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TOPIC HIGHLIGHT

2016 Inflammatory Bowel Disease: Global view

Pharmacological- and non-pharmacological therapeutic approaches in inflammatory bowel disease in adults

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Abstract

Inflammatory bowel diseases (IBDs) are a group of chronic inflammatory conditions mainly of the colon and small intestine. Crohn's disease (CD) and ulcerative colitis (UC) are the most frequent types of IBD. IBD is a complex disease which arises as a result of the interaction of environmental, genetic and immunological factors. It is increasingly thought that alterations of immunological reactions of the patients to their own enterable bacteria (microfilm) may contribute to inflammation. It is characterized by mucosal and sub mucosal inflammation, perpetuated by infiltration of activated leukocytes. CD may affect the whole gastrointestinal tract while UC only attacks the large intestine. The therapeutic goal is to achieve a steroid-free long lasting remission in both entities. UC has the possibility to be cured by a total colectomy, while CD never can be cured by any operation. A lifelong intake of drugs is mostly necessary and essential. Medical treatment of IBD has to be individualized to each patient and usually starts with anti-inflammatory drugs. The choice what kind of drugs and what route administered (oral, rectal, intravenous) depends on factors including the type, the localization, and severity of the patient's disease. IBD may require immune-suppression to control symptoms such as prednisolone, thiopurines, calcineurin or sometimes folic acid inhibitors or biologics like TNF-α inhibitors or anti-integrin antibodies. For both types of disease (CD, UC) the same drugs are available but they differ in their preference in efficacy between CD and UC as 5-aminosalicylic acid for UC or budesonide for ileocecal CD. As therapeutic alternative the main mediators of the disease, namely the activated pro-inflammatory cytokine producing leukocytes can be selectively removed *via* two apheresis systems (Adacolumn and Cellsorba) in steroid-refractory or dependent cases. Extracorporeal photopheresis results in an increase of regulatory B cells, regulatory $CD8^+$ T cells and T-regs Type 1. Both types of apheresis were able to induce clinical remission and mucosal healing accompanied by tapering of steroids.

Key words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Extracorporeal treatment; Step up/top down; Psychological aspects in inflammatory bowel disease; Current medical treatment of inflammatory bowel disease; Future therapeutical strategies

Core tip: This review describes current and future therapeutic strategies in Crohn's disease and ulcerative colitis and outlines the most important publications in this field. It comprises surgical, medical and extracorporeal treatment options. All described treatment options are carefully reviewed regarding therapeutic effects and side effects. Extracorporeal treatment options are a potent measure to withdraw patients from steroids. Standard treatment as well as innovative therapeutic approaches, like autologous stem cell transplantation are addressed, which revealed promising results in therapy refractory patients.

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INTRODUCTION

Inflammatory bowel diseases (IBDs) are a group of inflammatory conditions of the colon and small intestine. Crohn's disease (CD) and ulcerative colitis (UC) are the leading entities in IBD. While UC primarily affects the colon, CD can be related to the whole gut. The disease was named after gastroenterologist Burrill Bernard Crohn who described a series of patients with inflammation of the terminal ileum of the small intestine, the area most commonly affected by the illness, in 1932, together with two other colleagues at Mount Sinai Hospital in New York[1]. We will never know who described UC for the 1st time although the disease was primarily referred to by name in 1859 by Sir Samuel Wilkes. Among his major discoveries, Wilks recognized UC, differentiating it from bacterial dysentery. His work was confirmed by Sir Arthur Hirst 1931[2]. IBD is a complex disease which arises as a result of the interaction of genetic dispositions, environment and alterations in the function of the immune system[3]. It is also increasingly thought that altered immunological reactions to patient's own enteral bacteria may contribute to inflammatory gut diseases[4]. IBD affected individuals have been found to have 30%-50% reduced biodiversity of commensalism bacteria such as a decrease in Firmicutes (namely Lachnospiraceae) and Bacteroidetes[5]. Further evidence of the role of gut flora in the cause of IBD-besides animal and *in vitro* studies - is that IBD affected individuals are more likely to have been prescribed antibiotics in the 2-5 year period before their diagnosis than unaffected individuals[6,7].

Table 1 Complications[11]

	Crohn's disease		Ulcerative colitis	
	Females	Males	Females	Males
Primary sclerosing cholangitis	0.3%	0.4%	3.2%	0.9%
Ankylosing spondylitis	0.7%	2.7%	1.0%	3.0%
Pyoderma gangrenosum	1.2%	1.3%	0.8%	1.5%
Erythema nodosum	1.9%	0.6%	0.8%	0.7%

The enteral bacteria can be altered by environmental factors, such as diets or oral medications (antibiotics or oral iron preparations)[8].

Genetics

There is strong evidence to suggest a genetic basis for IBD, including familial clustering and racial and ethnic differences in risk for IBD. Ten to 20% of affected individuals will have family history of IBD, with the highest risk among first-degree relatives. A strong association between HLA B27 and ankylosing spondylitis is known since the early 1970s which is also classified as extra intestinal complication in patients with IBD (Table 1)[9-11]. The genetic contribution is poorly understood and seems to arise from the small contribution of dozens of genes. In 2012, 163 IBD susceptibility loci were confirmed which means that 163 different alleles may increase the susceptibility to the disease. These 163 loci explain from 8.2% to a 13.6% of variance in CD and 4.1% to 7.5% in UC. The 163 loci were related to 300 known genes. The most well-known and frequent gene associated with CD is the NOD2/CARD15 gene[12-14].

Environmental factors

There is evidence that IBD is primarily a disease of the developed countries. The rise in certain regions (*i.e.*, India, China) parallelizes the industrialization of these countries. It seems likely that environmental factors may also influence the normal intestinal commensal flora and thus trigger an inappropriate mucosal immune response.

A number of environmental risk factors have been explored, including smoking, appendectomy, oral contraceptives, diet, breastfeeding, infections/vaccinations, antibiotics, and childhood hygiene. However, most of these identified risk factors have demonstrated inconsistent findings so that further investigations are warranted. Smoking and infections in childhood may trigger IBD especially CD[15-18].

Immune system

The intestinal immune system defends against pathogens and entry of excessive intestinal microbes;

Table 2 Sensitivity and specificity of atypical perinuclear anti-neutrophil cytoplasmic antibody/anti-Saccharomyces cerevisiae antibody combinations for ulcerative colitis and Crohn's disease in patients with inflammatory bowel disease[24]

Marker	UC		CD	
	Sensitivity	Specificity	Sensitivity	Specificity
pANCA+/ASCA-	51%	94%	-	-
pANCA-/ASCA+	-	-	55%	93%

pANCA: Atypical perinuclear anti-neutrophil cytoplasmic antibody; ASCA: Anti-Saccharomyces cerevisiae antibody; CD: Crohn's disease; UC: Ulcerative colitis.

simultaneously, a state of immune tolerance to resident intestinal microbes must be maintained. Perturbation of this balance is associated with intestinal inflammation in various mouse models and is thought to predispose humans to IBD. The immune system continuously monitors resident microbiota and utilizes constitutive antimicrobial mechanisms to maintain immune homeostasis. There is increasing evidence that intestinal microbes influence host immune development, immune responses, and susceptibility to human diseases such as IBD[19].

An imbalanced intestinal immune defense and intestinal immune tolerance is one of the risks for developing IBD. A numerous of inflammatory and anti-inflammatory cytokines as well as immune active cells, like T-and B-cells, T-regs are involved in this intact mechanism. Although UC and CD can usually be differentiated on the basis of clinical, radiographic, endoscopic, and histological findings, these conditions can be difficult to distinguish in about 10% to 15% of IBD patients[20]. Numerous studies have investigated the utility of 2 serologic markers in differentiating between UC and CD: Atypical perinuclear anti-neutrophil cytoplasmic antibody (pANCA) and anti-Saccharomyces cerevisiae antibody (ASCA). Unlike the pANCA or cytoplasmic ANCA found in vasculitis, the IBD-associated pANCA has an "atypical" perinuclear staining pattern. This atypical pANCA is detected in about 40% to 80% of UC patients but only in 5% to 25% of CD patients[21,22]. ASCA, on the other hand, is detected in 40% to 68% of CD patients[21,22] but only in about 6% to 12% of UC patients[20,23]. Table 2, based on a meta-analysis of 60 studies comprising 7860 IBD patients, summarizes the sensitivity and specificity of pANCA/ASCA combinations for UC and CD[22]. The diagnostic and therapeutic value of serological markers (more than pANCA/ASCA) was reviewed by Andrea T Kuna[24] in 2013. Due to the lack of sensitivity, serological markers were not advised for their use in the diagnosis of IBD but rather in differentiating CD from UC. The most important clinical utility of serological markers could be in stratifying patients according to risk for aggressive disease phenotype or postoperative complications. At the current time, there is no usefulness of serological markers in monitoring the treatment of IBD patients[24].

Calprotectin level in feces, produced from granulocytes, is a useful marker to measure disease activity and can predict disease recurrence. It is more precise than the common used markers like CRP and ESR[25].

Laboratory findings

Beside chemical parameters like increase of unspecific inflammatory markers as CRP (activity marker) and erythrocyte sedimentation rate, iron deficiency and anemia in different severities, there is also found a distinguished pattern of specific cytokines.

In IBD, increased amounts of soluble and membrane-bound TNF are produced by various immune and stromal cell populations, such as macrophages, dendritic cells (DCs), effector T cells, adipocytes and fibroblasts. TNF has been shown to exert various pro-inflammatory functions in the inflamed mucosa in IBD. In particular, TNF induces hypervascularization and angiogenesis, augments pro-inflammatory cytokine production by macrophages and T cells. TNF-specific antibodies may alleviate disease by simultaneously suppressing several pro-inflammatory pathways in patients with IBD. There are many proteins involved in gastrointestinal angiogenesis, including pro-inflammatory cytokines, vascular growth factors, and adhesion molecules[26].

A promising approach in getting more insight in the pathophysiology of IBD may be the development of new biomarkers. The techniques available for biomarkers development are genomics and proteomics. In the future it is expected that all these biomarkers will be implemented in an integrated molecular diagnostic and prognostic approach[27].

The heterogeneous nature of IBD implicates heterogeneous therapeutic strategies. Acute flares as well as the chronic status are treated with a variety of medications. Current therapies include the use of corticosteroids, anti-inflammatories, immune suppressive drugs, antibiotics and biologicals.

CD

The active disease is categorized into mild-, moderate- and severe localized ileocaecal disease, colonic disease, extensive small bowel disease and esophageal and gastroduodenal disease. It is graded by the Crohn's Disease Activity Index (CDAI) which ranges between 150 and 450 points and more for heavily active disease and acute flare, established in 1978[28]. This calculator is primary a research tool, but is increasingly used to define responses and remissions (< 150 pt)[29]. Besides CDAI, there is a variety of scoring systems which partly are very time consuming and require compliance of the patients (exception: Bradshaw index). Thus their use is rather limited to clinical trials (Tables 3 and 4)[30,31].

CD is a chronic disease (as well as UC) and the

Table 3 Crohn's disease activity index scoring system

Clinical or laboratory variable	Multiplication factor
Number of liquid or soft stools each day for seven days	× 2
Abdominal pain (graded from 0-3 on severity) each day for seven days	× 5
General wellbeing, subjectively assessed from 0 (well) to 4 (terrible) each day for seven days	× 7
Presence of complications[1]	× 20
Taking Lomotil or opiates for diarrhea	× 30
Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite)	× 10
Hematocrit of < 47% in men and < 42% in women	× 6
Percentage deviation from standard weight	× 1

[1]One point each is added for each set of complications.

Table 4 Harvey-Bradshaw index

General well-being	Very well	Below average	Poor	Very poor	Terrible
	0	1	2	3	4
Abdominal pain	None	Mild	Moderate	Severe	
	0	1	2	3	
# liquid stools/d	#	#	#	#	#
Abdominal mass	None	Dubious	Definite	Tender	
	0	1	2	3	

A score of less than 5 is generally considered to represent clinical remission.

therapeutic goal is to achieve sustained, steroid-free remission. Medical therapy is considered to be the treatment modality of choice for most patients. According to the severity of CD current therapy strategies include nutritional approaches, anti-inflammatory drugs, immunosuppression, chemotherapy and biologicals. The therapeutic decision is influenced by the extent of severity, the presence of septic complications and extra-intestinal manifestations. The surgical management is reserved for individuals who fail medical treatment or develop potentially life-threatening complications. The surgical management has changed substantially during the last 10 years. Surgical treatment of CD is solely symptomatic. In addition, medical therapy always precedes surgery and almost always continues afterwards. The indications for surgical treatment are failure of medical treatment and progressive complications (*e.g.*, fistula, abscess, obstruction)[32]. Hulten described 1988 disease recurrence of about 50% within 10 years post operation[33]. Bernell described a significantly higher relative risk for recurrence after first resection in CD in women and when the small bowel or the continuous ileocolonic was affected[34,35].

When operating on advanced CD, usually associated with abscess or fistula, a significantly higher complication rate (49%) was reported than after surgery for otherwise uncomplicated CD (12% complication rate)[36].

Postoperative medical treatment can hardly prevent recurrence of CD, therefore an aggressive medical intervention is recommended when objective signs of active disease are found in endoscopy or X ray[37]. There is still a need for preventive strategies[37]. A recent investigation postulated that TNF-α blockers are most effective in treatment and prevention of postoperative disease recurrence[38-41]. Currently there is no consent among the experts concerning the optimal time between TNF-α blocker treatment and surgery[42].

Recommended by the ECCO guidelines 2010[42] surgery should be considered as a primary treatment option in selected cases as localized ileocaecal disease with obstruction but without inflammation[19,43-45]. Patients with a maximum of 40 cm affected bowel, obstructions and clinical symptoms who failed to respond to steroids (CDAI > 220) will also require surgery during the course of disease[46-49]. In general the methods depend on the extent, the localization and severity of morphological complications (ECCO 2010)[42].

Medical treatment of active CD should always be balanced between the potential of the chosen drugs and their side effects. It has to take the state of the disease (*e.g.*, relapse, steroid-refractoriness, quality of life) the severity and extra-intestinal manifestations (Table 2) into account.

A nutritional approach inclusive probiotics was shown to be less effective in these patients even with a mild pattern of disease[50,51]. Neither Omega-3 fatty acid diet, nor probiotics nor nutritional supplementation were convincing in modulating the disease positively[52-54], although a recent study showed a disease controlling effect from whey and soy proteins especially when the patients were treated with TNF-α antibodies and azathioprine[55]. A randomized controlled trial conducted by Takagi has shown the effectiveness of half elemental diet in maintenance therapy in selected patients[56].

However a benefit in reducing pain can be attributed to n-3 unsaturated fatty acids[57]. Thus nutritional therapy as supplementation to medical treatment may be helpful in induction and maintenance of remission or controlling symptoms especially in children[50,56].

It is important to be aware that a considerable portion of patients suffer only from a mild type of CD and need no medical therapy as pointed out in a systematic review of clinical trials by Su *et al*[58]. In general the initial therapy should consist of steroids as immune-modulating agent and mesalazine as antiphlogistic medication. Mesalazine is an amino-derivative of salicylic acid [5-amino-salicylic-acid (5-ASA)]. Beside antiphlogistic activity, which is due to a suppressive effect on pro-inflammatory cytokines (IL1, TNF-α) by inhibition of interleukin-1 stimulated Re1A phosphorylation[59] and by inhibiting macrophage chemotaxis, 5-ASA is also thought to be an antioxidant and traps free radicals which are found to be present in CD[60]. The therapeutic effect of 5-ASA in mild to moderate CD is discussed controversially in the

literature. Tromm found no difference in the efficacy to induce remission in moderate CD of 5-ASA compared to budesonide. Remission rate for budesonide was 69% *vs* 62% for 5-ASA[61]. These data have to compare with a previous meta-analysis which showed 5-ASA no more effective than placebo[62]. The minimal efficient dose is 4 g/d. High dose (6 g/d) for active CD is currently under investigation[42]. One medication of choice to induce remission in mild to moderate CD is budesonide, a synthetic glucocorticoid with limited systemic bioavailability due to extensive first-pass hepatic metabolism. It is effective for induction of remission and causes almost no side effects due to its low bioavailability. It seems to be superior to 5-ASA in moderate disease[63]. Both are also applied as topical treatment in mild types of disease. The systemic administration of corticosteroids/prednisolone is of course much more effective in induction of clinical remission[64,65], but commonly causes more side effects than budesonide[63,64,66]. Two recent studies support this observation even in high dose 5-ASA therapy[67]. The risk to develop Cushing syndrome due to systemic steroid therapy is known at a daily dose of 7.5 mg prednisolone. Therefore, disease control under dose reduction or discontinuation of steroids should be achieved, especially as steroids commonly fail to maintain clinical remission in the majority of patients with active disease[68]. Thus the early onset of the monoclonal antibody anti TNF-α may help to achieve clinical remission even in steroid free or steroid naive conditions[69]. TNF-α is a cell signaling protein which is involved in systemic inflammation.

It is produced mainly by activated macrophages[70]. Antibodies to tumor necrosis factor (anti TNF-α) are highly efficient immune-suppressive drugs. TNF-α inhibitors offer a targeted strategy that contrasts with the nonspecific immune-suppressive agents traditionally used to treat most inflammatory diseases. Anti TNF-α suppresses immune responses in CD by binding to membrane-bound and soluble TNF (mTNF)[71]. Several trials prove the efficacy of Anti TNF-α in achieving clinical remission[72-74]. A recent study, conducted by a Danish group, confirmed the results from previous investigations. Among 492 patients with CD and 267 patients with UC, 74%/13%/14% and 65%/12%/24% were responders, partial responders and non-responders to anti-TNF therapy, respectively[75]. Atreya R developed a method to predict the response rate of this therapy, in brief: Topical antibody administration in 25 patients with CD led to detection of intestinal membrane-bound TNF (mTNF) immune cells during confocal laser endomicroscopy. Patients with high numbers of mTNF cells showed significantly higher short-term response rates (92%) at week 12 upon subsequent anti-TNF therapy as compared to patients with low amounts of mTNF cells (15%). These data indicate that molecular imaging with fluorescent antibodies has the potential to predict therapeutic responses to biological treatment and can be used for personalized medicine in CD and other autoimmune or inflammatory disorders[76]. Due to their mode of action TNF-α-blockers may cause expected and paradoxical side effects, like "*de novo* psoriasis", described by Joyau *et al*[77]. In general patients treated with TNF-α-blockers are at increased risk to develop life threatening opportunistic infections[78-80]. There are also reports of developing rare white blood cell cancer (hepatosplenic T-cell lymphoma) in combination with thiopurines[81].

The disease modulating relevance of antibiotics is restricted to their use in septic complications. The efficacy of metronidazole and ciprofloxacin alone is similar to mesalazine (5-ASA), but inferior to steroids[82,83]. A meta-analysis of 6 trials showed no convincing positive influence on the disease[82-84].

Thiopurines are purine antimetabolites which are widely used in the treatment of autoimmune disorders (*e.g.*, CD, rheumatoid arthritis), and organ transplant recipients[85]. The leading substances are azothioprine (AZA) and mercaptopurine (6-MP). Azathioprine acts as a prodrug for mercaptopurine, inhibiting an enzyme required for the synthesis of DNA. Thus, it most strongly affects proliferating cells, such as the T- and B-cells of the immune system[86,87]. The main adverse effects of thiopurines are bone marrow suppression, hepatotoxicity and pancreatitis and may result in a withdrawal of this drug[86,88] AZA was shown to be efficient in inducing and maintaining remission after tapering of steroids. It is used in the management of moderately to severely or chronically active CD and in corticosteroid-dependent patients[89,90]. Azathioprine treatment is associated with an increased risk of lymphoma, but it is unclear if this is due to the drug or to a predisposition related to CD[91,92]. A recent study provides evidence that In CD, treatment with azathioprine shortly after diagnosis was no more likely to result in corticosteroid-free remission than standard care or placebo[93,94]. No such investigations were performed for 6-MP but as 6-MP is a metabolite of AZA it is considered equivalent. Thioguanine, a 3rd related drug may be an alternative in patients, who are refractory or intolerant to AZA and 6-MP (occurs in up to 15% of long term exposed patients)[92,95]. Patients who relapse under thiopurine therapy should have their dose optimized. Also a switch to TNF-α blockers or MTX should be considered. A long term combination of AZA/6-MP and TNF-α blockers should be avoided in young male patients due to the risk of hepatosplenic T-cell lymphoma[43].

Methotrexate (MTX) is a folic acid inhibitor and thus interferes with cell-growth[96]. It is used predominantly for immunosuppression in autoimmune diseases and as chemotherapy. In CD it has - to date - remained in treatment algorithms as a salvage therapy for patients who have failed to respond or became intolerant to azathioprine[97]. However, its use is not so common in the clinical routine for CD but MTX seems to be sufficient in maintenance therapy. Recently a user's

guide was published which favors the safe and efficient use of MTX in several clinical conditions of CD and UC. The authors Swaminath *et al*[97] provided an ease to use algorithm. MTX is largely used as a second line therapy after AZA failure.

Cyclosporin A (CSA), tacrolimus and mycophenolat-mofetil currently play only a minor role CD as evidence for induction and maintenance of remission is lacking[42].

Current treatment algorithm for CD is displayed in the Guidelines for the Management of CD by Ye *et al*[98] and IBD Study Group of the Korean Association for the Study of the Intestinal Diseases.

UC

UC is graded into 4 disease activities (mild, moderate, sever and remission) and divided into 3 different distribution patterns (proctitis, left-sided, pancolitis).

The severity of the disease is classified by a clinical activity index (CAI)-Rachmilewitz index or Mayo score including stool frequency, rectal bleeding, the endoscopic activity of the colon, and a physician rating of disease activity. Each of these items is given a number from 0 to 3, with 3 being the highest rating for disease activity[99]. A drop to less than 2 points is defined as a clinical relevant remission[99].

The therapeutic goal in UC is to induce steroid-free clinical long-term remission or to increase intervals of acute flare[100]. A cancer surveillance in UC patients is strongly recommended as these individuals have an elevated risk to develop a colon cancer within 10 years. Advanced endoscopic and imaging techniques are warranted to optimize the diagnosis as cancer in UC is a clear indication for surgery[100,101].

Therapeutic management of active UC

The choice of the appropriate medication depends on severity, the previous course (relapsed or persistent active disease) and the localization of the disease. The topical use of 5-ASA (mesalazine) is still the treatment of choice for proctitis or left sided mild to moderate disease or topical steroids although topical steroids (budesonide) were found to be less effective than topical mesalazine[102]. The systemic use of aminosalicyl-derivatives is additionally recommended in more extensive or severe cases[100]. Mesalazine is comparable with newer substances (balsalazide) in its efficacy to induce remission and is better tolerated[103-105]. As previously described two studies have shown that patients treated with oral mesalazine 4 g/d and 1 g/d mesalazine enema experienced a shorter time to resolution of rectal bleeding than those treated with oral therapy alone (P = 0.0025)[106,107]. A smaller study of patients with frequently relapsing disease found that dose escalation of oral mesalazine combined with the addition of topical 5-ASA significantly reduced the number of disease recurrences and courses of steroids (P < 0.0001)[108]. Patients on high dose sulfasalazine (prodrug of mesalazine) require folic supplementation (1 mg/d) to maintain normal cell division. This is of specific importance for patients who receive additionally MTX[96]. Steroids have been a mainstay of UC therapy for many years, based on a thoroughly established efficacy profile for the induction of remission[109,110]. For severe UC, and in patients refractory to 5-ASA, the need for systemic steroids is a general knowledge[100,111-113]. The combination of oral steroids and 5-ASA in escalating doses in case of treatment failure with 5-ASA alone is strongly recommended[109]. Steroids should be tapered as soon as possible as they usually fail to maintain remission and have a problematic safety profile[42,100,114,115]. A therapeutic challenge in UC (similar to CD) is the steroid-dependent or steroid-refractory patient. In this setting additional immune-modulating therapy with thiopurines is recommended[100,111,116-118]. In contrast to CD calcineurin-inhibitors as CSA or tacrolimus play a disease modulating role in UC. Due to the binding-mechanism to calcineurin, transcriptions for pro-inflammatory cytokines IL-2 and TNF-α are inhibited. Side effects as renal impairment or hypomagnesaemia are common in about 50% of the patients, but the main concerns are opportunistic infections. Arts found an incidence of 3.5% (3/86) to die of such infections[119].

Thiopurines [azathioprine (AZA)/mercaptopurine (6-MP)] have limited utility in the acute setting of UC, but are recommended in the maintenance therapy of UC and have a steroid sparing effect[100,111]. CSA in combination with thiopurines are effective to induce remission and avoid colectomy in patients at risk[120]. The treatment with TNF-α blockers (infliximab, adalimumab) is discussed controversial in the literature. Two large well conducted placebo-controlled trials described the induction and maintenance of steroid-free remission in about 26%[121] and 13%[122] at 12 mo of enrolled patients. These data could not be confirmed by a real life observation[111,123]. Only a short term clinical response was observed. A recently presented study suggested a benefit from a combination therapy of TNF-α blockers and thiopurines in early stage of active UC. A steroid free response was seen in 40% of patients at week 16[124,125]. The major drawbacks of TNF-α blockers are already discussed in CD section. Although luminal bacteria are thought to play a major role in pathogenesis of IBD the use of *antibiotics* in UC is also restricted to the therapy of complications due to infections[114].

Surgical interventions

The cumulative risk for colectomy in relation to time of diagnosis has been reported as 13.1% in 5 years[126]. A recent population based UC study observed the global risk for colectomy by 8.7% over 10 years[100]. About 27% of patients with severe UC require colectomy[114,126]. Early surgery, within 3 mo of diagnosis is increasingly performed in patient >

65 years but should not be favored as older patients (> 50 years) have a reduced risk to need colectomy during their course of disease[127-129]. They are more likely to respond to pharmacologicals than younger people[130]. Emergency colectomy or ileostomy due to toxic megacolon, bleeding or perforation is associated with a complication risk or death of 5%[131].

Elective surgery is indicated in chronic therapy refractory cases or when signs of dysplasia are found. Here the common surgery therapy is total proctocolectomy with ileal-pouch anal anastomosis (IPAA)[100,111]. This surgical intervention may have a high curative potential in UC but high rates (up to 20%) of postoperative complications are still emerging problems[100,132-134].

High dose steroids should be weaned before surgery because they are a risk factor for complications[111]. Neither thiopurines nor calcineurin inhibitors seem to increase the risk of postoperative complications while biologicals may be associated with a higher complication rate[111].

Maintenance therapy

Generally maintenance therapy is recommended for all patients. The goal is to keep a steroid free clinical and endoscopic remission. The medication of choice again is 5-ASA (masalazine) topically and/or orally depending on the site and severity of inflammation as long term treatment since this may reduce the risk of colon cancer[100,111]. In steroid dependent patients thiopurines (AZA) are steroid sparing medications. MTX is generally not recommended for UC as the beneficial effect is not proven, although in selected patients (intolerant to the other immunosuppressants) MTX was seen to be effective[100,111,114,135,136]. A large retrospective cohort study of 91 patients reported that one-third of patients were successfully weaned off steroids with MTX therapy. MTX may be considered in the long-term management of patients with UC on steroids[137]. TNF-α blockers are recommended in patients who were treated with this medication initially and achieved remission[121].

A detailed figure of current treatment algorithm for UC is published by Meier and Sturm[100] in *World J Gastroenterology* 2011.

NON-PHARMOCOLOGICAL OPTIONS IN IBD

Granulocyte monocyte apheresis

A special challenge in this setting is the steroid refractory and steroid dependent type of IBD as well as azathioprine-intolerant or - resistant patients. These patients are at high risk to undergo surgery. Thus a Japanese group developed a non-pharmacological therapeutic alternative to conventional therapy. It is an apheresis system, which removes activated monocytes/macrophages (one of the main disease mediators), from the patient's blood circulation (GMA = granulocyte monocyte apheresis). Currently two systems are available, the Adacolumn® system which is approved by the Japanese Ministry of Health and Welfare and is CE marked in Japan and Europe by the TUV since 1999[138,139], and the Cellsorba® System. It is also approved by the Japanese Ministry of Health and Welfare since 1989[140]. Both systems are defined to selectively remove activated WBC, especially granulocytes, monocytes and macrophages (source of TNF-α) from the patients' blood circulation without compromising patients' peripheral blood counts[141]. With the Cellsorba® System additionally activated platelets are removed. The action is based on columns (cellulose-acetate beads in Adasystem and polyester fibers, respectively in Cellsorba) in both systems. The severity of the disease (CD, UC) and mucosal damage correlate with the excess of mucosal granulocyte infiltration[142-144]. Both systems have a great immune-modulating effect. The exact mode of action is not yet sufficiently understood, but certainly, a modulation of the immune system takes place[145]. As a result, less pro-inflammatory cytokines are released. Furthermore, the production of interleukin-1-receptor-antagonist with its anti-inflammatory property is increased and the apoptosis of granulocytes boosted. The decreased LECAM-1-expression on leucocytes impedes the leukotaxis to the inflamed tissue and CD10-negative immature granulocytes appear in the peripheral blood[141,146,147]. Another effect to be mentioned is the removal of the peripheral DCs[148] and the leachate of regulatory T-cells (T-regs)[30,149,150]. Pro-inflammatory cytokines decrease while anti-inflammatory cytokines increase[151]. The induction of clinical and morphological remission of IBD can be explained by this mechanism of action.

Most clinical trials are conducted using the Adacolumn® system for GMA in both, UC and CD whereby UC is the leading entity. The best responders seem to be steroid naive patients followed by steroid dependent patients or steroid refractory patients with a short history of disease[152,153]. A recent study tried to define predictive factors to identify patients with UC who are likely to respond to GMA[154]. In this trial 43 patients with active UC were enrolled. Best responders to GMA were those treated immediately (< 49.5 d) after relapse. Also an initial low WBC count (< 10 G/L) was predictive for a good response. They conclude that in these selected patients GMA is efficient as mono-therapy inducing remission (defined by CAI). Sacco investigated 118 steroid dependent or refractory patients (UC *n* = 83, CD *n* = 35). GMA was efficient in inducing and maintaining remission during a follow up of 12 mo, irrespective the entity or the steroid status (UC: CAI = 6; CD: CDAI < 150)[155].

Also a combination therapy (thiopurines and GMA) promises a rapid induced high remission rate in patients with active early diagnosed CD[156]. In this study 22 steroid and biological naïve patients were

treated with thiopurines and GMA. The rate of mucosal healing was 50% after 1 year.

A meta-analysis by Yoshino *et al*[157] 2014 revealed that intensive granulocyte and monocyte adsorption apheresis is a safe and effective treatment with higher rates of clinical remission and response for UC compared with corticosteroids.

GMA treatment is known to have an excellent safety profile. Almost no side effects occur[153,158]. Up to now no treatment had to be discontinued because of adverse events[158]. There is a strong recommendation to introduce GMA at an early state of disease before patients develop extensive mucosal damage and become dependent or refractory to drugs (similar to a TNF-α therapy)[159].

There is still a controversy regarding the optimal treatment schedule. Five sessions in 5 wk *vs* 10 sessions in 8 wk was shown to be similar efficient[160]. Therefore Vecchi recommended in his review the perpetuation of the traditional treatment schedule of 5 sessions in 5 wk (1/wk) as it is seems not to be inferior to the more intensive version, more convenient to the patients and more cost effective[158].

Still more randomized sham controlled double blind trials with a long term surveillance to evaluate the long term outcome, treatment schedules and cost effectiveness (equipment, pharmacological therapy, avoidance of surgical intervention) are required, although several reports attest comparable costs to conventional therapy as the good safety profile should comprise higher costs[161].

According to current data the American Society for Apheresis (ASFA) assigned 2013 GMA in UC to category Ⅱ/Ⅲ with a recommendation level of Grade 1B/2B (strong to weak recommendation, moderate quality evidence) and the CD to category Ⅲ, recommendation 1B (strong, but randomized controlled trials with important limitations)[162].

ASFA defines its categories as below

Cat Ⅱ: Disorders for which apheresis is accepted as second-line therapy; either as a stand alone treatment or in conjunction with other modes of treatment[162].

Cat Ⅲ: Optimum role of apheresis therapy is not established. Decision making should be individualized.

Centrifugal lymphocytapheresis

In the 80ties Bicks *et al*[163] described successful treatment of active CD by centrifugal lymphocytapheresis (CLA) and lymphoplasmapheresis[164]. Nowadays these treatment options are replaced by selective adsorption systems (Adacolumn and Cellsorba).

Extracorporealphotopheresis

Two uncontrolled case series have been published suggesting that extracorporealphotopheresis (ECP) can promote remission for a proportion of patients in the category of steroid and/or immunosuppressant intolerant or refractory CD[165,166].

The domain of ECP is T-cell mediated diseases, like T-cell lymphoma or acute or chronic graft *vs* host disease (GvHD). The mode of action is, like for all extracorporeal treatments, elusive. The mechanism of this treatment is likely due to the induction of anticlonotypic immunity directed against pathogenic clones of T lymphocytes. Treatment induces apoptotic death of pathogenic T-cells, and it is postulated that activation of antigen-presenting cells has important effects in this process[167]. More recently, it has been suggested that ECP may induce Ag-specific immune-modulation *via* regulatory T-cells, which could explain its efficacy in immune-mediated diseases and lack of toxicities. The frequency of T-regs was significantly increased in the blood of ECP-treated patients[168]. *In vitro* these cells exerted suppressive activity and showed features of T-regs. The best-characterized subtypes of T-regs are those expressing CD4 and CD25[149,150]. It is also suggested that ECP induces IL-10 producing regulatory B cells, regulatory $CD8^+$ T cells and IL-10 producing T-regs Type 1[167,169,170]. IL-10, also known as cytokine-synthesis inhibitory factor, is a potent anti-inflammatory cytokine[171]. Abreu *et al*[165] observed in 28 patients with moderate-to-severely active CD (mean baseline CDAI 324) who were refractory to or intolerant of immunosuppressants and/or anti-TNF agents that ECP was well tolerated and induced clinical response (50%) and remission (25%) in patients with CD[165]. Reinisch confirmed these results in 31 CD patients, ECP permitted reduction or discontinuation in steroid dependent or - refractory patients[166].

As sham controlled trials are still missing ASFA recommends assigned ECP in CD to category Ⅲ with a recommendation level 2[162].

Currently ECP plays a minor role in the treatment of CD (weak recommendation due to low quality of evidence).

FUTURE ASPECTS IN THE MANAGEMENT OF IBD

CD and UC are complex disorders which need complex therapeutic strategies and a continuous development of treatment managements, new drugs and alternative measures. Despite the high prevalence of mental health co-morbidities in IBD, psychological illness remains largely under treated, with studies showing that 60% of IBD patients experiencing mental health problems do not receive adequate help. Therapeutic approaches must always be chosen in agreement with the patients to increase the patients' compliance[172].

Due to the complexity of the disease a collaboration of medical specialists is necessary to cover all complications and to improve treatment success[173].

A new scoring system for CD, the Lémann score,

is developed to allow a better identification of patients with severe epithelial damage and those with rapid progression of damage. This system monitors the cumulative damage. It measures cumulative structural bowel progression at a specific time point, based on medical and disease history, by endoscopy and other imaging methods[173,174]. This instrument can also be used to assess the effect of various medical therapies on the progression of bowel damage.

The big hope is set on advances in biologicals with different mechanism of action (*i.e.*, anti TNF vaccination, TNF gene silencing and TNF neutralizing nanobodies) so that in case of treatment failure other biologicals or even combinations are available[175]. As mentioned earlier (in the CD section), laboratory assays to identify TNF-α blocker responders and non- responders would be very helpful in treatment optimization[176]. Further drugs targeting other pro-inflammatory cytokines are in evaluation[175]. Another therapeutic approach is given by vedolizumab, a biological which targets cell adhesion molecules (CAMs), a monoclonal antibody that inhibits mucosal leukocyte infiltration[177]. In contrast to natalizumab (α_4-integrin-inhibitor, Tysabri®) vedolizumab ($\alpha_4\beta_7$ integrin-inhibitor, Entyvio®) modulates the adaptive immune system without systemic side effects[178].

Enteric bacteria, viruses or fungi may induce IBD, thus fecal microbiota transplantation or fecal bacteriotherapy (from a healthy individual) is also a therapeutic option in IBD[179]. Autologous hematopoietic stem cell transplantation (aHSCT) has been used as a treatment for severe, active and therapy-refractory autoimmune diseases for more than 13 years[180,181]. In 2012 the EBMT published guidelines for the selection of patients with autoimmune diseases[182]. Among disorders like multiple sclerosis, systemic lupus erythematosus, myasthenia gravis also severe active CD refractory to conventional therapy has been proposed as a potential indication for aHSCT[180]. Meanwhile several studies were conducted, which revealed promising results. The majority of so treated patients showed clinical and endoscopic remission within 6 mo, and remained free of medical therapy for at least one year. In relapsing patients a disease control with low dose steroids and immune-suppressive therapy was achieved[183,184].

Another point in therapeutic care in IBD is a harmonization between different countries and centers. Two retrospective cross sectional studies from 2009 describe country and care-setting specific therapeutic variations. The impact on outcome is not yet clear[185,186].

Step up and top down strategy

The current clinical practice and recommended treatment for CD is the "step-up" approach which refers to a sequential treatment strategy that often begins with a less potent and less toxic treatment strategy, such as topical steroids or aminosalicylates with escalation to the highly effective but potentially more toxic treatment strategies[42,187]. The top down strategy refers to the use highly effective but potentially more toxic treatment strategies early in the course of a chronic illness to prevent disease progression and achieve remission[188].

The introduction of biologic therapy, and particularly the use of anti TNF-α therapy, has provided a powerful tool in the treatment and management of IBD. The prevention of structural damage by achievement of "mucosal healing", however, is associated with the more "aggressive" treatment and an earlier use of immune-suppressants and biologicals[189]. A recent study from D'Haens[190] has provided evidence suggesting that reversing the treatment paradigm from a "step-up" to a "top-down" approach may positively alter the natural course of this illness by mucosal healing[188,190]. Several further studies show, that the onset of biologicals in the early course of disease results in better mucosal healing, earlier tapering of steroids, less complications and less need for surgery. Also the incidence of relapse is reduced[191]. On the other hand one must be aware, that the early use of biologicals, especially TNF-α blockers, may result in an increased risk of complications, particularly server life threatening infections. LIN described that about 30% of patients might be over-treated by the top down strategy[188]. Thus it is certainly a crucial point to identify high-risk patients who clearly would benefit from the early use of a more aggressive treatment so that the expected benefit outweighs increased risk for probably severe side effects.

In UC conventional treatment strategies (step-up) are still favored as aminosalycylate derivatives (5-ASA) seem to prevent cancer, the most important complication in UC. Therefore, at present, there is little rationale for a top-down approach to managing UC. Although, Sandborn[192] did not exclude that a top down approach for a selected subgroup of patients with UC (patients at high risk to develop complicated or therapy refractory disease) may profit from the administration of biologicals or other immune-suppressants at early stage of the disease.

CONCLUSION

Up to now there is no cure for IBD. This review describes shortly current and advanced therapeutic options for patients with IBD. They all have limitations due to side effects, refractoriness or unresponsiveness of the patients due to known and unknown causes. There are still a number of individuals in whom the current strategies are insufficient in controlling symptoms. Further studies are in progress to develop new therapeutic options or to improve those already in use in order to achieve durable remission in the majority of patients. The future strategy aims at early hard therapy of patients at risk for severe course

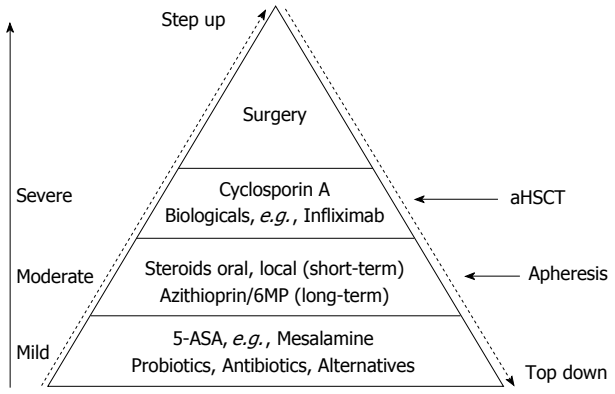

Figure 1 Therapeutic approaches in inflammatory bowel disease. 5-ASA: 5-amino-salicylate-acid; aHSCT: Autologous stem cell transplantation.

of IBD- even with combined immunosuppression, if necessary. After achieving complete remission-endoscopic and biologic (comprising normal stool calprotectin) - tapering of immunosuppression might be possible. A lot of new pharmacological and immune modifying therapies are currently studied in phase Ⅱ and Ⅲ studies in IBD and are the hope for therapy refractory patients. Even for patients with short bowel syndrome a new therapeutic approach with a GLP-2 analog - teduglutide - is on the market and fighting for coverage by insurance companies[193]. Patients with malnutrition and weight loss of more than 5% within 3 mo should be treated with appropriate medication but also with oral nutritional therapy to avoid further complications like opportunistic infections, long hospitalization and higher mortality. Serum levels of Vit B12, folic acid, Vit D and zinc should be monitored carefully[194]. Figure 1 comprises current therapeutic options in IBD including alternative strategies, like extracorporeal techniques and autologous stem cell transplantation.

At present, clinical manifestations are the most useful way to make therapeutic decisions.

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