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Novel Drug Therapies for the Treatment of Crohn's Disease

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Abstract

Introduction: There was a recent revolution in the medical therapy of inflammatory bowel disease with the advent of anti-TNF inhibitors. Treatment paradigms have evolved from a slow step-up approach to accelerated care with early introduction of immunosuppression and biologicals.

Areas covered: The authors review clinical efficacy and safety of new anti-TNFs and new action biologicals including anti-cytokine therapies and cell adhesion inhibitors in both Crohn's disease. Some of the agents were already approved by both FDA and EMA.

Expert opinion: Anti-TNF agents will remain the mainstay of biological therapy in in Crohn's disease in the near future. However; the proportion of anti-TNF refractory patient population is growing. In addition; there is a change in the cost structure of inflammatory dowel disease and anti-TNFs became responsible for a great proportion of the direct costs; therefore new biololegicals including biosimilar anti-TNFS are urgently awaited. The addition of these drugy into the armamentarium will provide additional treatment option for both bionaive and refractory patients and hopefully it will lead to improved outcomes and on the long run to a lesser economic burden of the disease.

Keywords: Treatment; Crohn's disease; Ulcerative colitis; Anti-TNFS; Biosimilars; Cell adhesion inhibitors; Anti-integrins

Introduction

Crohn's disease (CD) is a chronic remitting and relapsing inflammatory disease of the gut; and a member of the inflammatory bowel disease (IBD) beside ulcerative colitis (UC) and unclassified IBD (IBD-U). The diagnosis of IBD was rare several decades ago. However; the current incidence rates was observed as high as app. 20/100 000 per person years in North America and some countries in Europe [1,2]. Estimated prevalence of IBD is about 2.5-3 million people in Europe [2] and 1-1.5 million people in North America [3]. Up to third-half of these patients suffer CD and app. 10-15% of IBD is staring in the childhood; which will lead to an explosion of the patient numbers in adult care in the next decades. As the disease has a peak incidence in the 2nd-4th decade of the life; it affects the most productive age-group of the society. Previously observed significant east-west gradient of the incidence of CD in Europe became less prominent; and increasing incidence was reported from the middle and far east [4].

CD is a progressive inflammatory disorder. During the disease course a high proportion of patients develop complications; such as bowel strictures; perianal fistulas and abscesses [5]. Prevention of these complications became a major therapeutic goal that could not be achieved in the majority of the patients with conventional medical therapy.

Sulphasalazine and mesalazine were the first drugs in the therapy of CD these were regarded to be ineffective in the meta-analysis of the Cochrane group in 2010 [6]. In addition; although corticosteroids are able to induce clinical remission; but they are associated with lots of adverse events; and they are unable to induce mucosal healing and long term use is discouraged [7]. Azathioprine (AZA) is a potent drug to maintain clinical remission in CD; but it has a slow onset of action and long term benefit on the natural history of the disease became conflictive [8,9].

In the 1990s the availability of the first anti-TNF has led to a revolution of the medical care and changed the everyday treatment strategy in moderate to severe patients. Infliximab (IFX); the first in class molecule; is a mouse-human chimeric type 1 immunoglobulin G against tumour necrosis factor alpha (TNFα) was introduced to the market at start of the century. It was proved to be as an efficacious induction and maintenance therapy of the inflammatory and penetrating type of CD [10,11]. Several years later; the human anti-TNF agent adalimumab (ADA) was also observed to be efficacious in CD. However; loss of response is relatively common and accumulating in patients with long-term exposure and the anti-TNF resistance patient population is growing; which prompts the need for drug monitoring; a further challenge in the optimization of drug use. A proportion of these events are attributed to the development of antidrug antibodies leading to undetectable drug trough levels [12].

Novel anti-cytokine agents and other biologically produced molecules with a different mechanism of action are in development. This review aims to summarize the currently available evidence on the new biological agents against CD.

New Anti-TNF Agents

Drugs of the near future

In addition to IFX and ADA; some other anti-TNF antibodies have been developed against TNF-alpha. Certolizumab pegol (CZP) was also proved to be efficacious in CD in an early short term trial [13]. Later on; the PRECISE 1 and 2 trials showed that CZP induce and maintain the clinical remission in CD [14]. However; it has a limited availability; since it is approved only in the USA and Switzerland. In contrast; the Committee for Medical Products for Human of the European Medical Agency refused the approval of CZP for the treatment of CD.

Another "early" anti-TNF agent; etanercept structurally differs from IFX and ADA. It fuses the TNF receptor to the constant end of the human IgG1 antibody. Etanercept is approved for the treatment of rheumatoid arthritis (RA); juvenile rheumatoid arthritis; plaque psoriasis psoriatic arthritis; ankylosing spondylitis and plaque psoriasis. However; it was shown to be inefficacious in inducing remission in CD [15].

Golimumab (GOL) is the newest anti-TNF agent. It is a transgenic human monoclonal antibody against TNF-alpha. Golimumab is synthesized with a hybridoma technique after immunizing transgenic mice containing human immunoglobulin genes. Mechanism of action of GOL is very similar to that of IFX; ADA and CZP. It neutralizes both circulating and membrane-bound forms of human TNF. Despite this similarity; based on the results from clinical trials [16,17] GOL was recently approved in ulcerative colitis (UC); but not CD. In addition; anit-TNF exposed patients were not tested. Safety profile was comparable to the previous anti-TNF agents. As anti-TNF agents traditionally have superior efficacy in CD than UC; the mechanism explaining this difference may be very interesting. It was showed that the molecular properties of GOL differ significantly from IFX and ADA [8]. The affinity of GOL for soluble human TNF-alpha was higher than that of IFX and significantly higher than that ADA. The concentration of GOL necessary to neutralize TNF-alpha induced E-selectin expression on human endothelial cells by 50% lower than those for IFX (3.2-fold; p=0.017) or ADA (3.3-fold; p=0.008). Finally; the conformational stability of GOL was higher compared to that of IFX. Due to these differences GOL was expected to be efficacious in CD patients who loosed their response to the first anti-TNF agent.

Ben-Bassat et al. [18] evaluated the efficacy of GOL in patients who had lost response to IFX and failed a second anti-TNF agent or a non-anti-TNF agent in a small open labelled study. This small group of patients was very heterogeneous based on their clinical characteristics and previous medications. At the end of the 12 weeks observational period; the authors concluded; that patients who lost their response to a previous anti-TNF agent may have clinical benefit with GOL; but further studies are needed to find the optimal dosing.

Finally; infliximab biosimilair (CT-P13) was approved by the EMA recently for the treatment of CD in 2013. Based on the extensive in vitro experiments and extrapolation of the clinical efficacy data from another inflammatory disease; this agent was identified as an infliximab biosimilar. Of note; the PLANETAS study [19] proved its similar efficacy and safety in RA patients. Due to the lack of the direct evidence on its safety and efficacy in inflammatory bowel diseases; EMA requested a long-term post-marketing surveillance program and the European Crohn's and Colitis Organisation (ECCO) suggested post-marketing clinical trials in IBD [20].

Further prospects in the anti-TNF field

Despite success in developing highly specific antibody therapies against the different inflammatory cytokines; a polyclonal antibody might have some advantages in different clinical situations. Polyclonal antibodies might have better clinical efficacy than monoclonal ones; because they are produced by multiple B cell clones each generating antibodies to a multiple epitope. Moreover; bovine antibodies from milk or colostrum might be suitable for oral delivery by their known stability to digestion in the gut. A novel polyclonal human anti-TNF antibody was recently tested. AVX-470 was isolated from the colostrum of dairy cows that had been immunized with TNF; and in vitro its activity was compared to IFX. A surrogate murine polyclonal anti-TNF antibody (AXN-470m) was also examined in a mice IBD model [21]. Specificity; neutralizing potency; and affinity of AVX-470 were reported to be comparable with IFX. Moreover; the orally administered AVX-470m effectively reduced disease activity in mouse model; and it was comparable with that of oral prednisolone.

Dersalazine another interesting compound is a combination of a platelet activating factor antagonist (PAF) and a 5-aminosalicylic acid (5-ASA). It has been shown to inhibit the enhanced colonic production of TNF alpha in TNBS induced colitis in mice. In addition; it decreased the concentration other Th1 cytokines (IL-1β; IL-6 and IL-17) and induced nitric oxide synthase expression [22]. Since its structure resembles similarities with sulphasalazine (SS); the efficacy of PAF-5-ASA combination was compared to SS. Dersalazine was showed to be superior in reducing inflammatory cytokine production in animal models showing that PAF agonist moiety of dersalazine (UR-12715) may be an interesting compound for further development.

HMPL-004 is a plant (Andrographis paniculata) extract inhibiting T-cell proliferation and TH1/TH17 responses and inhibits inflammatory cytokine expression (TNF-alpha; IL-1beta; IL-6; IL-22) [23]. HMPL-004 was reported to be efficacious in preventing the development of chronic colitis in a T-cell-driven model of colitis. Efficacy of 1200 mg/day HMPL-004 was compared to mesalazine (4500 mg/day slow release granules) in a 8-week long parallel group phase II study in mild-to-moderate UC [24]. Clinical remission and response have not differed significantly from that of 5-ASA (21% and 76% in HMPL-004 group; and 16% and 82% in mesalazine group respectively). A randomized-controlled trial was also conducted in CD in 101 patients; yet results were not released yet.

DLX105 is a novel anti-TNF agent; currently tested in dermatology as a local agent. Locally administered DLX-105 was also studied in fistulising CD (NCT01624376); however the results are not published yet.

Vaccination against TNF-alpha may be another interesting mechanism of action to be tested. Debio-0512 is a keyhole limpet hemocyanin (KLH)-human TNF-alpha heterocomplex (TNF-kinoid). TNF-alpha kinoid-immunized mice were observed to be resistant against human TNF-alpha-driven shock in 2006 [25]. The advantage of the kinoid therapy compared to monoclonal antibodies is that it induces the production of neutralizing polyclonal antibodies by the patient and by that it prevents the possible loss of efficacy by the production of antidrug antibodies. There are ongoing clinical trials with TNF-kinoid in rheumatoid arthritis and in CD. First published results showed a favourable safety profiles and a high clinical response (76%) and remission rates (Crohn's disease activity index at or below 150 points) in almost half the patients (43%). Out of 21 treated CD patients 17 produced anti-TNF antibodies [26,27]. In animal models;

concomitant immunosuppression was not enhancing the efficacy of TNF-kinoid therapy [28]. Therefore; monotherapy with this agent and the avoidance of additional immunosuppressive therapy would be another advantage in the daily clinical practice.

Cell Adhesion Inhibitors

Anti-integrins

However; theoretically the anti-inflammatory cytokine therapies should be ranked to the second position of this review; recent results showing that cell adhesion molecule (CAM) inhibitors may play a more significant role in the therapy of IBDs in the near future. These agents are able to reduce the ability of immune cells to attach the epithelium of the small vessels in the intestine; and prevent the diapedesis of these cells into the site of the inflammation. The leukocyte infiltration is governed by expression of integrins; chemokine receptors (CCR) on immune cells and adhesion molecules; like intercellular adhesion molecule 1 (ICAM-1); vascular cell adhesion molecule1 (VCAM-1) and mucosal addressin cell adhesion molecule (MAdCAM-1) on the endothelium of the guts' vessels. CAM-inhibitors aim to inhibit the different subunits of these adhesion molecules [9].

Natalizumab was the first monoclonal none-gut specific antibody against the cell adhesion molecule α4-integrin. ENACT I and ENACT II trials showed clinical efficacy in inducing and maintaining remission in CD [29]. However; due to a rare; severe; John Cunningham (JC) virus associated neurologic adverse event (progressive multifocal leukoencephalopathy - PML) its development was halted for years and it was only approved for the treatment of CD in US but not Europe; however the label is rather restrictive.. Interestingly; another orally administrable anti-α4 integrin agent; the AJM300 was reported to be efficacious in short term trial (8 weeks) in 71 Japanese patients [30].

More recent trials focused on gut-selective cell adhesion inhibitor molecules.

Vedolizumab (VDZ) is a humanized monoclonal antibody that inhibits adhesion and migration of leukocytes into the gastrointestinal tract by preventing the α4β7 integrin subunit from binding to mucosal cell adhesion molecule-1 (MAdCAM-1). Its efficacy and safety in CD was tested in the GEMINI 2 trial [31]. At week 6; a total of 14.5% of the 368 patients in cohort 1 who received VDZ at week 0 and 2; and 6.8% who received placebo at the same time points were in clinical remission defined by the CDAI lower than 150 points (p=0.02). Similarly; higher rates of clinical response (≥100-point decrease in the CDAI score) were observed in the VDZ treated group (31.4% and placebo: 25.7%; p=0.23). There were a further 747 patients who received open-label VDZ induction (cohort 2). In the maintenance arm; the 461 patients showing a clinical to VDZ from cohort 1 and 2 were randomly assigned to receive placebo or VDZ every 8 or 4 weeks until week 52. Clinical remission rates at week 52 were 39.0% and 36.4% in those assigned to VDZ every 8 weeks and every 4 weeks; ; as compared with 21.6% in those assigned to placebo (p<0.001 and p=0.004 compared to the VDZ groups; respectively). Although adverse event rate was higher in the VDZ group; there were no PML cases registered in this trial. Based on these results VDZ was licenced for induction and maintanence of remission in CD and UC in the European Union in the spring of 2014. Of note; antidrug antibody positivity was only observed in 4.1% of the patients (with multiple positive sera in 0.4%); while concomitant immunosuppression was associated with lower antibody levels.

Another compound (AMG 181) against α4β7 is also under development for the treatment of IBD patients [32]. Based on the favourable pharmacokinetics and pharmakodinamic results; AMG 181 seemed to be suitable further testing in subjects with IBD. AMG 181 is under evaluation in both UC (Traffic-UC) and CD (Traffic-CD) [33,34].

There are some other innovative agents aiming to inhibit the migration of the inflammatory cells into the wall of the gut. While natalizumab acts on α4; and vedolizumab selectively on the α4β7 subunit; other possible targets include β7; α2β2 and α4β1. An interesting member of this group showing promise is etrolizumab; a human monoclonal IgG1type anti-β7 antibody (rhuMab-β7). It blocks both α4β7 and αEβ7 integrins. It was shown to be efficacious in inducing remission in moderately-to-severly active UC [35]. There is no published data on of its efficacy in CD in CD.

A further molecule; TRK-170; a novel orally active alpha4beta1/alpha4beta7 integrin antagonist; is currently tested in IBD (NCT01345799).

Integrin receptor blockers

The other possibility to inhibit the migration of the inflammatory cells into the site of the inflammation is blocking the receptors of the integrins.

PF-00547659 is a novel monoclonal IgG2 antibody directed against MAdCAM. It inhibits the function of the β7+ memory T-cells and its affinity to mouse and human MAdCAM was proven [36]. Eighty moderately-severely active UC patients have been involved into a multicentre RCT study to evaluate the efficacy of PF00547659 [37]. Study drug was administered in an 0.03-10 mg/kg iv./sc. dose (or placebo) once or three times within 8 weeks. Overall clinical response and remission rates had not differed significantly in patients actively treated and the placebo group (52 and 13%; and 42 and 22% at week 4 and 12 in the pooled PF-00547659 doses; respectively; compared to 32 and 11%; and 21 and 0%; respectively; in the placebo group). Similarly; the endoscopic response was not different. Further studies are ongoing in CD patients [38]. A Phase II study compares the efficacy of anti-human MAdCAM antibody in induction (1:3 placebo controlled) and maintenance (open labelled) of remission in CD (OPERA I and II). A phase I open label study (TOSCA) with s.c administered PF-00547659 is also ongoing for CD patients who already had inadequate response or intolerance for anti-TNF agents. The first safety results of this study regarding the possible central nervous system adverse events are promising. The full induction regime with the highest dose of PF-00547659 among 24 anti-TNF and immunosuppressant experienced patients did not cause changes in t-cell numbers in the cerebrospinal fluid. Based on these results; this anti-human MAdCAM seems to be CNS sparing [39]. Other studies to evaluate the long term safety of the drug [40,41].

Anti-ICAM-1 (Alicaforsen; ISIS 2302) is an oligosense nucleotide developed against human ICAM-1. More than a decade ago its efficacy was evaluated in a phase I double blind placebo controlled trial in; active; steroid dependant CD (n=20) [42]. At the end of treatment 7 of 15 of ISIS 2302-treated and 1 of 5 (47% vs. 20%) of the placebo-treated patients were in remission. At the end of month 6; 5 of these 7 ISIS 2302-treated remitters were still in remission. Corticosteroid usage was significantly lower (P=0.0001) in the ISIS 2302-treated patients.

Later on; a larger trial involving 70 patients with steroid refractory; active (CDAI: 200-400) CD could not prove clinical efficacy of sc. administered ISIS 2302 [43]. Only 2 of 60 (3.3%) ISIS-2302-treated and none of placebo treated patients reached the primary endpoint; steroid free remission at week 14. A more recent study by Yasyshyn et al. [44] was also negative. A total of 299 patients were enrolled; with a mean baseline CDAI of 276 and steroid dose of 23 mg/day. Rates of steroid free remission were equivalent for the two ISIS 2302 treated groups (20.2% and 21.2%) and the placebo (18.8%). Of note; some secondary endpoints were reached; like decrease in CDAI and IBD score questionnaire improvement.

Chemokine- and chemokine receptor-blockers

Chemokine family consists of more than 50 small secreted polypetides; which direct the movement of circulating leukocytes to the site of the inflammation. Based on their structural features they can be divided into 4 groups (CC; CXC; CX3C and XCL1 chemokines). These circulating peptides are able to bind to one of the 18 of the chemokine receptors have been identified so far. This chemoattraction is an important process for the protection against infectious agents. However; immoderate chemokine activity might be harmful due to maintaining sustained responses against self-antigens which are responsible for the development of autoimmune inflammation.

The pioneer of the chemokine receptor blockers is vercirnon (CCX282B; anti-CCR9; or Traficet-EN). It has been studied in the PROTECT-1 study in patients (n=436) with moderate to severe CD (CDAI: 250-400; and C-reactive protein>7.5 mg/L) [45]. Subjects received placebo or CCX282-B (250 mg once or twice daily; or 500 mg once daily) for 12 weeks. Open label maintenance was given with 250 mg CCX282-B twice daily through week 16. Patients achieving clinical response (defined by 70 point drop in CDAI) at week 16 were randomly assigned to groups given placebo or CCX282-B (250 mg bid) for 36 weeks. At week 12; response rates were 47%; 56% (OR=1.44; p=0.168); 49% (OR=1.07; p=0.792); and 61% (OR=1.74; p=0.039) in patients receiving 1x250 mg; 2x250 mg or 500 mg CCX282-B; respectively. At the end of week 52; 47% of subjects on CCX282-B were in remission; compared to 31% on placebo (OR=2.01; p=0.012); 46% showed sustained clinical response; compared to 42% on placebo (OR=1.14; p=0.629).

Recently; CCX282-B has been evaluated in patients with moderately-to-severely active CD in a phase 3 RCT study. Efficacy and safety 500 mg once daily or 500 mg twice daily dose of the drug was compared to placebo up to 12 weeks. The primary endpoint was not met [46].

CXCL10 (IP10) is an IFN-gamma inducible chemokine. Anti CXCL10 (anti IP-10; BMS-936557) was evaluated in a Phase II study in moderate to severe patients with UC [47]. Pre-specified primary and secondary endpoints were not met. Investigators observed that higher drug exposure correlated with increasing clinical response and histological improvement. Further dose-response studies are planned.

Further developments regarding chemokine receptor blockers are expected; as other chemokine receptors are targeted with success in diabetes and other conditions.

Anti-Cytokine Therapies

Other than TNF-alpha proinflammatory cytokines are also targeted. An important target in the development is the IL-12/IL-23 cytokine system. IL-12 is a pivotal cytokine in promoting T-helper 1 cell responses. IL-12 is composed of a p40 and p35 subunits; while IL-23 consists of a p40 and a p19 subunit. Many agents used to assess the IL-12 activity react with the common p40 subunit meaning that activity previously referred to IL-12; may have been mediated by IL-23. Results of studies with anti-p19 agents show their anti-inflammatory ability; suggesting that IL-23 has an important role in regulation of the inflammation. Moreover; the IL-23 receptor (IL23R) consists of heterodimer of IL12Rb1 subunit and a novel IL23R subunit. IL-23 induces an IL-17 producing T-cell population which are distinct from Th1 and Th2 cells. High concentration of IL-17 was observed in the intestine of IBD patients; it induces inflammatory cytokine production by macrophages. However; neutralisation of IL-17 was not sufficient to inhibit colitis in IL-10-deficient mice [48]. It suggests that in the intestine IL-23 drives IL-17-independent inflammatory pathways.

Apilimod mesylate; SH-900222; briakinumab (ABT-874) and ustekinumab were manufactured to inhibit the effects of IL-12 and IL-23.

Apilimod mesylate is a small molecule inhibiting the transcription of IL-12 and IL-23. Its efficacy for induce and maintain remission in modrate-to-severe active CD was evaluated in a Phase II study [49]. Patients were stratified according to C-reactive protein (CRP) levels and corticosteroid use and were randomly assigned to receive placebo or apilimod mesylate 50 mg daily or 100 mg daily. Clinical response was similar in the 50-mg daily group (n=73; 18 patients (24.7%)) and in the 100 mg daily group (n=74; 19 patients (25.7%)) and placebo (n=73; 21 patients (28.8%)) on day 29 (P=0.71 for each comparison). No significant adverse safety signals were observed.

SCH-90022 (or mk-3222) is an antibody targeting the p19 subunit of IL-23. Thus; theoretically it could to inhibit both the IL-12 and IL-23 pathway. It was studied in a Phase II trial in patients with psoriasis; but not in IBD yet. BI 655066 is another humanized IgG1 mAb that binds and neutralizes the p19 subunit of IL-23 (NCT02031276) and Medi2070 an IL-23 antibody are currently tested in clinical trials (NCT01714726).

Briakinumab (ABT-874) is a recombinant; exclusively human-sequence; full-length IgG1 antibody genetically modified to recognize IL-12 p40 protein. Its efficacy and safety was evaluated in a double blind trial including 79 patients with active CD. Patients were randomly assigned to receive 7 weekly subcutaneous injections of 1 mg or 3 mg/kg of briakinumab or placebo; with either a four-week interval between the first and second injection (Cohort 1) or no interruption between the two injections (Cohort 2). Safety was the primary end point; and the rates of clinical response (defined by drop of CDAI of at least 100 points) and remission (defined by a CDAI score of 150 or less) were secondary end points. Briakinumab showed a short term efficacy. Seven weeks of uninterrupted treatment with 3 mg/kg of briakinumab resulted in higher response rates than did placebo (75% vs. 25%; p=0.03). At 18 weeks of follow-up; the difference in response rates was no longer significant (69% vs. 25%; p=0.08). The rate of adverse events among patients receiving briakinumab was similar to those receiving placebo.

A further player is ustekinumab. It is a fully human IgG1κ monoclonal antibody; blocking the activity of IL-12 and IL-23 through

their common p40 subunit. It inhibits receptors of these two cytokines on T cells; natural killer cells; and antigen-presenting cells. Sandborn et al. [50] evaluated its efficacy in moderately-to-severely active CD patients who had been resistant to anti-TNF agent. One; 3 and 6 mg/kg intravenous ustekinumab or placebo were administered to 526 randomly assigned patients at the start of the study. Patients who responded to the therapy (n=145) at week 6 were randomized to receive subcutaneous ustekinumab (90 mg) or placebo at week 8 and 16. Higher rate of clinical response was observed in patients receiving ustekinumab independently from the dose compared to placebo (36.6%; 34.1%; and 39.7% vs. 23.5%; p=0.005). Maintenance therapy with ustekinumab; as compared with placebo; resulted in significantly increased rates of clinical remission (41.7% vs. 27.4%; P=0.03) and response (69.4% vs. 42.5%; P<0.001) at 22 weeks. Based on the results ustekinumab might be a reasonable choice in patients who lose respone to anti-TNF agents.

Receptors of other proinflammatory cytokines are also a theoretical therapeutic target in the therapy of IBD. The most important representatives of this group are the IL-2 receptor's (IL2R; CD25) alpha subunit blockers; daclizumab and basiliximab. Blocking the IL2R was approved to prevent the rejection after renal transplant. Paracrine role of IL-2 seems to be responsible partially the steroid resistance of the T cells – steroid resistant individuals produce higher levels of IL-2 than steroid-sensitives [51].

Results of an early open labelled; uncontrolled study suggested that basiliximab might be effective in steroid resistant UC [52]. Nine of ten patients receiving a single dose of 40 mg intravenous basiliximab achieved clinical remission within 8 weeks; and seven of them maintained the good clinical state at week 24. However; basliximab was ineffective in a later steroid-resistant UC trial [53]. At week 8; the rates of clinical remission (defined by Mayo score </=2; no subscore>1) was 29% in placebo; while 29% and 26% in the 40-mg and 20 mg basiliximab groups (p=1.00 vs. placebo for each dose).

Daclizumab has also showed some clinical benefit in UC in and early small phase study [54]; but it failed in subsequent large clinical trials with moderate-to-severely active UC [55]. However; the drug was not tested in CD.

In addition; other anti-proinflammatory cytokine agents were developed and tested in the recent years. IL-6 mediates the inflammatory process in IBD also [56]. There are ongoing studies with the fully human (PF-04236921 – ANDANTE trials) and humanized anti-IL-6 antibodies (olokizumab and BMS-945429) in IBD; however; as anti-IL-6 antibodies has also an anti-tumour effect; these agents are under evaluation in oncology. Tocilizumab is a fully human anti-IL-6 receptor (IL6R) antibody that showed a beneficial effect in a small phase II study in active CD [57]. Binding proteins are a class of proteins that bind the cytokine and inhibit its action on their receptors. C326 is a member of this avimer (short form of avidity multimer) group showing a good anti-IL-6 activity in mice [58]. This agent was also tried in CD; however results are awaited.

Tofacitinib (CP690550) is an oral Janus kinase (JAK) inhibitor having also an IL-6 blocking activity. Moreover; as JAKs have a determining role in the signalling pathways of many pro-inflammatory cytokines (IL-2; IL-4; IL-7; IL-9; IL-15; IL-21). Therefore blocking JAK kinases is able to inhibit the inflammatory process via many different ways. However; a phase II study investigating the efficacy and safety of tofacitinib; a JAK3 inhibitor in moderate-to severe CD; was negative and there was no difference in the rate of clinical response and remission in the patients receiving tocafitinib compared to placebo [59]. Moreover; a significant elevation of low-density lipoprotein cholesterol levels was observed requiring further long term safety observations. There is an ongoing open labelled; long term study in patients with CD evaluating the safety of tofacitinib (NCT01470599). Other JAK inhibitors (GLPG0634) are also under evaluation (NCT02048618).

Besides TNF-alpha; IL-12/IL-23 system and IL-6; IFN-gamma is one of the most potent proinflammatory cytokine produced by active Th1 cells. Reinisch et al. [60] studied the efficacy of fontolizumab in 201 CD patients with moderate-to-severe active disease (CDAI: 250-450). Clinical response defined by drop of CDAI by 100 points was the primary endpoint. Efficacy of intravenous dose of 1.0 or 4.0 mg/kg fontolizumab followed by up to 3 subcutaneous doses of 0.1 or 1.0 mg/kg fontolizumab every 4 weeks was compared to placebo. Although a strong clinical response to fontolizumab was not observed (response rates was observed to be 31-38% of patients in all treatment groups) at subsequent time points a significantly greater proportion of patients in the fontolizumab group had clinical response and significantly greater improvement in the CDAI score compared with patients who received placebo. Moreover; all fontolizumab groups had significant improvement in C-reactive protein levels.

IL-13 seems to play a role in the pathogenesis of UC and fistulising CD and there is a Phase II trial with anti-IL-13 therapy (QAX567) in fistulising CD.

As elevated levels of IL-17; IL-18 and IL-21 are also observed in the inflamed mucosa of IBD patients and these cytokines were also targeted. Failure of anti-IL-17 secukinumab (AIN457) in CD is a warning sign and highlights that signals identified as important during the pathogenesis may play a dual role in vivo and simply targeting these molecules can lead to adverse outcome. In fact; this is one of the few trials when the medication worsened the outcom [61]. 21% of patients on secukinumab and 10% of patients on placebo had to be stopped prematurely due to insufficient therapeutic effect; and patients on secukinumab showed higher rates of adverse events. In addition; success of secukinumab therapy in other immune mediated inflammatory diseases (rheumatoid arthritis and psoriasis); suggests that extrapolation of efficacy data from one immune mediated disease to another is not always without problems [39]. As Th17 cells seems to be controlled by the small intestine [62]; modulating the IL-17 activity could produce different biological effect in the inflammatory disease of the gut. Making a twist in the tale; vidoflumidus (SC12267 or 4SC-101); another anti-IL-17 agent have been shown to be efficacious in a pilot maintaining clinical remission in steroid dependent IBD [63]. Thirty four steroid dependent CD or UC patients were treated with 35 mg oral vidoflumidus over 12 weeks. After the observational period 8 out of 14 (57.1%) patients with CD and 6 out of 12 (50.0%) patients with UC were in steroid-free remission. Other anti-IL-17 antibody (AMG-827) has been tested recently (NCT01150890); but this trial was also terminated.

A further phase I study was completed using anti-IL-18 antibody (GSK1070806) in CD recently; but no results published until now (NCT01035645). Interestingly; a trial evaluating the efficacy of anti-IL-21 antibody ATR-107 (PF-05230900) has been prematurely terminated due to high anti-drug body titer in 70% of the patients (NCT01162889). Another anti-IL-21 antibody (NNC0114-0006) is currently tested in CD (NCT01751152).

Anti-Inflammatory Cytokine Therapies

The other side of the coin is to promote the activity of the anti-inflammatory cytokines. The most important member of this group is IL-10; IL-11 and IFN-beta.

Since IL-10 deficient mice develop spontaneous IBD like colitis; it was rational to try IL-10 based therapies in IBD. In an early study by van Deventer et al. [64] five doses of recombinant human IL-10 (0.5; 1; 5; 10; or 25 micrograms/kg) or placebo was administered once daily by intravenous bolus injection over 7 consecutive days. The proportion of patients that experienced a complete remission at any time in the 3-week follow-up period was 50% in the IL-10 treated group and 23% in placebo. Despite this early result and the theoretical potential of the drug (Tenovil); recombinant IL-10 was neither efficacious in inducing and maintaining remission of CD [65]; nor in prevention of endoscopic recurrence in postoperative CD [66]. Moreover; a significant dose dependent thrombopenia and anaemia were observed [67]. More optimal patient selection and improving local delivery of the drug might improve the therapeutic efficacy of recombinant IL-10 therapy [68].

In vitro studies indicate that recombinant human IL-11 inhibits TNF-alpha; IL-1beta; IL-12; IL-6 production in activated macrophages. Herrlinger et al. compared the efficacy of rhIL-11 versus prednisolone in induction of remission in CD in 2006 [69]. Remission rates for rhIL-11 (1 mg once weekly) versus prednisolone (60mg/day) were 4% versus 46% at week 4 ($p < 0.001$) and 19% versus 50% at week 6 ($p < 0.05$). Response to treatment (defined by >100 point drop of CDAI) was seen in 19% (rhIL-11) versus 63% (prednisolone) after 4 weeks ($p<0.002$) and 37% versus 63% after 6 weeks ($p=0.1$). After 12 weeks of treatment; it was observed that 22% (rhIL-11) versus 21% (prednisolone) had remained in remission. Based on the results authors concluded that both treatments appeared to be poor in maintaining remission over a period of 3 months.

There is only one Phase II; dose finding clinical study evaluating the efficacy of IFN-beta1a in maintaining clinical remission in steroid induced remission of CD [70]. The study was terminated early based on the results of a planned interim analysis at week 26. The proportion of patients who remained relapse-free at week 26 did not differ between the placebo group (5/16; 31%) and the IFN beta-1a 44 mcg twice weekly (6/17; 35%; $p=0.497$); 44 mcg three times weekly (7/16; 44%; $p=0.280$) or 66 mcg three times weekly (2/18; 11%; $p=0.333$) groups. Moreover; IFN-beta induced IBD in patients treated with this agent against multiple sclerosis.

Modifying T Cell Functions

During the parallel use of anti-TNF agents in the every practice and the much more specific anti-cytokine agents in clinical studies we have learnt; that too specific targeting is not always the best strategy in IBD. Broader spectrum agents modifying basic T cell functions are the other end of our therapeutic spectrum.

Blocking the different parts of the T cell receptor (TCR) is the most widely used approach. Visilizumab is a humanized monoclonal antibody against CD3 causing a T cell apoptosis. Plevy et al. [71] observed 84% clinical response and 41% clinical remission and 44% endoscopic remission in patients with severe ulcerative colitis who had not responded corticosteroids in 2007. Forty five percent of these patients did not require colectomy or other salvage therapy among the treated patients. However; every patient had some side effects (flue like syndrome and liver injury) connected to the cytokine release [72]. Some years later Baumgart et al. [73] conducted a dose escalating study involving 104 steroid refractory UC patients. All of the patients experienced adverse events. Serious adverse events included abdominal abscess; cytomegalovirus infection; atrial fibrillation; herpes zoster; and esophageal candidiasis. Primary endpoint was not met; in fact more patients in the visilizumab group needed colectomy compared to placebo. An other anti CD3 antibody (OPC-6535) is under study in CD patients (NCT00630643).

Rituximab is an anti CD-20 antibody targeting the TCR of B cells. It is widely used in hematology to cure non-Hodgkin lymphomas. Due to its theoretical effects on B cells; it was also tested in steroid resistant UC patients. The rate of induction of remission was similar in the rituximab compared to placebo [74]. However; rituximab was observed to exacerbate the symptoms of UC in one case [75] and de novo UC developed in some patients treated with rituximab due to other conditions like nephrotic syndrome [76]; follicular lymphoma [77] and Grave's disease [78]. Due to the adverse events; rituximab was not tested further in IBD.

Functioning of TCR needs the activity of some co-stimulatory factors. Inhibiting of these molecules may inhibit the full activation of these immune cells. CD28 is expressed on T cells and interacts its ligands CD80 and CD 86 on antigen presenting cells (APC). This interaction is could be blocked by a cytotoxic T-lymphocyte associated antigen 4 (CTLA4). Abatacept is a soluble recombinant fusion protein containing CTLA4 and an IgG1 molecule. A large RCT was conducted to evaluate the efficacy and safety of abatacept in the induction and maintenance in both CD (n=451) and UC (n=490) patients. In the induction phase 17.2%; 10.2%; and 15.5% of CD patients receiving abatacept 30; 10; and 3 mg/kg achieved a clinical response at weeks 8 and 12; vs. 14.4% receiving placebo ($p=0.611$; $p=0.311$; and $p=0.812$; respectively). Clinical response in the induction phase was achieved in 21.4%; 19.0%; and 20.3% of UC patients receiving abatacept 30; 10; and 3 mg/kg at week 12; vs. 29.5% receiving placebo ($p=0.124$; $p=0.043$; and $p=0.158$; respectively). Based on these results further development of the drug in IBD is unlikely.

Finally; human NKG2D forms complexes with DAP10; a membrane adaptor protein; and has the ability to costimulate multiple NK activation receptors. Efficacy and safety of nti NKG2D antibody (NNC 0142-0000-0002) was studied recently (NCT01203631); but the results have not been published until now.

Further Developments

The pipeline of IBD drugs is broad.

Historically; the most important is the use of the different growth factor. These agents enhance the functions of the innate immune system. Since dysregulation of the innate immunity is thought to be the most probable cause of IBD; the manipulating of the cellular and soluble factors of innate immunity is a reasonable target. Recombinant human granulocyte colony stimulating factor (G-CSF) filgatsrim and lenogastrim have been tested in CD. Twenty patients had been included to an open label 12 week trail to evaluate the efficacy of filgastrim in inducing clinical response or remission [79]. At week 12; 11 patients (55%) demonstrated a decrease of at least 70 points; five (25%) achieved a sustained remission. The mean decrease was statistically significant at each assessment time-point. However; filgastrim was regarded as a safe and potencially efficacious therapy in

CD; further development of recombinant G-CSF in IBD is questionable.

Sargramostim is a recombinant granulocyte-monocyte colony stimutaing factor (GM-CSF). Results of the clinical trials were summarized in a recent meta-analysis by Roth at al. [80]. Three randomized studies (total 537 patients) were included into the metaanalysis. There was no statistically significant difference in the proportion of patients who achieved clinical remission with GM-CSF treatment compared to placebo (25.3% vs. 17.5%; relative risk [RR] 1.67; 95% confidence interval [CI] 0.80-3.50; p=0.17); or 100-point clinical response (GM-CSF 38.3%; placebo 24.8%; RR 1.71 95% CI 0.98-2.97; P=0.06). Furthermore; there was no statistically significant difference in the proportion of patients who experienced adverse events or serious adverse events. Based on this metaanalysis GM-CSF does not appear to be more effective than placebo for induction of clinical remission or improvement in CD.

There are 17 clinical trials in IBD are registered at the National Institute of Health of the USA at this moment. Autologous mesenteric stem cells; hematopoietic stem cells; human placenta derived stem cells; non-myeloablative allogeneic hematopoietic stem cell are used to treat inflammatory type of CD; and expanded allogen adipose tissue derived stem cells applied intralesionally are used to cure fistulising CD. The autologous Stem Cell Transplantation International Crohn's disease (ASTIC) trial recruited 48 patients until the start of 2012 [81]. After a standard conditioning patients received bone marrow by the infusion of an unselected graft of 3-8 x 10(6)/kg CD34-positive stem cells. Twelve months after stem cell transplantation (early or delayed) the CDAI) fell from 324 (median; interquartile range 229-411) to 161 (85-257; n=17) compared to 351 (287-443) to 272 (214-331) following mobilisation alone (n=11). Endoscopic severity also improved: the Crohn's Disease Endoscopic Index of Severity fell from 18 (10-25) to 5 (1-11) following transplantation versus 14 (12-16) to 9 (4-22) following mobilisation. Three patients achieved the goal of a normal CDAI; no drug therapy and normal upper and lower endoscopy 1 year after transplantation; but so did 1 patient following mobilisation alone. As expected; the rate of adverse events was high; hospitalisation must have been elongated in 42 cases due to infections. Haemopoietic stem cell transplantation appears to be an effective treatment for some patients with CD; although patient selection must be careful.

There are numerous of other therapeutic approaches under study at this moment (Table 1). Some apply drugs which are approved for some other conditions (antibiotics; anti-parasite agents; sclerosis multiplex; hypercholesterolemia; depression; etc). There are some trying herbal extracts originating from the Far East. Some use sophisticated procedures and machineries (leukocyta apheresis; hyperbaric oxygen therapy); while others seems to be very simple (like AST-120 and Halevy Kit). Efficacy of nutritional supplementation (vitamins; special nutritional elements) and modification of the bacterial flora (even with probiotics; faecal transplant; nutritional supporters; etc.) needed to study further to judge their efficacy.

Agent/procedure	Mechanism of action	Registration No. /Reference	Status
Semapimod	nitric oxide synthesis inhibitor	NCT00739986;	Completed
(CNI-1493)		NCT00038766	Terminated
		NCT00740103	
			Completed
Extracorporeal Photoimmune Therapy	unknown	NCT00221026	Completed
Celegne (CC-5013)	thalidromid derivate	NCT00446433	Completed
CP-461	cyclic GMP inhibitor	NCT00042055	Completed
ITF2357	histone deacylate inhibitor	NCT00792740	Terminated
HMPL-004	inhibiting T-cell proliferation and TH1/TH17 responses	NCT00655733	Completed
Daikenchuto (Japanese herbal medicine)	activating nicotinic acetylcholine receptors	NCT01388933	Terminated
OPC-6535;	a superoxide anion production inhibitor	NCT00092508	Completed
ERB-041	selective estrogen receptor antagonist	NCT00245947	Completed
Bupropion	antidepressant	NCT00126373	Completed
EPANOVAÒ	omega 3 fatty acid	NCT00613197	Completed
RR110	interact between G-quadruplexes and small-molecule ligands	NCT00417391	Completed
ALX-0600	glucagon-like peptide analogue	NCT00308438	Completed
VSL3#	probiotic	NCT00114465	Completed
		NCT00367705	Unknown

Naltrexon	opiate receptor antagonist	NCT00715117; [82]	Completed
		NCT00663117; [83]	Completed
Adacolum	leukocyte pheresis	NCT00162942; [84]	Completed
Hyperbaric oxygen therapy		NCT01828190	Ongoing
Rifabutin; Clarithromycin; and Clofazimine	antibiotic regimen directed against Mycobacterium avium paratuberculosis	NCT00513552	Unknown
Cannabis	not known	NCT01826188	Ongoing
		NCT01040910	Unknown
Acupuncture and Moxibustion	not known	NCT01696838	Invited participants
Fecal microbiota transplantation	gut flora modification	NCT01793831	Ongoing
		NCT02108821	Ongoing
		NCT01757964	Ongoing
Extracorporeal Photopheresis	not known	NCT00056355	Completed
Tripterygium Glycoside	chinese herbal medicine	NCT02044952	Ongoing
Halevy Kit	biological adhesive for fistulas	NCT00653094	Unknown
Nitazoxanide	antiprotozoal agent	NCT00130390	Terminated
AST-120	spherical carbon adsorbent	NCT00321412; [85]	Completed
Laquinimod	immunemodulator	NCT00737932	Completed
Tenia suis ova	modulating Th2 activity	NCT01576471	ongoing
Rifaximin	antibiotic	NCT00603616	Unknown
Vitamin D	modulating the immune response	NCT02010762	Ongoing
		NCT00672763	Withdrawn
Chondroitin sulphate	nutritional supplements aiming protect cartilages	NCT01245088	Withdrawn
glatiramer acetate	random polymer of four amino acids: glutamic acid; lysine; alanine; and tyrosine; may work as a decoy for the immune system	NCT00731172	Unknown
Beta Carotene	anti-oxidant	NCT00275418	Unknown
Atorvastatin	decreasing chemokine expression	NCT00454545; [86]	Completed
Clarithromycin	antibiotics	NCT00269386	Completed
T2	chloroform/methanol extract of Tripterygium wilfordii hook	NCT01015391	Ongoing
Mare's milk	unknown	NCT00940576	Completed
pectin	modifying intestinal colonisation	NCT02016469	Ongoing

Table 1: Ongoing and recently completed clinical trials in inflammatory bowel diseases. (Results of completed trials are highlighted in the text, results of other completed trials has not been published until the close of this review).

Expert Opinion

First representatives of biologics; the anti-TNF agents revolutionized not only the treatment strategy; but the patient stratification; management and monitoring in IBD. Despite our growing knowledge regarding the use of approved agents; their use in the everyday practice is still far from the optimal. Moreover; numerous new compounds are under evaluation.

Unfortunately; parallel with the duration treatment patients lose their response to anti-TNFs and the proportion of anti-TNF resistant patients in increasing. Optimization of their use is therefore crucial;

including drug trough level and antidrug antibody monitoring; as well as critical evaluation of patient with clinical relapses and concomitant immunosuppression. Further techniques; preventing or reversing the antibody formation are awaited to improve the long term outcomes in patients under antiTNFs. However; GOL;a classic monoclonal antibody against TNF-alpha; with a modified technology (hybridoma technique); is able to partially overcome this limitation. The level of anti-GOL antibodies was significantly lower compared to antibody levels against IFX or even the fully human ADA. In contrast; it has not been tested in patients exposed to anti-TNFs and efficacy was only proven in UC. Another development may be the use of polyclonal antibodies and/or the kinoids. Both groups of drugs may be theoretically associated with less anti-drug antibody production compared to classic anti-TNF antibody agents; which might be associated with longer and/or better efficacy and favourable safety profiles. However; early clinical data with these compounds are results discouraging.

Finally; a new drug class became available with the approval of vedolizumab. A question is however; the optimal positioning; and long term-efficacy/safety profile of these drugs remain to be elucidated. Shall these be reserved for anti-TNF refractory patients or can we use them in bio naïve patients? What is the efficacy in fistulising patients? Shall we apply parallel immunosuppressive? Can we combine them with anti-TNFs? Do we have to monitor drug through-antibody levels? These are all relevant; unanswered questions for the everyday clinic. A close monitoring of the clinical outcomes and adverse events will be needed with further high quality clinical trials aiming to answer one or the other above question.

Some other very specific targets proved to be ineffective and further development of similar class targets will be rather questionable. Patient heterogeneity is high in CD. Probably a better patient stratification in the future by clustering patients based on genetic/serology or other markers could better explain why these studies have failed and if we can select a specific patient population in whom; parallel to oncology; tailored targeting these mechanisms can be successful. However; unlike in oncology; these mechanisms are responsible for chronic inflammation rather than the development of a malignant clone and so a differentiation between normal and pathological strata may be more difficult. Nonetheless; it is unlikely that tailored approaches became standard in the treatment of IBDs in the near future. At least this can be suspected already due to the relative small specific patient populations and high drug development costs.

In the same time; anti-T-cell therapies confirm that dramatic modification of the core host immunological milieu may be rather harmful. Any trials applying these strategies (e.g. stem cell transplantation) should be very carefully planned with close follow-up and monitoring of long-term outcomes.

Finally we believe that clinical trial designs evaluating the new therapeutic options have to be better harmonized with regards to induction; randomization; outcome measures and follow-up intervals to enable better comparability of efficacy and safety and specific; hard-to-treat patient subgroups (e.g. fistulising disease; or anti-TNF exposed patients) should be specifically targeted.

However; the aims of the best- clinical care today in gastroenterology is the same as tomorrow; to provide the best available outcomes to our patients through early patient stratification; optimized long-term; tailored therapeutic strategy; regular objective monitoring/reassessment and critical evaluation of patients with symptomatic relapses. Systematically applying these rules together with the availability of new therapies will hopefully lead to superior clinical outcomes today or tomorrow.

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