In recent years, landmark progress has been made in the treatment of patients with inflammatory bowel disease (IBD). The anti-tumour necrosis factor (TNF-α) antibody era has shown that mucosal healing is a key therapeutic goal, and may predict the sustainability of remission or resection-free survival in IBD patients. Further, the anti-TNF-α antibody infliximab (IFX) became an alternative medication for refractory UC in 2010 under the Japan national health reimbursement scheme. However, to induce remission in steroid-refractory UC, currently several therapeutic options are available in Japan including cytapheresis, tacrolimus, and anti-TNF-α biologics, but as yet, there are no guidelines for the sequence and timing of these therapeutic interventions. Additionally, there are many patients who do not respond, or are intolerant, to anti-TNF-α biologics. Recently, new strategies like faecal microbiota transplantation and anti-leucocyte infiltration have been tested for induction and maintenance of remission in IBD patients. This paper provides an overview of the latest treatment options and future perspectives in IBD therapy.

Key words: ulcerative colitis, Crohn's disease, cytapheresis, tacrolimus, anti-TNF-α biologics

Introduction

Inflammatory bowel diseases (IBD) are chronic immune disorders of the gastrointestinal tract with a relapsing and remitting course. The two most common phenotypes of IBD are ulcerative colitis (UC) and Crohn's disease (CD), which affect millions of individuals throughout the world with morbidities that seriously impair performance and quality of life. However, whereas UC typically manifests as contiguous inflammation involving only the superficial mucosal and submucosal layers in the large intestine (rectum and colon), CD may affect any part of the digestive tract from the mouth to the perianal region, and up to 65% of CD patients may have small intestinal involvement. Additionally, CD is typified by trans-mural ulcerations resulting in fissures that may perforate the intestinal wall and affect other organs including the bladder and the uterus.

Clinically, IBD symptoms may include or result from chronic diarrhoea, malabsorption, weight loss, rectal bleeding, abdominal discomfort, stenoses, abscesses, and fistulae formation. Over the long term, many patients require surgery to resect the affected gut segment when the disease reaches a fulminant phase. Further, while mild cases of IBD may respond to aminosalicylates for induction and maintenance of remission, for management of severe IBD the current situation is far from satisfactory, especially in cases with steroid dependent or steroid refractory IBD, or for patients who are intolerant to corticosteroids.

A large number of different therapeutic options have been tried in the last decade, mainly with anti-tumour necrosis factor (TNF-α) antibodies known as biologics, targeting cytokines involved in the exacerbation and the perpetuation of intestinal inflammation. Although anti-TNF-α agents have significantly increased the treatment options for patients with refractory IBD, such treatment comes with the risk of serious adverse side effects.
including lymphoma and opportunistic infections as additional morbidity factors.

However, both CD and UC are known to be associated with dysregulated T helper (Th) type 1 and Th2 responses, respectively. More recent studies have demonstrated that tissue damage results from mucosal inflammation mainly mediated by pro-inflammatory Th1 and Th17 lymphocyte subpopulations and their respective pro-inflammatory effector cytokines. In the gut of CD patients, activated Th1 and Th17 cells produce interferon (IFN)-γ and interleukin (IL)-17, respectively, which stimulate macrophages and induce production of other inflammatory cytokines including IL-1β and TNF-α that subsequently promote matrix metalloproteinase (MMP) production by stroma cells leading to mucosal damage. Thus, it is now widely believed that TNF-α has a strategic role in IBD pathophysiology, in the crosstalk of different inflammatory pathways involved in the gut mucosal inflammation. Biologics have been approved for the treatment of moderate to severe IBD. In addition, anti-TNF biologics have shown efficacy in various extraintestinal manifestations of IBD including primary sclerosing cholangitis, ankylosing spondylitis, iritis/uveitis, pyoderma gangrenosum, erythema nodosum and immune-mediated diseases like asthma, psoriasis, and rheumatoid arthritis.

Although the precise aetiology of IBD remains incompletely understood, several factors are believed to have a pathologic role in IBD initiation and progression, including host genotype, dysregulated immune function, and the composition of microbial communities resident in the gastrointestinal tract. This paper provides an overview on the latest treatment options which have become available since the start of the 21st century, as well as future perspectives.

### Cytapheresis

Activated granulocytes and monocytes represent a major source of pro-inflammatory cytokines in the intestinal mucosa and have a pivotal role in inducing and maintaining intestinal inflammation. When circulating leucocytes are activated, they release large amounts of pro-inflammatory cytokines including IL-1, IL-6, IL-8, and TNF-α in addition to free radicals. Lately, apheresis (which means ‘to take away’) to remove leucocytes from peripheral blood via extracorporeal circulation has been applied as a feasible, safe and effective therapy for IBD. To date, two methods are commercially available and used in clinical practice for therapeutic leucocytapheresis in patients with IBD or rheumatological conditions. These include the Adacolumn for selective granulocyte and monocyte apheresis (GMA) developed by JIMRO (Takasaki, Japan). The Adacolumn is filled with cellulose acetate beads which serve as the column adsorptive carriers for granulocytes, monocytes, and platelets, but spares lymphocytes. In the second type, leukocytapheresis (LCAP) is done with the Cellsorba filter column (Asahi Medical, Tokyo, Japan). The LCAP filter column is made of non-woven polyester fiber filter and is able to remove about 90–100% of granulocytes and monocytes, 30–60% of lymphocytes and a certain fraction of platelets (30% in the first 30 minutes of a treatment session) from peripheral blood. With either the Adacolumn, or Cellsorba, therapeutic removal of leucocytes from the peripheral blood per se may not be the only mechanism responsible for the observed clinical efficacy of apheresis. In patients with UC, GMA significantly decreases the mucosal levels of neutrophils and the mucosal tissue levels of the inflammatory cytokines IL-1β, IL-6, IL-8 and TNF-α (Table-1). LCAP has been reported to decrease the circulating concentrations of cytokines, including TNF-α, IL-1β, IL-2, IL-8, and interferon (IFN)-γ.

In recent years, there have been many reports from Japan as well as from Europe and the United States on the efficacy of GMA in IBD. The clinical data show that GMA in patients

<table>
<thead>
<tr>
<th>Table-1</th>
<th>Major actions of Adacolumn GMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>①</td>
<td>Selective depletion of elevated and activated myeloid lineage leucocytes</td>
</tr>
<tr>
<td>②</td>
<td>Changes in cytokine profile: Suppression of pro-inflammatory cytokine production (TNF-α, IL-1β, IL-6, IL-8); elevated blood level of the anti-inflammatory cytokines, IL-10, and IL-1 receptor antagonist; release of soluble TNF-α receptor</td>
</tr>
<tr>
<td>③</td>
<td>Changes in cell population profiles: An increase in peripheral regulatory T-cells; enhanced regulatory B-cell function</td>
</tr>
<tr>
<td>④</td>
<td>Reduction in activated platelets</td>
</tr>
<tr>
<td>⑤</td>
<td>Neutrophil apoptosis induced by reactive oxygen species</td>
</tr>
<tr>
<td>⑥</td>
<td>Modifications of cell adhesion molecules on post-column granulocytes</td>
</tr>
<tr>
<td>⑦</td>
<td>Mobilization of immature and naive neutrophils from the bone marrow</td>
</tr>
</tbody>
</table>

589
with steroid-dependent or steroid-refractory UC was associated with significant clinical efficacy and corticosteroid tapering. Similarly, in steroid-naive patients, GMA spared patients from exposure to corticosteroids. Further, Sakuraba et al. reported that intensive GMA (two sessions per week) was superior to weekly GMA both in efficacy rate and time to clinical remission. Efficacy rates for LCAP are reported to be 70-80\%\(^{30}\).

**A complicated case of UC treated by cytapheresis**

A 50-year-old woman was diagnosed to have moderate to severe pancolitis based on endoscopic and histological investigations nine years ago. She had been treated with mesalazine (3 g/day) and oral corticosteroids at another medical institution. According to the patient's medical records, the total dose of corticosteroid she had received was 14 g. This time, the patient presented with severe arthralgia, flare with pain and swellings in both lower legs (Figure-1). She could not walk unaided because of severe pain, but did not have abdominal pain, diarrhoea or bloody stool. She was admitted to our hospital to be treated for her extraintestinal manifestations of UC. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were 6.2 mg/dl (normal level < 0.3 mg/dl), and 76 mm/hr (< 25 mm/hr), respectively. The patient refused continuing steroid therapy as she had steroid-dependent IBD. GMA with the Adacolumn was considered as a non-pharmacological and safe therapeutic option. The patient received two GMA sessions per week for two consecutive weeks as an inpatient. Her severe arthralgia and bilateral pain in the lower legs ceased soon after the first GMA session, and bilateral erythema and swelling in the lower legs remitted after two weeks of GMA treatment (Figure-2). Likewise, CRP and ESR decreased to normal levels after the course of GMA therapy. Oral steroids were discontinued one month after the introduction of GMA therapy. The clinical course of this patient is shown in Figure-3.

![Figure 1](image1.jpg)

**Figure 1** Before treatment with adsorptive granulocyte and monocyte apheresis (GMA)
The patient presented with severe arthralgia, flare with bilateral pain and swellings in the lower legs (A). Marked erythema was seen in the patient’s right lower leg (B).

![Figure 2](image2.jpg)

**Figure 2** Two weeks after introduction of GMA
Bilateral erythema and swellings in the lower legs remitted (A) (B).
Tacrolimus is a macroclide antibiotic, which has immune-modulatory actions similar to cyclosporine A (CsA). Tacrolimus inhibits T cell activation by forming an intracellular complex with immunophilins. This complex binds to, and inhibits, calcineurin, a key enzyme regulating transcription factors. The majority of clinical experience comes from solid organ transplantation where tacrolimus is effective against rejection. In contrast to methotrexate (MTX) and mycophenolate mofetil (MMF), tacrolimus does not inhibit cell division via inhibition of DNA synthesis, but rather stops proliferation of T lymphocytes by inhibiting the production of proliferative cytokines including IL-2. Tacrolimus' mechanism of action is similar to CsA. As for UC, the introduction of CsA for severe, steroid-refractory UC has provided an effective alternative therapeutic option for patients who otherwise had to opt for surgical interventions.

Ogata, et al. have reported the results of a placebo-controlled double blind study, which showed that oral tacrolimus improved disease activity by 68.4% in the high trough group compared with 10.0% in the placebo group (p < 0.001). In the high trough group, 20.0% of patients achieved clinical remission and 78.9% of these had mucosal healing (complete remission). In an open label extension, 55.2% of all patients had an improved disease activity score at week 10. Tacrolimus also allowed reduced steroid use. The most common adverse event was mild finger tremor. The results of this study demonstrated dose-dependent efficacy and safety for oral tacrolimus remission induction therapy in patients with refractory UC. In July 2009, oral tacrolimus became an alternative medication for refractory UC under the national health insurance reimbursement scheme in Japan.

TNF-α inhibitors

TNF-α is a pro-inflammatory cytokine with a major role in the immunopathogenesis of CD and UC. Abundantly expressed in the gastrointestinal tract of patients with IBD, TNF is believed to contribute to intestinal mucosal inflammation through several mechanisms including disruption of the epithelial barrier, induction of apoptosis of the villous epithelial cells, and induction of chemokine secretion by intestinal epithelial cells. Accordingly, there has been keen interest in developing novel strategies aimed at reducing the activity of TNF in patients with IBD. The effects of TNF-α are known to be mediated by TNF receptors I (TNF-RI) and II (TNF-RII). Activation of
TNF-RI, which is expressed on a wide range of immune and nonimmune cells results in NF-κB activation, cytotoxicity, and induction of pro-inflammatory cytokines and chemokines as well as antiapoptotic peptides.

Based on the aforementioned knowledge, currently, TNF-α is a major target molecule for biologic therapy in CD and UC. Numerous randomized clinical trials and meta-analyses have been published on the efficacy of monoclonal antibodies like infliximab (IFX) or adalimumab (ADA) to TNF-α for both induction and maintenance of remission in both CD and UC. TNF-α inhibitors showed better efficacy in inducing steroid-free clinical remission when combined with an immunomodulator as compared with anti-TNF monotherapy in CD or UC. Additionally, a few studies used IFX or ADA in active fistulizing CD in adult patients. However, although 60 to 80 percent of patients showed a good initial response to anti-TNF therapy for CD and UC, only one third of patients remained in clinical remission without steroids at one year.

Currently, IFX (Remicade; Mitsubishi Tanabe Pharma Corp, Tokyo, Japan) is a chimeric immunoglobulin G (IgG) human (75%)/murine (25%) mAb administered by intravenous infusion, is indicated for induction and maintenance of remission in adult and paediatric CD and for induction and maintenance of remission in patients with UC. IFX is also approved for other chronic inflammatory conditions like rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. The murine component of this antibody has been implicated in the development of immunogenicity to the drug and the formation of human antichimeric antibodies, also known as antibodies to infliximab (ATI). Another anti-TNF agent, ADA (Humira, AbbVie Inc., North Chicago, IL, USA) is a self-injected, fully humanized recombinant mAb. This agent is indicated for induction and maintenance of remission in adult CD and UC, as well as for rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis. IFX and ADA have high binding affinity for both soluble and transmembrane forms of TNF, blocking interaction of TNF with p55 and p75 cell surface TNF receptors and neutralizing its biologic activity. However, it is appropriate to mention here that very severe and life threatening adverse events like lymphoma and opportunistic infections including tuberculosis are reported for anti-TNF biologics.

A case of CD treated with a TNF-α inhibitor

A 30-year-old man was diagnosed to have CD based on endoscopic and barium enema X-ray findings 20 years ago. This patient had been treated with elemental diet for three years. His CD had responded well to nutritional therapy without any drug for the past 20 years. He presented with mild abdominal discomfort, diarrhoea, oral ulcers, which had appeared 6 months earlier. At first, he had treated himself with alimentotherapy, but his CD had not responded to self-administered alimentotherapy. He was admitted to our hospital to receive treatment for his active CD. Serum CRP and blood ESR were 7.9 mg/dl and 51 mm/hr, respectively. Colonoscopic findings included cobble stone appearance and longitudinal ulcers running from the ascending colon to the transverse sigmoid colon (Figure-4). In our hospital, he was found to have active CD. The patient opted for IFX, 5 mg/kg as an inpatient. His abdominal pain, diarrhoea and oral

![Figure-4](Endoscopic findings in a CD case prior to IFX infusion)

Endoscopic findings showed cobble stone appearance and longitudinal ulcers from the ascending to the sigmoid colon.

A. Caecum, B. Ascending colon, C. Sigmoid colon.
ulcers improved soon after treatment with IFX. CRP and ESR decreased to normal levels after a course of IFX therapy. Endoscopic findings at two months after the initiation of IFX therapy are shown in Figure-5. The figure shows mucosal healing in the large intestine. Following clinical remission, IFX was administrated to this patient at 8 week intervals as maintenance therapy.

**Faecal bacteriotherapy**

The precise aetiology of IBD is not fully known at present, but interactions between bacterial and host cells seem to be involved in its immunopathogenesis. The distal gastrointestinal tract contains a large and diverse array of microorganisms of which bacteria are the most dominant living organisms. A community of at least $10^{14}$ bacteria is dominated by strict anaerobes and includes thousands of different species, many of which have not yet been cultured. These bacteria can interact with the intestinal mucosa and dietary contents of the intestine to influence intestinal permeability, and immunogenicity. This so-called intestinal microbiota is important for the absorption, distribution, metabolism, and excretion of nutrients and can trigger autoimmune as well.

However, in patients with IBD, the intestinal microbiota of patients appears to have a reduced diversity: 25% fewer microbial genes are present compared with healthy individuals. Patients with IBD have reduced numbers of the phyla Firmicutes and Bacteroidetes and increased numbers of Actinobacteria and Proteobacteria. Fusobacterium varium was reported to be present in the colonic mucosa of a large proportion (84%) of UC patients. Butyric acid, a product of Fusobacterium varium culture supernatants was also shown to cause UC-like lesions in mice. On the basis of these observations, Ohkusa, et al. used an antibiotic combination regimen to which Fusobacterium varium was susceptible (amoxicillin, tetracycline, and metronidazole (ATM)) and showed in a double-blind placebo-controlled multicenter trial that this regimen had significant efficacy in patients with active UC. Likewise, a 2-week antibiotic combination therapy to faecal microbiota was effective in patients with active UC. On the other hand, butyric acid is a major energy source for colonocytes and is known to be effective for intestinal healing as well. Recently, the anti-inflammatory efficacy of butyrate has been demonstrated in *in-vitro*, and in *in-vivo* settings, and has provided a rationale for assessing its therapeutic potential. Therefore, it appears that butyrate has diverse actions in intestinal inflammation.

**Faecal microbiota transplantation**

Faecal microbiota transplantation (FMT) is a new and underexplored strategy to alter the composition of the gastrointestinal microbiota using human donor faeces as a therapeutic intervention. The first application of FMT in mainstream medicine was described in 1958 for the treatment of pseudomembranous colitis, presumably due to *Clostridium difficile* infection (CDI) by Eiseman, et al. The most frequently reported use of FMT has been in the treatment of patients with CDI. In a recent randomized controlled trial, duodenal infusion of healthy donor faecal samples resolved recurrent CDI in 82% of patients as defined by the absence of *Clostridium difficile*-associated diarrhoea, without relapse within 10 weeks. In contrast,
vancomycin resolved CDI in only 31% of the patients (66).

The rationale for an FMT strategy to treat patients with UC was reported in 1988 (67). The first patient with idiopathic UC was treated with FMT, resulting in durable clinical and histological remission. Then, a case report published in 2003 documented a complete clinical, colonoscopic, and histological reversal of UC in 6 patients with severe, relapsing–remitting UC (68). More recent trials have confirmed these earlier findings. A meta-analysis on FMT for patients with IBD, conducted by Anderson, et al. (69) found that 63% of patients with UC entered remission, 76% were able to stop taking medications for IBD, and 76% experienced a reduction in gastrointestinal symptoms. These findings indicate that remission of UC is possible with (multiple) FMTs. Though effective in only a subgroup of patients, FMT is expected to be a new and fundamental treatment with few side effects for patients with refractory IBD. We are currently conducting a registered trial testing combination therapy with both antibiotics and FMT in patients with UC.

Prospective

Much progress has been made in understanding the aetiology of IBD, and therefore, in introducing better treatment strategies to tame these debilitating immune disorders. New and potentially promising medications are under development. A major new approach to biological therapy in IBD has been the development of inhibitors to stop uncontrolled leucocyte infiltration into the gut mucosa where they can exacerbate IBD by releasing inflammatory cytokines and tissue damaging proteases and reactive oxygen species. Biological agents (biosimilars) that target the integrins include the monoclonal antibodies natalizumab and ELND–004, which bind to α4, vedolizumb (MLN–02) and etrolizumab (RG–7413), which block α4β7, as well as rHuMab β7, which binds to β7. In addition AJM–300 is a small molecule inhibitor of the α4 integrin subunit and ASP–2002 is an integrin antagonist with as yet unknown clinical efficacy. A recent meta-analysis of all controlled trials of natalizumab concluded that the therapy was superior to placebo in inducing remission in patients with CD (70). Despite the success of natalizumab, it remains a second–line therapy for use in patients with treatment–refractory CD due to the increased risk of infection with the opportunistic human polyoma JC virus, which results in progressive multifocal leukoencephalopathy (PML), a risk that may be common to other adhesion molecule inhibitors. Despite life–threatening risks associated with all biologics, development of novel biologics and biosimilars in recent years represents landmark progress in IBD therapy. The anti–TNF era has shown that mucosal healing is a key goal for therapy that predicts sustained clinical remission and resection–free survival in IBD patients. As many patients do not respond to anti–TNF therapy, new targets have been recently tested for induction of mucosal healing as well as for induction and maintenance of remission in IBD patients. It is expected that new treatment options with relatively few side effects will have a marked impact on future treatment of IBD.

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