Treatment Perspectives in Crohn's Disease

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Abstract

Background: Crohn's disease (CD) is a chronic immune-mediated disorder of the gastrointestinal tract. The pathophysiological understanding of this disease is limited and no curative therapy is available so far. Therefore, most patients require long-lasting or even life-long immunosuppressive therapies for the suppression of symptoms to improve quality of life and reduction of long-term risks. However, in a relevant subgroup of patients, these therapeutic goals cannot be sufficiently attained. **Summary:** Clinically established therapies in active CD comprise corticosteroids and immunosuppressants such as azathioprine. After the introduction of anti-TNF α (Tumor necrosis factor alpha) antibodies, other biologicals (e.g., vedolizumab and ustekinumab) have also been approved. New drugs in the pipeline like filgotinib, upadacitinib, risankizumab or rifaximin could improve the therapy of CD in the near future. Thus, an individualized therapy management, based on optimal selection of therapeutic agents will become more important. Additionally, the local application of mesenchymal stem cells might be helpful in the management of fistulas. **Key Messages:** The targeted biological therapeutic agents (anti-TNF α antibodies, vedolizumab, ustekinumab) are well established for therapy in CD. There are several new substances in the pipe-

line with promising results in phase II trials (filgotinib, rifaximin, risankizumab, upadacitinib). The upcoming extension of the therapeutic arsenal will require methods for an optimized selection of substances, thus enabling a more individualized therapy.

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Introduction

Inflammatory bowel diseases are marked by a chronic, immune-mediated inflammation of the gut [1]. In the case of Crohn's disease (CD), the inflammation may be observed in all parts of the gastrointestinal tract. The origin of this disease remains unclear but seems to result from a combination of genetic predisposition and multiple environmental factors [2]. The intestinal microbiome could be involved in the pathogenesis [3]. According to epidemiological data, the incidence of CD is increasing [4]. Patients are affected by abdominal pain, (bloody) diarrhea, fatigue and are at risk of fistulas, malnutrition, osteoporosis and colon cancer in the long term [5].

Importantly, no curative therapy for CD is available. In order to improve the quality of life and reduce risk of long-term complications, most patients require an immunosuppressive therapy for many years or even their whole life [1, 6]. These advantages must outweigh the potential side effects of the therapeutic substance(s) [7].

In the following sections, we discuss therapy objectives, present established and new substances and address the topic of individualized therapy.

Therapy in CD – Goals and Controls

The therapeutic goals in CD are reduction of symptoms, improvement of life quality and prevention of long-term complications. In the previous years, an increasing number of clinical studies demonstrated the relevance to reach mucosal healing as well [8]. Mucosal healing is associated with a reduction of the need of surgery [9] and longer time of remission [10]. However, there is lack of agreement about the definition of mucosal healing so far [11, 12]. Finally, the suppression of inflammatory activity could avoid long-term risks like colorectal carcinoma and postoperative short bowel syndromes. The therapeutic efficacy of the applied drugs should outweigh their side effects. Typical adverse effects of some immunosuppressive substances such as azathioprine are an increased risk for infections and possibly a low risk for lymphoma and non-melanoma skin cancer in the long term [7, 13, 14]. Moreover, there are substance-specific side effects like azathioprine-induced acute pancreatitis [15] or infliximab-associated anaphylactic reactions [16].

Clinical assessments with the determination of the CD activity index (CDAI; remission: <150) or the Harvey-Bradshaw-Index (remission: <5) may be helpful for the estimation of inflammatory activity. This should be complemented by the measurement of biomarkers like C-reactive protein (CRP) or calprotectin [17]. In the CALM-Study, the consequent adaption of immunosuppressive therapy based on these biomarkers and symptoms led to a higher rate of mucosal healing after 1 year when compared to the pure symptom-driven therapy management (45.9 vs. 30.3%). The frequency of adverse effects for both groups was similar [18]. In patients after ileocecal resection, calprotectin correlates better with the endoscopic degree of inflammation than CRP, leukocytes or the CDAI [19]. Colonoscopy should be performed in non-responders, flares or before de-escalation of therapy. In the case of a non-response or severe flare, testing for a potential infection with *Clostridium difficile* or cytomegalovirus should be considered before escalation of therapy [17]. In patients with extensive small bowel or ileocaecal disease, regular duplex sonographic control is an additional option. Another, more sensitive method for the detection of inflammation in the small intestine is capsule endoscopy [20]. Possibly, multispectral optoacoustic tomography could improve the

sensitivity for non-invasive detection of inflammation in the gut in the future [21, 22]. Direct drug-monitoring could also become important in the future [23].

Approved Substances – State of the Art

In the previous years, the number of available drugs for the therapy of CD has remarkably increased. Substance-specific characteristics are described in the following sections and Figure 1 gives an overview about the therapeutic management.

Glucocorticoids

Glucocorticoids have been used for the therapy of CD since decades and they have pleiotropic effects. The immunosuppressive effects are achieved by binding to intranuclear receptors, which regulate the activation of various transcription factors (e.g., Activator Protein 1). This in turn leads to the inhibition of NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells) activation and thus finally decreases the production of pro-inflammatory cytokines (e.g., tumor necrosis factor alpha [TNFα]) [24]. Due to the fast therapeutic effect and potent immunosuppression, this class of substances is suitable for the therapy of flares in CD [25]. However, due to multiple side effects and especially the lack of potency to maintain remission [26], it is not reasonable to use glucocorticoids in the long term. Glucocorticoids can worsen diabetes mellitus and osteoporosis [27] and may induce steroid acne, alopecia and depression. Adrenal insufficiency can be avoided by the slow tapering of systemic glucocorticoids. Systemic side effects can be reduced by the usage of budesonide, which has a pronounced first-pass effect. According to the European Crohn's and Colitis Organisation guidelines from 2016, budesonide is preferred in the case of mild inflammation and equivalent to systemic steroids in moderately active, localized ileocaecal CD [8, 28]. However, in more severe cases or extended disease conditions, conventional steroids are more effective in attaining remission [8].

Immunomodulators – Thiopurines and Methotrexate

Thiopurines are Rac1 blockers and purine antimetabolites, whereby azathioprine is a precursor of 6-mercaptopurine. Due to its great effect latency, these drugs are not suitable to treat flares of CD [29] but can maintain remission in a fraction of CD patients [30, 31]. Typical side effects of thiopurines are, for example, fatigue, acute pancreatitis, increased susceptibility for infections and in the long-term potentially lymphoma and non-melanoma

Fig. 1. Overview of therapeutic options in Crohn's disease (based on ECCO [European Crohn's and Colitis Organisation] Guidelines 2016, modified [8]). The acute therapy depends on the location and the degree of inflammatory activity. The sacrifice of nicotine should be recommended to each patient [60]. The requirement for long-term immunosuppression depends on individual risk factors (young age at diagnosis, demand for steroids

during the first flare, the presence of an ileocolonic disease or perianal disease and no sufficient mucosal healing). Surgical options should be considered during therapeutic management. * Alpha-betic sequence; Selection of the substance according to the individual risk-benefit ratio, patient's preferences and economic aspects. PPI, proton-pump inhibitor; TNF α , tumor necrosis factor alpha.

skin cancer [8, 32]. The strongest risk factor for azathioprine-induced acute pancreatitis is smoking [15]. Because of convincing data for biologicals, immunomodulators were less frequently used in recent years [32]. On the one hand, the SONIC study could demonstrate that the anti-TNF α antibody infliximab is superior to azathioprine therapy in maintenance of remission in CD. On the other hand, the combination of both substances was even more effective, which encourages the use of immunomodulators as combination partners [33]. Moreover, a phase II study was able to demonstrate that a delayed release formulation of 6-mercaptopurine is able to improve the ratio between efficacy and adverse side effects [34].

Methotrexate not only inhibits the dihydrofolate reductase but also inhibits cytokine and eicosanoid synthesis [35]. For the subcutaneous or intramuscular application, a probably positive effect concerning induction and maintenance of remission in patients with CD has been demonstrated [36, 37]. For these indications, methotrexate is an alternative after the usage of thiopurines and biologicals [8]. Controls of liver enzymes are necessary during therapy.

Anti-TNF α Agents

Several anti-TNF α antibodies have been approved for clinical use in CD (infliximab [38], adalimumab [39, 40] in the United States and Switzerland along with certolizumab [41]). These substances induce apoptosis of CD4⁺-T-cells and macrophages and influence the cytokine milieu by

binding to soluble and membrane-bound TNF [42]. Due to the lack of an Fc region in certolizumab, some effects are only observed with adalimumab and infliximab [43].

Anti-TNF α antibodies are efficient in inducing and maintaining remission in patients with CD [38–41]. According to some meta-analyses, there are no relevant differences in therapeutic efficacy between adalimumab and infliximab, whereas certolizumab might be less effective [44–46]. However, there are no head-to-head studies, which make a direct comparison difficult [8]. As with other substances, only a subgroup of patients profits clinically and endoscopically from a therapy with anti-TNF α antibodies. For approximately one third of the patients, a complete remission can be induced and only in half of these patients remission can be maintained for at least 12 months [47].

Rarely, anti-TNF α antibodies can induce an allergic reaction. The main side effect is a probably increased risk for infections, especially a reactivation of latent tuberculosis [7, 13]. There is also a theoretically increased risk for malignant diseases; however, a final proof is still absent [48].

Anti-TNF α antibodies are well suited for the maintenance of remission and are potent inducers of remission in steroid-refractory or steroid-intolerant patients. Other fields of possible applications are therapy of extensive CD, arthritis associated with CD, localized but severely active ileocaecal CD or fistulating disease [8].

A significant improvement in clinical and endoscopic outcome was observed by the adaption of the dose of adali-

Fig. 2. Endoscopic response to vedolizumab in a patient with Crohn's disease. Patient data: female, 33 years old. **a** Without vedolizumab and **(b)** after 6 months vedolizumab.

mumab not only symptom-driven but also based on CRP and calprotectin (CALM-Study) [18]. In the case of insufficient response or loss of efficacy, it can be worth trying another anti-TNF α antibody. In a placebo-controlled multicenter study with patients being affected by adverse effects of infliximab or insufficiently controlled disease under this substance, adalimumab was able to induce remission (adalimumab vs. placebo: 52 vs. 34%) [49]. However, changing from infliximab to adalimumab in a patient with sufficiently controlled CD might lead to worse outcomes [50]. For infliximab, the SONIC study was able to show that the efficacy can be increased by a combination with azathioprine [33]. However, the potential risks could also increase during combination therapy [51].

Available data for infliximab suggest that the therapeutic effects of infliximab biosimilars are equivalent to the infliximab originator [8]. The development of biosimilars will make this substance class economically more attractive [52]. Biosimilars for adalimumab are expected in the last quarter of 2018.

Vedolizumab

Vedolizumab is an antibody, which inhibits the homing of T cells to the gut by interaction with $\alpha 4 \beta 7$ -integrins [53]. This mechanism is more specific than that of natalizumab, which inhibits $\alpha 4$ -integrin and is able to cause progressive multifocal leukoencephalopathy in patients with CD [54]. In some countries (e.g., USA), natalizumab is approved for therapy-refractory CD. The GEMINI-2 study was able to demonstrate the superiority of vedolizumab to induce and maintain remission compared to placebo in CD over 2 years of observation [55]. Recently, the positive clinical effect was also observed in a meta-analysis. A disadvantage is the pronounced latency of therapeutic effect (6–12 weeks) in CD, which makes vedolizumab less attractive for induction of remission. Patients with a failed anti-TNF α therapy showed less response to vedolizumab than anti-TNF α naïve pa-

tients and it took even more time until clinical remission was superior to the placebo group [56]. A typical side effect of vedolizumab is nasopharyngitis; however, in general, this substance seems to be well tolerated [57]. This is probably a result from the mainly local mechanism of action (Fig. 2).

Ustekinumab

Ustekinumab is a monoclonal antibody, which inhibits the p40 subunit of interleukin-12 (IL-12) and IL-23. These cytokines mainly interact with type 1 T-helper cells (Th1) and Th17 cell subsets [58]. In the UNITI-1 and UNITI-2 studies, clinical remission and a clinical response induced by Ustekinumab was observed in active CD. Moreover, levels of CRP and calprotectin were reduced on administration of therapy. The IM-UNITI study was able to demonstrate the potential of Ustekinumab for maintenance of remission over 44 weeks [59]. In the UNITI trials and in patients with psoriasis, no relevant major side effects were observed so far. However, potential adverse effects by immunosuppression cannot be excluded at that point.

New Substances in the Pipeline – Reason to Hope

CD is heterogenous and only a part of the patients will respond to approved substances. Moreover, a remarkable number of patients show secondary non-response after a variable duration of time. These limitations substantiate the strong need for new potent and well-tolerated drugs.

Mongersen is an antisense nucleotide, which binds the mRNA of SMAD7 (Mothers against decapentaplegic homolog 7; https://www.genenames.org/cgi-bin/gene_symbol_report?hgnc_id=HGNC:6773) [60]. This in turn strengthens the TGF β signaling pathway, which exerts predominantly anti-inflammatory effects [61]. After very promising results were achieved in a phase II study, [62] the currently performed phase III was not able to detect

any advantage in an interim analysis in comparison to placebo [63]. Therefore, this study was interrupted and we have to wait for subgroup analyses.

The orally delivered substance filgotinib is an inhibitor of Janus-kinase 1 (JAK1) [64]. In a randomized, double-blinded phase II trial, filgotinib was effective in the induction of clinical remission, but it failed to reach an endoscopic improvement ($n = 174$). Filgotinib seems to increase the risk of infections [65]. Two phase III studies are currently recruiting patients for further investigation of therapeutic and potential side effects (NCT02914600, NCT02914561). Upadacitinib (ABT-494) is another oral JAK1 inhibitor. A randomized, double-blind study was able to demonstrate the potential of Upadacitinib to induce clinical and endoscopical response in patients with moderate-to-severe CD ($n = 220$). The side effects were similar to other JAK inhibitors. Phase III trials have been started (NCT03345836, NCT03345849, NCT03345823) [66].

Unlike ustekinumab, risankizumab inhibits the p19 subunit of IL-23, and thus the cytokine IL-12 is not affected. In a randomized, double-blinded phase II trial, risankizumab was able to induce clinical remission in patients with moderate-to-severe CD. There were no relevant differences concerning adverse effects between the placebo and the treatment group [67]. Currently, phase III trials with risankizumab in CD are recruiting (NCT03105128, NCT03104413, NCT03105102).

The manipulation of the intestinal microbiome in CD represents another interesting therapeutic approach. While substantial data for probiotics or fecal microbiome transfer in CD is still missing, [68] the application of rifaximin could have positive effects [69]. Rifaximin has limited effects on the intestinal microbiome but could also induce effects on epithelial cells, for example, by antagonizing the TNF α -receptor [69]. In a randomized, double-blind phase II trial with 402 patients, the administration of 1,600 mg Rifaximin per day induced clinical remission in patients with moderately active CD [70]. Only a few patients withdrew therapy due to side effects, and there were no significant differences concerning adverse effects between placebo and treatment groups. The effect of rifaximin is further investigated in phase III studies (NCT02240108, NCT02240121, NCT03185611).

Individualized Therapy – The Agony of Choice

To make a decision for or against an immunosuppressive therapy after the first flare in CD is not simple for each patient. Not only therapeutic side effects and the po-

tential therapeutic benefit must be considered but also risk factors for the individual disease course. According to different studies, young age at diagnosis, demand for steroids during the first flare and the presence of an ileocolonic or perianal disease are risk factors for a severe or complicated disease course [8, 71, 72]. Moreover, the failure of reaching mucosal healing is also a negative predictor [8, 73]. To decide if the individual patient could profit from a more aggressive “top-down” strategy, these risk factors have to be taken into account [74].

Due to the development of new substances in the recent past, we are now in the pleasant situation to offer several potent substances to our patients for maintenance of remission. Indeed, it is difficult to decide which of these drugs is optimal for the individual patient. Some meta-analyses compared the therapeutic efficacy and observed a potential superiority of the anti-TNF α antibodies adalimumab and infliximab [44, 45]. However, due to differences in the patient populations and lack of head-to-head studies, no general recommendation for one substance against others is justified. Instead, the disease history and risk factors, as well as the patient’s preferences and local costs must be considered for an optimized individual therapy management.

The mentioned general orientation points are helpful but not sufficient in the clinical routine for the specific patient. It would be interesting to know the response of the patient before starting therapy. This knowledge would spare a lot of time, especially when drugs with a pronounced latency of therapeutic effect, such as vedolizumab, are applied. Moreover, side effects by individual ineffective substances could be avoided.

Atreya et al. [76] were able to test *a priori* the response to anti-TNF α antibodies and vedolizumab. Here, patients underwent a fluorescence endomicroscopy during colonoscopy with the staining of membrane-bound TNF α or $\alpha 4\beta 7$ -integrin. In patients with a high density of these receptors on the epithelium, the probability of a clinical response was significantly higher [76]. Greater studies will have to confirm these results, yet we are convinced that this is a promising approach.

Fistulae – Prominence of Medical Therapy

Approximately half of the patients with CD are affected by one or more fistulas. These are mainly localized at the perianal region but can also occur at other sites (e.g., enterocutaneous, enteroenteric) [77].

Concerning perianal fistulae, a simple form is differentiated from complex perianal fistulae. For sufficient as-

assessment of the fistulae and optimal therapy, a pelvis MRI scan is recommended. In the case of a symptomatic simple perianal fistula, a combination of an antibiotic therapy (ciprofloxacin and/or metronidazole) and Seton placement is the standard therapy. Some meta-analyses were able to demonstrate a positive effect of these antibiotic therapies; however, this impact endures only for a limited period of time [77, 78].

In patients with simple perianal fistulas and therapy failure or in patients with complex perianal fistulae, the addition of infliximab or adalimumab and more extensive surgical methods are recommended [77, 79]. For infliximab, a randomized placebo controlled study showed a significant improvement concerning the complete closure of fistulae after 54 weeks (36 vs. 19%) [80]. The addition of ciprofloxacin to adalimumab led to a higher fistula closure rate than adalimumab alone [81].

However, still a remarkable proportion of fistulae cannot be treated sufficiently. Therefore, new avenues have been explored in the therapy of fistulae. One promising approach is the local application of mesenchymal stem cells (MSC). Due to their low immunogenic potential, which is partly ascribed to the weak presentation of antigens by their major histocompatibility complex (MHC-I) and no expression of MHC-II, allogeneic transplantations without human leukocyte antigen matching are also possible [82]. In a randomized, double-blind, placebo-controlled study, the local application of MSC led to a significant higher amount of combined (clinical plus radiological) remission than saline solution, which was used as placebo (50 vs. 34%; $n = 212$). Here, the number of all adverse events was similar in both study groups, whereas the treatment-related adverse events were higher after ap-

plication of placebo than MSC (29 vs. 17%). The main adverse local effects were anal abscess and proctalgia [83]. A recent meta-analysis, where most of the patients derived from the study above, showed that the therapeutic success is greater in new fistulas than in chronic fistulas, and the usage of adipose-derived MSC seems to be superior to those derived from the bone marrow [84]. In summary, the local application of MSC seems to be an attractive therapy of fistulae; however, further work has to address the standardization of these cells [85], and potential risks like carcinogenesis cannot be excluded at this point of time [82].

Conclusion

In the years gone by, several new targeted substances have enriched the therapeutic options in CD. Due to some drugs with promising results in phase II trials (filgotinib, rifaximin, risankizumab, upadacitinib) we are looking into the future with cautious optimism. As a result of the growing number of therapeutic agents, an individualized therapy will become more and more important. The local application of MSC might improve fistula healing. We believe that the optimization of drug formulations, nutrition and the specific manipulation of the intestinal microbiome represent further important research topics in the upcoming years.

Disclosure Statement

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