Therapeutic approaches in inflammatory bowel disease based on the immunopathogenesis

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Abstract

Our understanding of the etiology and pathogenesis of IBD has improved extensively over the past years. At the center of the pathogenesis seems to be an excessive pro-inflammatory immune reaction towards normal intestinal flora. The different factors involved in this concept will form the focus of this review. The initial phase of antigen processing and presentation can be influenced by either modulation of the intestinal flora via antibiotics or probiotics or by direct stimulation of macrophages through GM-CSF treatment. Antigen recognition and activation of T-cells can be down-regulated by immunosuppressives such as azathioprine, CsA or methotrexate thus building the basis for current treatment in IBD. The pro-inflammatory character of the immune reaction is defined by the predominance of certain T-cell subpopulations. By targeting cytokines the disbalance of these subpopulation should be reconstituted. Here we will focus first on preliminary clinical as well as experimental data for the pro-inflammatory mediators IL-12 and IL-18 as well as for the anti-inflammatory cytokine IL-10. Second, the clinical data for the TNFα antibody that has been proven to be efficacious in Crohn's disease and the associated risks will be discussed. Last, recent clinical and experimental data on targeting cell adhesion as well as intracellular signaling pathways will be presented. In summary, with regard to this review, treatments, which intervene as early as possible in the initiation of the pathological immune reaction and simultaneously have a favorable side-effect profile, must be the focus of future research.

Key words: inflammatory bowel disease, mucosa, therapy.

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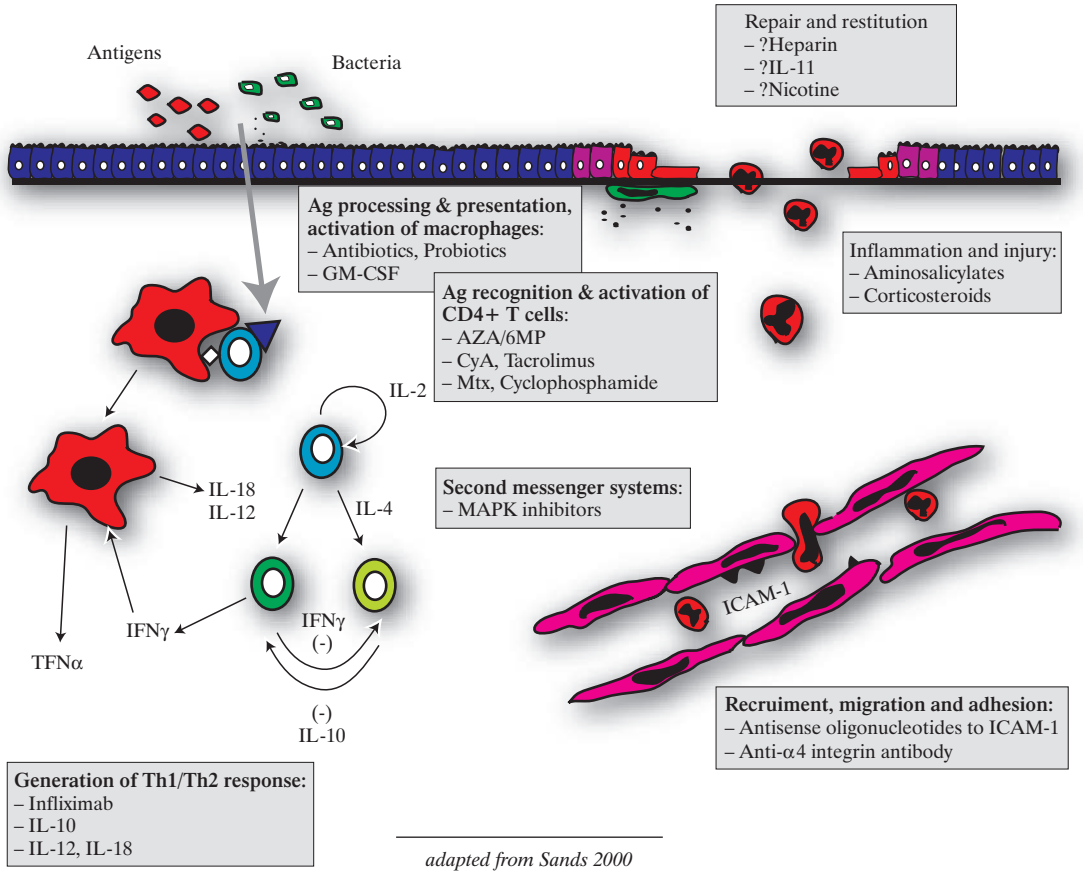
Introduction

The entire etiology and pathogenesis of inflammatory bowel diseases (IBD) is still unresolved, however, the understanding has improved extensively over the past years. In light of the diversity of substances and bacteria within the intestinal lumen, it is remarkable that the gut is not perpetually inflamed. The presence of low-level physiologic inflammation within the healthy intestinal mucosa represents a state of preparedness to deal with potentially harmful agents, but a more vigorous response would be not appropriate if directed toward the innocuous commensal flora of the gut. Inflammation is kept in check through an active process of immune tolerance. The dysregulation of the process of tolerance accompanied by an excessive pro-inflammatory immune reaction towards normal intestinal flora builds the current basis for the understanding of the pathogenesis of IBD, and furthermore, this concept creates the basis for distinct immunomodulatory approaches.

The present review will provide a systematical overview of the immunomodulatory approaches in IBD. As illustrated in *Fig. 1*, we will first focus on antigen processing, presentation and activation of macrophages and underline the therapeutic impact of probiotics and antibiotics. In addition, the potential role of granulocyte macrophage-colony stimulating factor (GM-CSF) therapy will be discussed. Activation of macrophages results in T-cell activation thus in a second step antigen recognition and activation of $CD4^+$ T-cells will build the focus. The unspecific suppression of the T-cell response by the classic immunosuppressive drugs azathioprine, cyclosporine A, methotrexate and cyclophosphamide and their efficacy in IBD

Figure 1. **Pathogenesis of inflammatory bowel disease and potential therapeutic targets. The different steps from antigens/bacteria crossing the epithelial barrier to phagocytosis and antigen presentation by antigen-presenting cells followed by T-cell activation and subsequent release of pro- and anti-inflammatory mediators and the migration of inflammatory cells via adhesion molecules is shown. The bold printed headings in the boxes indicate the different steps that will be discussed in this review**



therapy will be evaluated. In particular, the recently described mechanism of action for azathioprine will be summarized. The broad T-cell activation is followed by the generation of a T-helper cell type 1 and 2 response with distinct functions. Targeting of cytokines has been a promising approach within the last years. The clinical and experimental data of IL-10, IL-12 and IL-18 will be described. The anti-TNFα therapy with infliximab will serve as example to outline therapeutic impact as well as difficulties associated with anti-cytokine therapy, in particular infectious complications. Cytokines and other mediators activate second messenger systems which then perpetuate the inflammatory process. MAPK inhibitors targeting these signaling pathways are currently in phase II clinical trials for Crohn's disease. Last, inflammatory cells require the expression of adhesion molecules to allow for cell recruitment, migration, and adhesion, therefore blockade or neutralization of these adhesion molecules seems to be an attractive approach, clinical data are as yet not that conclusive.

The overview provided, does not claim to be complete, however, it may serve to facilitate the understanding of the complex variety of immunomodulatory approaches in IBD (*Fig. 1*).

Immunomodulatory approaches

Antigen processing and presentation

There is evidence that specific microbes in the commensal gut microflora are more important than sporadic infections in atopic disease prevention. Gastrointestinal flora is essential for the maintenance of mucosal tolerance, which is disrupted in patients with inflammatory bowel disease. Several processes seem to be involved in this mechanism: T-helper cell type immunity [1], induction of oral tolerance [2], and IgA production, an essential component of immune defense [3]. Inflammatory bowel disease is a relapsing inflammatory disorder of unknown cause in which genetic, immunological, and environmental factors may be involved [4]. It has also been postulated that ulcerative colitis is at least partly caused by infection because there are common histological features with infectious colitis and it is difficult to induce colonic inflammation in germ-free animals [4].

Probiotics

Probiotics are cultures of potentially beneficial bacteria of healthy gut microflora [5]. Several bacteria have been proven to

express beneficial effects in vivo. Kaliomäki and colleagues could demonstrate that *Lactobacillus GG* was effective in prevention of early atopic disease in children at high risk [6]. In addition, treatment with a non-pathogenic *E. coli* has an equivalent effect to mesalazine in maintaining remission of ulcerative colitis. Furthermore, Gionchetti and colleagues demonstrated that oral administration of a probiotic preparation is effective in preventing flar-ups of chronic pouchitis [7].

Antibiotics

Several studies indicate an efficacy of a combinational therapy of metronidazole plus ciprofloxacin with or without steroids in the treatment of recurrent or refractory pouchitis [8-10]. In addition, patients with Crohn's disease and involvement of the colon might benefit from this combined antibiotic therapy [11].

Granulocyte-macrophage colony stimulating factor

Clinical data

Granulocyte-macrophage colony stimulating factor (GM-CSF) is a growth factor that has been in clinical practice for years in particular in oncology in order to reconstitute the immune system after chemotherapy or bone marrow transplantation. It appears to be a provocative approach to introduce GM-CSF in the treatment of IBD where immunosuppressive strategies have been dominating for decades. In a pilot study performed at the University of Washington, St. Louis, USA, eleven patients with Crohn's disease were treated with GM-CSF. Nine out of 11 treated patients showed a significant decrease in the Crohn's disease activity index (CDAI) [12]. Six out of 11 patients went into remission while treatment with GM-CSF. In one patient a fistula closure was observed. After the GM-CSF treatment period, 2 patients presented with a relapse, however responded again after readministration of GM-CSF [12]. However, these are preliminary data, in order to evaluate efficacy and to be able to compare GM-CSF treatment with standard therapy the results of the planned double-blind multi center trial will provide conclusive data.

Potential way of mechanism

GM-CSF is targeting one of the first steps by supporting potentially weak cell populations in IBD patients, the macrophages and granulocytes [13]. Both are responsible for the unspecific immune defense against invading bacteria. Is this unspecific defense failing, the specific immune response is stimulated and followed by an exacerbation of inflammation. GM-CSF is expressing anti-inflammatory potency by supporting the unspecific immune system and therefore inhibition of the specific immune response. Preliminary data show promising results in patients with IBD, but the results of the phase II trial will have to proof this approach.

T-cell recognition and activation of $CD4^+$ T-cells

The early steps of T-cell activation in the mucosa can be down-regulated in by immunosuppressives such as azathioprine, cyclosporine A, methotrexate or cyclophosphamide.

Azathioprine

Clinical data

The thioprine analogues azathioprine and 6-mercaptopurine have been considered as treatments for Crohn's disease since the initial report of Brooke and colleagues describing healing of fistulas with azathioprine [14]. A decade later the efficacy of this drug was proved in a randomized controlled trial by Present and colleagues [15]. A meta-analysis of studies of azathioprine and 6-mercaptopurine in Crohn's disease has provided the best summary of the effects of these drugs. For active disease, treatment produced an odds ratio of response of 3.09 compared with placebo, with improved response when treatment was continued for at least 17 weeks [16]. Convincing evidence of benefit was also seen in maintenance of remission (odds ratio over placebo 2.27) [16]; glucocorticoid sparing [17, 18], and improvement in fistulas [16]. In addition, a recent study provided important information to the question whether or not one has to discontinue ongoing immunosuppressive therapy with azathioprine/6-mercaptopurine before elective surgery? The study by Aberra and colleagues demonstrated convincingly that azathioprine/6-mercaptopurine alone and the addition of azathioprine/6-mercaptopurine to corticosteroid therapy did not result in a significant increased risk of postoperative infectious complications [19]. Overall, approximately one half to two thirds of patients may respond to therapy. In contrast to glucocorticoids, mucosal healing is frequently seen with adequate dosing of thioprine agents [20].

Mechanisms of action

The molecular mechanism of azathioprine action however has been unresolved. Recent data suggest that azathioprine and its metabolites 6-mercaptopurine as well as 6-thioguanine induce apoptosis in primary intestinal lymphocytes [21]. Additional studies revealed a suppression of NF-κB and the MEK kinase phosphorylation after azathioprine treatment. The authors explain this by binding of the azathioprine-generated 6-Thio-GTP to GTPase Rac1 instead of GTP. This is resulting in an inhibition of the Rac/MEKK/NF-κB pathway and a following caspase-9-dependent apoptosis. The affinity of the 6-Thio-GTP Rac binding is 20-times lower than that of regular GTP which is explaining the delay of therapeutic efficacy well known for azathioprine. In summary, these data suggest that azathioprine is inducing a selective apoptosis of activated T-lymphocytes in the lamina propria and therefore expressing anti-inflammatory potency.

Cyclosporine A

Cyclosporine is being used increasingly in severe ulcerative colitis. Favorable results have been reported for intravenous use (4 mg/kg) and have been confirmed in a placebo-controlled trial [22]. From 50 to 80% of patients with severe attacks who fail to respond to intravenous glucocorticoids may avoid colectomy during the attack. Anecdotally, patients appear to respond well but tend to relapse soon after treatment is stopped. In contrast, there appears to be no significant role for cyclosporine in Crohn's disease. A series of uncontrolled and randomized controlled trials has shown high doses of cyclosporine to be efficacious in treating inflammatory disease and fistulas but an unacceptable high cost in adverse effects [23].

Methotrexate

Clinical data

A promising open-labeled study of methotrexate in IBD [24] led to a randomized controlled trial in Crohn's disease. Patients with chronic active Crohn's disease despite at least 3 months of prednisone 12.5 mg/day or more with at least one failed attempt to taper off treatment were enrolled [25]. Overall, 39.4% of patients assigned to methotrexate achieved remission off prednisone compared with 19.1% of placebo-treated patients [25]. Methotrexate is also beneficial in maintenance of remission. A follow-up study randomized patients who achieved remission on methotrexate 25 mg once weekly i.m. to receive either placebo injections or 15 mg methotrexate i.m. At week 40, 65% of patients treated with methotrexate were still in remission compared with 39% of placebo-treated patients [26]. Treatment was well tolerated.

Experimental data

Although methotrexate is a folate antagonist, the drug is often given with folic acid to prevent nausea and stomatitis. Therefore, other modes of action are likely responsible for its efficacy. The drugs possess a variety of immune-modulating and anti-inflammatory effects, including inhibition of IL-1, IL-2, IL-6 and induction of adenosine, which has direct immunosuppressive properties [27].

Methotrexate may be considered as an alternative to the thiopurine analogs, particularly among patients who do not tolerate these drugs. Some patients who fail to respond to 6-mercaptopurine may respond to methotrexate [28].

Cyclophosphamide

One major problem in the management of steroid refractory attacks of patients with IBD is the establishment of a rapidly acting immunosuppressive regimen. Previous studies investigating the efficacy of cyclophosphamide in Crohn's disease are either single case reports or low dose oral cyclophosphamide instead of intravenous pulse therapy was administered [29,30]. Intravenous cyclophosphamide pulse therapy is well known for its efficacy in vasculitis. Based on these experiences seven steroid-refractory patients, five with Crohn's disease, two with indeterminate colitis, received 4 to 6 cycles of monthly treatment of intravenous cyclophosphamide (750 mg) in a prospective, uncontrolled pilot study [31]. All patients improved after two intravenous pulses of cyclophosphamide and six of seven patients achieved complete remission. Tapering to low dose steroids was possible in all responders. Remission was maintained in all patients for 18 months but required a second course of cyclophosphamide in one patient. The drug was well tolerated, except for two episodes of candida esophagitis. These preliminary results are promising and merit evaluation in a controlled trial [31].

Generation of a Th1/Th2 response

With the targeted use of cytokines attempts have been made to influence the balance between the T-cell subpopulations. IL-10 as well as the blockade of TNFα, IL-12 and IL-18 should be mentioned in this context. The problems which occur when a specific immune mediator is blocked will be discussed in more detail with the available data from the infliximab therapy.

Interleukin-10

Clinical data

IL-10 has first been described in 1989 as anti-inflammatory cytokine and came soon into the focus of interest as potential new anti-inflammatory mediator [32]. Administration of rhIL-10 to healthy volunteers is well tolerated. In higher concentrations a non-clinical significant decrease in hemoglobin as well as platelet count has been described [33]. Because of the promising in vitro and experimental data as further described below, IL-10 was tested as potential therapeutic agent for inflammatory bowel disease, in particular Crohn's disease. However so far, multiple placebo-controlled studies have been performed without proving clinical efficacy. Different subgroups have been studied, for instance: mild to moderately active Crohn's disease (n=95) [34] and therapy refractory Crohn's disease (n=329) [35]. In both studies IL-10 was well tolerated and a tendency towards clinical improvement could be demonstrated but no remission was observed. An additional study by Colombel and colleagues showed that treatment for 12 weeks after intestinal resection was safe and well tolerated, but there was also no evidence of prevention of endoscopic recurrence of Crohn's disease observed [36].

Anti- and pro-inflammatory properties of Interleukin-10

IL-10 as a T-helper cell type 2 cytokine is directly inhibiting several pro-inflammatory mediators known to contribute to the inflammatory process in inflammatory bowel disease [37]. In the last years IL-10 has in addition been described as predominant cytokine of so-called regulatory T-cells [38]. However, there are data from the recent literature suggesting a distinct pro-inflammatory role for IL-10. In particular, when LPS administered to humans followed by an injection

of IL-10, IL-10 enhanced IFNγ release as well as the release of the IFNγ-dependent chemokines IFNγ-inducible protein-10 and the monokine induced by IFNγ [39]. In addition, when administering IL-10 to Crohn's disease patients the serum neopterin concentrations of IL-10-treated patients increased as well as the IFNγ release after post treatment in vitro stimulation [40].

IL-10 and experimental evidence in animal models

Still, experimental models strongly indicate that the local IL-10 concentration at the site of inflammation might represent the crucial factor. For instance, *Lactococcus lactis* secreting IL-10 administered orally to mice prevented dextran sulphate sodium-induced colitis [41]. In addition, the CD4 $CD45Rb^{low}$ cells, the population known to prevent colitis induction by CD4 $CD45Rb^{high}$ cells, is not mediating this protective effect when isolated from IL-10 knockout mice [42]. Therefore current strategies are focusing on technical approaches facilitating an increased IL-10 synthesis at the site of inflammation.

Interleukin-12

Clinical data

IL-12 represents the predominant cytokine responsible for the development of Th1 cells, the T-cell population known to contribute significantly to the inflammatory process in particular in Crohn's disease [43-45]. Currently an antibody against the IL-12 receptor is under investigation in a phase IIa clinical trial in ulcerative colitis patients and in addition, an anti-IL-12 antibody is under investigation in a phase II trial in patients with Crohn's disease.

Experimental data

Early experimental data suggest that the neutralization of IL-12 might results in an amelioration of disease. For instance, administration of monoclonal anti-IL-12 antibodies to mice suffering from trinitrobenzene sulfonic acid-induced colitis led to a striking improvement in both the clinical and histopathological aspects of the disease and frequently abrogated the established colitis completely [46]. In later studies it could be demonstrated that the amelioration of disease severity after anti-IL-12 treatment is associated with an increase in apoptosis at the site of inflammation [47]. An increase in apoptosis and the association with disease improvement has been demonstrated in several experimental models for a variety of mediators [48, 49] and there exists additional evidence in humans that this mechanism may in fact be of significance [50].

Interleukin-18

Clinical evidence

Several studies provide strong direct and indirect evidence for a significant role of IL-18 in intestinal inflammation. Consistent with an increased Th1 response in Crohn's disease, several groups could independently demonstrate a significant up-regulation of IL-18 expression in the inflamed lesions of the intestine, mostly localized to macrophages and epithelial cells [51,52]. This is of particular interest mainly because no up-regulation of IL-18 was observed in patients with active ulcerative colitis or healthy controls. While increased IL-18 expression is providing first evidence for a possible role in disease, in order to prove that IL-18 participates in the inflammatory process of intestinal inflammation it has to be demonstrated that blockade of IL-18 results in amelioration of disease severity.

Experimental data

In the recent literature, four studies using different animal models of colitis and different ways of IL-18 neutralization approach this question. Convincingly, all groups demonstrate a therapeutic efficacy for all anti-IL-18 strategies employed independently from the model investigated [53-56]. Results from these experimental models, in combination with the descriptive data from patients with Crohn's disease, suggest an important function of IL-18. IL-18 requires the cleavage of the interleukin-1β converting enzyme (ICE) in order to become activated [57]. Recent studies examined the acute and chronic model of DSS-induced colitis in ICE knockout mice [49]. In particular, during chronic administration of DSS, ICE knockout mice presented with an almost complete absence of colitis. Several ICE inhibitors are available for experimental use. For instance, Pralnacasan is currently in phase II trials in rheumatoid arthritis. No toxic side effects have been observed [58]. Compared to currently used strategies to suppress specific cytokines, which mostly implicate antibody therapy, the possibility of having an orally available drug whose half-life can be easily controlled is highly intriguing.

Tumor necrosis factor-α

Clinical studies

The TNFα antibody infliximab has proved to be effective in certain clinical situations in Crohn's disease. Targan and colleagues could first demonstrate in a multicenter, double blind, placebo-controlled trial over 12 weeks, the efficacy of infliximab in patients with moderate-to-severe, treatment-resistant Crohn's disease [59]. 48% of patients were in remission 4 weeks after single 5 mg/kg BW infusion compared to 4% in the placebo groups [59]. Interestingly, administration of 5 mg/kg BW was clearly superior to 10 or 20 mg/kg BW treatment. D'Haens and colleagues subsequently investigated the endoscopic scores after treatment with 5, 10 or 20 mg/kg BW infliximab [60]. The Crohn's disease endoscopic index of severity decreased significantly, 62%, 68% and 21% in the 5 mg/kg BW, 10 mg/kg BW and the placebo group, respectively [60]. The clinical improvement was accompanied by significant healing of the endoscopic lesions and a disappearance of the mucosal inflammatory infiltrates. In the recently published ACCENT I trial, Hanauer and colleagues evaluated the long-term efficacy of repeated infliximab administration [61]. Repeated infusions of either placebo, 5 mg/kg or 10 mg/kg BW, at 2, 4, 6 and then every 8 weeks were administered. 335 out of 580 patients showed a primary response. These results indicate that patients with Crohn's disease who respond to an initial dose of

Table 1. **International recommendations for infliximab therapy in Crohn's disease (CD)**

Target patient group	• Efficacy has been established in active CD, we recommend restriction to its use to refractory CD • Refractory = full and adequate dosed course of glucocorticoids in addition to immunomodulation has failed or other drugs are not tolerated or not appropriate and surgery is not indicated • First-Line use in non-fistulizing, uncomplicated CD is not recommended • Infliximab should be part of a long-term strategy
Administration	• Maximum of two infusions of infliximab within 4 weeks • Clinical benefits are of limited duration • Readministration is warranted in patients who relapse under adequate immunosuppressives

infliximab are more likely to be in clinical remission at week 30 and 54, to discontinue corticosteroids, and to maintain their response for a longer period of time, if infliximab treatment is maintained every 8 weeks [61]. Repeated infusions have been demonstrated to be associated with an increased risk of infusion reaction. A recent study by Baert and colleagues could confirm these findings and were able to provide evidence that the development of antibodies against infliximab is in addition associated with a reduced duration of response to treatment. In addition, the data from this study are indicating that concomitant immunosuppressive therapy reduces the magnitude of the immunogenic response [62].

However, it has become evident at the same time that such treatments are combined with corresponding risks: for instance, severe mycobacterial infections were observed in treated patients [63] and are discussed in more detail below.

Mystery of etanercept failure in the treatment of Crohn's disease

Etanercept is a construct of two identical extracellular chains of the soluble TNF-RII (also known as the p75 receptor) linked to the Fc domain of IgG1. It has been demonstrated to be highly effective in the treatment of rheumatoid arthritis [64]. Hence, it was first obvious to assume that etanercept administration would also prove to be effective in Crohn's disease patients. Sandborn and colleagues performed an eight-week placebo-controlled trial in 43 patients with moderate to severe active Crohn's disease. Etanercept was injected twice weekly in a concentration of 25 mg, the concentration which has been shown to be of therapeutic impact in patients with rheumatoid arthritis [64]. After 4 weeks 39% of etanercept-treated versus 45% of placebo-treated patients presented with a clinical response [65]. The authors concluded at this point that administration is safe but not effective and that higher doses may be required to attain a response in patients with active Crohn's disease. However, one might speculate whether or not the low dose or a different mechanism is responsible for the observed difference between etanercept and infliximab. Van Deventer suggests in the Editorial to this study that infliximab but not eternacept can induce apoptosis by binding to membrane-bound TNFα, thereby expressing its ant-inflammatory potency [66]. Since apoptosis induction seems to be crucial in order to achieve clinical improvement this might in fact represent the crucial difference in between the two therapeutic strategies.

Blockade of tumor necrosis factor-α and tuberculosis

Clinical studies

Infliximab is a humanized antibody against TNFα that is used in the treatment of Crohn's disease and rheumatoid arthritis. Approximately 147 000 patients throughout the world have received infliximab [63]. The half-life of infliximab is 10 days [67], and its biologic effect persists for up to 2 months. Keane and colleagues evaluated in a recent study the clinical pattern of disease and the interval between the initiation of infliximab therapy and the onset of disease in 70 reported cases of patients treated with infliximab [63]. Excess TNFα in association with TBC may cause weight loss and night sweats, yet in animal models it has a protective role in the host response to tuberculosis. There is no direct evidence of a protective role of TNFα in patients with TBC. The data by Keane and colleagues, although passive surveillance data are often insufficient to prove a causal relation between an adverse event and a drug, strongly suggest that the association observed is not coincidental. In particular, the pattern of TBC disease was unusual, the majority of patients had extrapulmonary TBC, and 24% had disseminated disease – forms of TBC that are associated with marked immunosuppression. In contrast, among cases of TBC that are not associated with HIV infection, approximately 18% are manifested as extrapulmonary disease, and disseminated disease accounts for less than 2% [68]. Although there is no complete information about the status of these patients with respect to TBC infection before they received infliximab, it is likely that most patients had a reactivation disease. Given the key role of TNFα in the innate immune response to TBC, patients receiving infliximab are probably also susceptible to disease after primary infection and exogenous reinfection with M. tuberculosis.

Consequences

As a consequence of the clinical and experimental data the European Agency for the Evaluation of Medicinal Products (EMEA) provided a public statement on infliximab with an update on safety concerns. The Committee for Proprietary Medicinal Products (CPMP) concluded that infliximab continues to have a positive benefit/risk balance in both Crohn's disease and rheumatoid arthritis, provided that specific changes to the product information restricting the indications in Crohn's disease and reinforcing the special precautions and special warnings have been made. Therefore, because of safety

concerns, the indications for treatment of Crohn's disease have been restricted as summarized in *Tab. 1* [67].

Cell recruitment, migration, and adhesion

Clinical data

In a multicenter, placebo-controlled trial conducted in 75 patients with steroid refractory Crohn's disease subcutaneous treatment with ISIS-2302, an antisense oligonucleotide directed against intercellular adhesion molecule-1 (ICAM-1), did not prove clinical efficacy based on primary endpoints [69]. Positive trends were observed in some of the secondary endpoints [69]. In agreement with these data, the second double-blind, placebo-controlled trial in active steroid-dependent Crohn's disease also failed to demonstrate efficacy [70].

Experimental data

However, the concept of blocking adhesion of inflammatory cells thereby preventing intestinal inflammation is intriguing and there are a variety of animal studies using different models and technical approaches for inhibition of adhesion molecules, supporting this target. While the efficacy of antisense strategies against ICAM-1 could be proven in the model HLA-B27/beta2 microglobuline transgenic rat model, this approach is questionable since no therapeutic benefit could be observed in human trials [71]. More detailed animal studies in the SAMP-1/Yit adoptive transfer model of Crohn's disease in mice could distinguish between an early acute phase and chronic phase of inflammation. These studies suggest that blocking of either ICAM-1 or VCAM-1, in this case by neutralizing antibodies, may have therapeutic benefit for the acute inflammatory component of Crohn's disease [72].

Future studies will have to prove whether for distinct indications this target might be of therapeutic significance.

Second messenger systems

Clinical data

A further possibility of intervention is the down-regulation of "second-messenger systems" which are significant for inflammatory immune reactions. Colonic biopsies from patients with Crohn's disease displayed enhanced JNK and p38 MAPK activation [73]. In a pilot study, 12 patients with severe Crohn's disease received the MAPK inhibitor (CNI-1493) for a total of 12 days. Treatment resulted in diminished JNK phosphorylation and tumor necrosis factor production as well as significant clinical benefit and rapid endoscopic ulcer healing. A clinical response was seen in 67% at 4 weeks and 58% at 8 weeks. Therefore, inhibition of MAPKs provides a novel therapeutic strategy [73]. The efficacy has to be confirmed in the phase II trials.

Experimental data

Phosphorylation of intracellular molecules by a protein kinase called mitogen-activated protein kinase (MAPK) with a molecular weight of 38 kDa plays a major role in the synthesis and activity of several proinflammatory cytokines, particularly IL-1β, TNFα, and the chemokines. Inhibitors of MAPK are non-specific anti-inflammatory agents. P38-MAPK is referred to as a stress kinase because it becomes activated (phosphorylated) in response to extracellular stresse such hyperthermia, hyperosmolarity, ultraviolet light, and radiation. Of major importance is the fact that this kinase, which contributes to the activity of IL-1β and TNFα, is itself activated by IL-1 and TNF. Therefore, phosphorylation of p38-MAPK can occur both via highly evolved, specific cytokine receptor signaling pathways and by the primitive and environmental stress responses common to all organisms. The mode of action of p38-MAPK inhibitors appears to be predominantly through suppression of pro-inflammatory cytokine production. In healthy human volunteers injected with endotoxin, the signs and symptoms of this systemic inflammatory response model were assessed following a single oral dose of a p38-MAPK inhibitor. No fever was observed, and peak circulating levels of TNFα, IL-6, and IL-8 were reduced by 90% [74].

Conclusions

This review provides an overview of the increasing variety of therapeutic approaches in IBD based on the pathogenesis. The advances in the last years in the understanding of mucosal immunology contributed significantly to the development of targeted therapies. Primary goals of therapy are to induce and maintain remission, thus ameliorating symptoms and improving the patient's quality of life. Summarizing all the different therapies discussed above, one has to conclude that, although specific treatments provide more insight in the understanding of disease, the general immunosuppressive drugs such as azathioprine appear to express the most efficacious balance between achieving the therapeutic goals and reducing side-effects. Distinct clinical situations may benefit from more specific therapies, for instance, infliximab treatment in therapy refractory fistulas. However, these more targeted drugs seem to be associated with a yet unknown spectrum of side-effects. Therefore, it is essential to consider the adverse consequences of therapy, particularly with regard to any durable consequences of short-term treatment and adverse effects of maintenance therapy.

Acknowledgment

Fig. 1 was reprinted from Gastroenterology 118 (2 Suppl 1), Sands BE, "Therapy of inflammatory bowel disease", 68-82, Copyright (2000), with permission from American Gastroenterological Association.

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