to local availability and expertise (25,26). Contraindications for CE include having a known or suspected gastrointestinal tract obstruction and/or known small bowel strictures, because of the increased risk of capsule retention in such patients (28) but a retained capsule endoscopy does not usually cause obstruction, and can remain intact for up to 4 years (29). Still there is need for better definition of specific lesions in inflammatory bowel disease, indications of the procedure in patients with unspecific symptoms, validation of activity scores, and the technical modifications to allow biopsy sampling (26).

5. MUCOSAL HEALING

Clinical assessment of disease activity in UC and CD has traditionally been accomplished by assessing symptoms such as the presence or absence of blood, the number of stools per day, and the presence or absence of evidence of systemic toxicity (30) or activity indices that are highly symptom based, such as the Crohn Disease Activity Index (CDAI) or Harvey-Bradshaw Index (HBI) in CD, and the Mayo score (31,32). More recently, fecal markers such as fecal calprotectin have shown promising results (33). Studies revealed disconnection between mucosal lesions and symptoms. Within a year after intestinalresection, at least 70% of patients have recurrent disease endoscopically, yet clinical recurrence occurs in only one-third by 3 years, implying that endoscopic lesions and symptoms may not correlate (34). An emerging measurement to define the effectiveness of new therapeutic agents in clinical trials, has been popularly labeled "mucosal healing". In practical terms, the assessment of mucosal healing is based largely on observational evaluation, which requires the use of repeated endoscopic studies before and after a defined treatment period, sometimes in conjunction with histological examination of mucosal biopsies, or other more indirect imaging methods, other surrogate markers or miscellaneous methods, such as measurements of intestinal permeability. Logically, however, but not yet conclusively shown, complete healing of the intestinal mucosa should result over the long term in reduced disease complications, hospitalization and surgical treatment (4). In a recent study, combination immunosuppressive therapy with infliximab and azathioprine led to significantly higher mucosal healing rates compared with conventional management (CM) in patients with newly diagnosed CD, despite comparable clinical steroid-free remission rates after 2 years of treatment (35).

Data about the advantages of achieving mucosal healing in the specific context of biologic agents who achieved mucosal healing tended toward lower rates of hospitalization (36,37), use of corticosteroids has not been associated with significant degrees of mucosal healing (37). Until recently, there were limited data regarding mucosal healing with the use of mesalamine in UC. However, with the recent development of Multi-Matrix System (MMX) mesalamine, there are mucosal healing data from trials in

UC. At 8 weeks, approximately 35% to 40% of patients on 2.4 to 4.8 g/d of MMX mesalamine achieved mucosal healing in 2 pivotal trials of this agent. There are no mucosal healing data for mesalamine in CD (37,39). There are currently no mucosal healing data for adalimumab or certolizumab pegol in UC and neither agent is currently indicated for this disease. Studies with adalimumab are ongoing (37). The current technology to assess mucosal healing in clinical trials and clinical practice remains limited, tends to be observational, and is not ideal because it does not evaluate transmural inflammation precisely, only the luminal surface mucosa. Repeated invasive endoscopic evaluations may not be optimal, particularly since these are largely one dimensional (4). New studies have appeared employing microarray technology in animal and human colitis, which have increased our understanding of the basic inflammatory process, along with possible mediators that might be regulated (40-41). Recent genome-wide association studies in ulcerative colitis have identified new susceptibility loci that suggest that changes in the integrity of the mucosal barrier are important in pathogenesis (44).

6. MANAGEMENT

Various theories have been developed as to the etiopathogenesis of inflammatory bowel disease (IBD), but so far none of them has led to a therapy with long-term efficacy and free of side effects (8). Conventional therapy employs the most benign drugs first, adding drugs with more potential side effects later. The IBD treatments currently available to clinicians include 5-aminosalicylates, sulfasalazine, antimicrobial therapy, corticosteroids, immunosuppressive agents, and monoclonal antibodies (mAbs). There are few commercially available mAbs, which include natalizumab, which is a mAb directed against alpha4-integrin, and the three antitumor necrosis factor (TNF) antibodies, namely, infliximab, adalimumab, and certolizumab pegol (45).

6.1. Diet, nutrition

The interrelationships between IBD and diet are complex, and are an area of great interest and confusion among both physicians and patients. There are a great deal of objective data outlining the nutritional complications caused by IBD, but in the area of cause or cure, information is sparse, anecdotal and often conflicting (5). The rise in the incidence and the prevalence of IBD has paralleled the social and economic development of populations and adaptation to a Western lifestyle that include diet changes, smoking, oral contraceptives and stress (46). The interaction of food and the GI mucosal immune system is an important factor in intestinal inflammation (47). Patients with UC demonstrate increased mucosal eosinophils and IgE in relation to certain foods The prevalence of IBD associated- malnutrition is high, ranging from 23% in outpatients to 85% in inpatients admitted for clinical exacerbation (48). Nutritional deficits occur in variable incidences, such as anemia (54 to 80%), hypoalbuminemia (25 to 80%), metals (iron, copper), trace elements (selenium, magnesium, zinc), vitamins (A, B, D, E, K) and reduction of enzymatic (superoxyde dismutase, catalase, gluthatione peroxydase) and non-enzymatic antioxidant activity (vitamins C, E, carotene, gluthatione, taurine) (49). On the other hand, can we consider dietary elements as causative factors, changes in the western diet and its global spread have been implicated as one of many theories contributing to the rising incidence worldwide. Most diet studies in IBD are case– control studies and prone to heterogeneity and recall bias. Attempting to isolate single nutrients or even patterns of nutrient intake is a daunting task, fraught with potential methodological pitfalls. Although evidence is far from definite, certain recurrent themes emerge (5).

The quantity and quality of fat intake has been associated with the increased risk of IBD, Other studies have also implicated a positive association between a fast-food type of diet and the development of CD in girls (50).European Investigation into Cancer and Nutrition (EPIC), a prospective cohort study of 203,193 patients across Europe, reported associations with fatty-acid intake with the development of UC(51).The consumption of refined sugars has also been associated with an increased risk for the development of IBD (52,53). Although the majority of published studies support the association of carbohydrate intake and increased risk of IBD, the studies of higher quality demonstrate no association (54). IBD patients have been observed, in population based studies, to have 21–40% increased risk of fractures compared with the general population Glucocorticoid use is strongly associated with osteoporosis risk; however, other factors may influence osteoporosis risk, such as inflammation and nutritional deficiency, in addition to calcium/vitamin D, was associated with an improvement in BMD (55).

Folate and vitamin B12 deficiency have been reported in IBD (5), Zinc deficiency is reported in up to 40% of CD patients, although overt clinical manifestations are uncommon (56). Which diet may alter the course of IBD? diet modification might remove a toxin or an antigenic stimulus. This may be the underlying mechanism for the benefits of elemental diets. Also, a change in diet may alter the bacterial flora increasing recognition that the intestinal flora may have an important role in the enthusiasm for probiotic therapy, role of prebiotics are a well-accepted mechanism of modulating the intestinal flora. Finally, dietary modification may alter intestinal fluid transport and gas production, minimizing symptoms, but has no direct effect on the disease itself (5). Eicosapentaenoic acid (EPA) derived from fish oil inhibits leukotriene activity. One study showed that fish oil dietary supplementation results in clinical improvement of active mild-to-moderate UC but is not associated with a significant reduction in mucosal leukotriene B4 production, compared with placebo therapy (57), Another randomized controlled trial showed that a fish oil-enriched oral supplement significantly decreased the

dose of prednisone required to control clinical symptoms (58)

6.2. Herbal therapy

Over 30% of western populations and up to 50% of IBD patients report the use of complementary and alternative medicines (59). Of complementary and alternative medicines, herbal therapies are the most commonly used. Several herbal therapies have demonstrated efficacy in clinical trials; however, the size and quality of studies to date do not yet endorse the routine use of herbal remedies in IBD (5). Curcumin is a natural compound from the plant *Curcuma longa* Linn and has been evaluated for use in both UC and CD. Curcumin exerts anti-inflammatory and antioxidant properties in animal models via suppression of the activation of NF-kB (5,60). Small randomized trials have been performed with other herbal remedies for UC. *Aloe vera* is a derivative of *Aloe barbadensis* Miller andcontains numerous biologically active compounds that have possible anti-inflammatory and antioxidant properties (61) but studies revealed no differences were detected for remission, endoscopic score or histologic score (62). Condensed tannins can help decrease the inflammation of UC patients who have been left vulnerable from a defect in GI mucin. The production of mucin by the intestinal globlet cells, the structural component of the colonic mucus layer, is found at lower levels in inflammatory bowel disease (63), condensed tannins can decrease intestinal permeability by mitigating GI inflammation caused by oxidative molecules, making them a good therapeutic option for UC (64). Condensed tannins can decrease the effect that food allergens have on GI inflammation in UC. Patients with UC display GI increased by the presence of higher levels of mucosal eosinophils and IgE in relation to certain foods. Data suggest an association between UC, tissue eosinophilia, and type-I allergy (64,65). Also, Green tea polyphenols have shown similar benefits in mice by attenuating colonic injury induced by experimental colitis (64,66).

6.3. Biologic TNF antagonists

Since the first license of biologic TNF antagonists for TNF Antagonists in Clinical Practice 181 clinical use in 1998, about 2 million patients worldwide have received these drugs for approved indications that include rheumatoid arthritis, inflammatory bowel disease, psoriatic arthritis, juvenile idiopathic arthritis, plaque psoriasis, ankylosing spondylitis and uveoretinitis associated with Adamantiades-Behcet's disease (approved indication in Japan). TNF antagonists have marked a new era in the treatment of these diseases which collectively affect 2–3% of the population. As a class, these drugs have shown remarkable efficacy and acceptable long-term safety profiles (67).

Infliximab (Remicade) is a chimeric monoclonal antibody directed against tumor TNF-alpha. It can be used for remission induction in moderate- to-severe UC patients who are either refractory to or intolerant of mesalazine (5-ASA) products and immunomodulators. Also it can be used for maintenance of remission in UC patients who have failed mesalamine and immunomodulators. The role of infliximab in UC patients who are dependant on steroids is unclear. Infliximab can be used in acute steroid- resistant UC patients who are reluctant to undergo surgery (68). Also, anti- TNF-alpha antibody agent, infliximab, has offered an important advance in the therapy for CD (69), the newest immunosuppressive agent with proven efficacy in CD treatment, the anti-alpha4 integrin IgG4 antibody natalizumab, has been efficacious in patients in whom anti-TNF therapy was ineffective (70).

It has been reported that visilizumab, a humanized IgG2 mAb against the CD3-epsilon chain of the T-cell receptor, may inhibit the inflammatory response in IBD by inducing apoptosis of activated T cells and may have other diverse immunomodulatory and chemotactic properties (45,71).

Currently in development are several new biological and pharmaceutical therapeutics that target T helper cell differentiation pathways, adhesion molecules, TNF-alpha, leukocyte activation and, most recently, the CXCR3 axis (29,96,97). It has been shown that anti-CD3 antibody can be used to treat UC by producing accumulation of IL10-expressing FoxP3- (Tr1) cells in the small intestine and IL10-expressing FoxP3+ T cells in the colonic LP (45,72,73).

Other molecular targets, including the IL2 receptor (targeted by daclizumab and basiliximab) in UC, the costimulatory molecule CD28 (targeted by the CD152 fusion protein abatacept) in both CD and UC, mitogen-activated protein kinases in CD, and the B cell marker CD20 (targeted by rituximab) in both CD and UC (45,74).

6.4. Stem cell-based therapy

Optimised use of immunosuppression and biological therapies can provide satisfactory disease control to a significant proportion of patients with inflammatory bowel disease (IBD). However, these treatments are never curative and may contribute substantially to long-term morbidity. In severely affected patients, the personal and societal costs of IBD and their treatments are very high, and lack of efficacy continues to result in progressive organ damage, a need for surgery, and chronic disability (75).

Various theories have been developed as to the etiopathogenesis of inflammatory bowel disease (IBD), but so far none of them has led to a therapy with long-term efficacy and free of side effects. The advancement of our knowledge of the biological basis of pathogenesis, combined with recent findings on the regenerative, trophic and immunoregulatory potential of stem cells, have triggered research that could lead to a significant evolution, or revolution, in the treatment of IBD (44). Only SC therapy can simultaneously repair the damaged intestinal tissue and correct immunological

abnormalities. SCs are essential for maintaining the integrity of almost all adult tissues. The precisely planned and controlled differentiation of adult SCs has great therapeutic potential for tissue regeneration and treatment of many degenerative diseases (45).

Mesenchymal and hematopoietic stem cells (MSCs and HSCs) are catalyzing the attention of IBD investigators, physicians and clinicians. After a number of case reports, and following initial steps within *in vitro* and *in vivo* models, cell-based approaches are now moving from the laboratory bench to the patient's bed. Stem cell transplantation may soon become a therapeutic option for IBD (44). Over the last decade, significant responses have been documented to HSCT in many treatment resistant inflammatory disorders. Relapse seems to be common following autologous HSCT, but early observations suggest restored sensitivity to previously ineffective therapy. The inflammatory response involves complex multidimensional and redundant cell and mediator interactions, in which very selective blockade may result ineffective; the strength of HSCT may relay on its ability to impact on a broad spectrum of targets and restore balance in an aberrant immune network (75). The epithelium is renewed every 3-5 days by SCs residing in the base of each crypt. The SCs first generate the rapidly cycling transit-amplifying (TA) cells, which divide every 12–16 hrs and generate about 300 cells per crypt per day. When the TA cells reach the crypt-villus junction, they rapidly differentiate into the four terminally differentiated (TD) cell types in the mucosa (76).

The entire intestinal epithelium is renewed every three days in mice (five days in humans); this length of time corresponds to the time needed for a differentiated cell to travel the distance between the base and the top of a villus, where about 1400 cells are exfoliated per day. These events establish a SC hierarchy in which SCs with maximum pluripotency and proliferating potential reside in the SC zone near the crypt base (77,78). There has been much progress due to a number of case reports; the hope is that the steps used in *in vitro* and *in vivo* models can be used to transfer the SC-based approach directly to human patients. Further, the immunosuppressive action of SCs would be very convenient in future clinical applications of these cells in IBD. SC- based studies couldultimately lead to the development of novel drugs that can cure IBD and can reduce the risk of IBD-associated complications. (45). ESCs are the subject of a significant area of research with promise for the future treatment of inflammatory disease. The unique pluripotent ability of ESCs has drawn many scientists to utilize ESCs to study the mechanisms by which congenital or acquired diseases occur (79). It has been reported that ESCs ameliorated piroxicam- induced colitis in IL10-/- mice ; this study has shown that *in vitro* pre-differentiated ESCs migrated and homed exclusively to the colon, small intestine, and the liver; engrafted for the long term; reduced inflammation and tissue damage; and restored immune balance (80).

The first case of CD regression after autologous HSC transplantation for hematopoietic malignancy was reported in 1993 (81)**.** Recently, complete normalization of the CD Activity Index (CDAI) was reported after HSC transplantation in two patients with severe, non-responsive, infliximab-resistant CD (45,82,83). A phase I clinical trial involving refractory CD patients showed clear evidence of recovery after autologous HSC transplantation (84). Successful pre-clinical studies using MSCs in models of autoimmunity, inflammation or tissue damage have paved the way for clinical trials. Ongoing studies are currently testing the viability of MSCs transplantation (either autologous or allogenic) in treating graftversus-host disease, multiple sclerosis, and Crohn's disease. These studies should shed light on the therapeutic potential of this cell-based therapy, as well as the benefits and risks for patients. Among the potential risks of transplanting MSCs is the ectopic differentiation of these cells, which can give rise to undesired cell types, as well as the possibility of genetic instability and tumour growth. Although these are important issues that must be thoroughly considered, the evidence thus far strongly supports the evaluation of cell-based therapies, and in particular MSC transplantation, in the treatment of refractory cases of Crohn's disease (75). A phase III clinical trial is currently enrolling patients to evaluate the efficacy of ProchymalTM, an allogeneic bone marrow derived MSC preparation, for the treatment of steroid refractory acute GVHD (85). Ways of recognizing easily accessible and noncontroversial new sources of pluripotent stem cells, such as term extraembryonal tissues (86).

Reports, studies and trials on HSC transplantation therapy for IBD encourage many scientists to think seriously about this route for long-term disease management. It has been suggested that allogeneic HSC transplantation could prevent and cure IBD and that long-lasting remission can be achieved following autologous HSC transplantation (45,87). A novel approach for delivering small bits of genetic material into the body to improve the treatment of inflammatory bowel diseases. Delivering short strands of RNA into cells has become a popular research area because of its potential therapeutic applications, but how to deliver them into targeted cells in a living organism has been an obstacle. researchers describe how they encapsulated short pieces of RNA into engineered particles called thioketal nanoparticles and orally delivered the genetic material directly to the inflamed intestines of animals. The thioketal nanoparticles protect the small interfering RNAs (siRNAs) from the harsh environment of the gastrointestinal tract and target them directly to the inflamed intestinal tissues. This localized approach is necessary because siRNAs can cause major side-effects if injected systemically. Tissue samples from the colons treated with siRNA delivered by these thioketal nanoparticles exhibited intact epitheliums, well-defined fingerlike "crypt" structures and lower levels of inflammation signs that the colon was protected against ulcerative colitis. "Polymer toxicity is something we'll have to investigate further, but during this study they

discovered that thioketal nanoparticles loaded with siRNA have a cell toxicity profile similar to nanoparticles formulated from the FDA-approved material poly(lactic-co-glycolic acid) (PLGA) (9).

In the future, thioketal nanoparticles may become a significant player in the treatment of numerous gastrointestinal diseases linked to intestinal inflammation, including gastrointestinal cancers, inflammatory bowel diseases and viral infections (8).

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