Ulcerative Colitis

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Key Words

Ulcerative colitis · Anti-integrins · Janus kinase inhibitor

Abstract

Background: Ulcerative colitis (UC) is a chronic inflammatory bowel disease that is chronically present in patients throughout their lives. Hence, the chronic nature of the disease invariably requires continuous medical treatment. Advances in medical therapy over the last decades and current developments offer increasing options and are closely associated with a better life quality in patients.

Summary: Recent developments in understanding the pathogenesis of UC are discussed. The current standard therapeutic regimens are outlined and recent developments and upcoming strategies introduced. **Key Points:** (1) Environmental factors that are yet to be defined contribute to the pathogenesis of UC. (2) An accelerated step-up therapy represents the current standard in UC. (3) Anti-integrins represent the most recently introduced pharmacological class in the therapy of UC. (4) Novel strategies including Janus kinase inhibitors are in the near future.

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Epidemiology of Ulcerative Colitis

Ulcerative colitis (UC) and Crohn's disease represent the 2 main entities of chronic inflammatory bowel diseases. The pathogenesis of UC is yet incompletely

understood. Hence, currently, there is no cure to treat this condition. While over 200 risk loci have been identified for inflammatory bowel diseases, only about one fourth of disease occurrences can be explained genetically [1, 2]. Considering in parallel the increasing incidence of inflammatory bowel diseases over the last decades, it is more likely that changes in our environment contribute to this increase [3]. Although not entirely deciphered, environmentally induced changes in our intestinal microbiota composition can be presumed to play a significant role. Experimental data strongly suggest that, in particular, the intestinal microbiota that is present early in life engraves the mucosal immune system, thus causing intestinal homeostasis [4]. With these conceptual considerations in mind clinical trials were initiated where fecal microbiota transplantation (FMT) served as treatment for UC. In the 2 placebo-controlled, randomized trials, the primary endpoint was not met [5, 6]. Nevertheless, 2 observations were of interest for future developments: (1) the diversity of the intestinal microbiota increased in patients with an amelioration of disease (independent of the treatment arm) and (2) the donor and hence the composition of the donor's intestinal microbiota seems to play a significant role [5, 6]. What are the conclusions drawn from these trials? Will there be FMT for UC patients? It is at this point very unlikely that FMT will enter routine treatment for UC patients; however, it is expected that a better defined microbiota-based therapy will play a role in future treatment.

Standard Therapy

Induction of Remission

The first strategy to induce remission in UC is the administration of mesalazine in a systemic, local or even combined manner [7, 8]. The key to success using this strategy is to use the maximum dose and take advantages of the combined systemic and local therapy [9]. If this is not resulting in the induction of remission, systemic steroids should be introduced. In moderate disease, 40 mg/day might suffice in moderate to severe disease, and 1 mg/kg body weight becomes mandatory [7, 8]. In a majority of cases, remission can be successfully introduced by applying this strategy. If steroid-free remission cannot be induced, 2 scenarios are possible:

- (1) The patient with this disease shows signs of recovery; however, the disease is steroid-dependent. In this case, an immunosuppressive strategy is used for treatment. As a first step and as part of this strategy, a thiopurine is used. If this is not tolerated or is found to be ineffective, the integrin-antagonist, vedolizumab, or a TNF-antibody are used as alternative treatment plans; this is discussed in more detail below.
- (2) The disease is steroid refractory. In this case, after trying steroid intravenously, 2 options are available: (1) the classic strategy cyclosporine is introduced [10] or (2) a TNF-antibody that has been proven to be not inferior to cyclosporine treatment is administered [11].

In rare cases, till today, disease progresses faster than anticipated and cannot be controlled by any conservative strategy. Under these circumstances, surgery is the preferred option.

Maintenance of Remission

The primary goal of medical therapy in remission of disease is to achieve a steroid-free condition. As mentioned earlier, this can be maintained by mesalazine that can be administered either systemically or locally [7–9]. In case of mesalazine intolerance, the probiotic *E. coli* Nissle 1917 has been shown to be equally efficacious in maintaining remission [12]. If neither mesalazine nor *E. coli* Nissle 1917 treatment is able to taper steroids completely, a long-term immunosuppressive strategy should be introduced. In the first step, a thiopurine will be introduced. In case the patient fails to respond to thiopurine therapy, the administration of either TNF-antibodies or the integrin-antagonist vedolizumab can be chosen as the next course of treatment. In selected cases, a combination therapy of a biological and thiopurine might be required. Here, the UC Success trial could demonstrate an addi-

Fig. 1. Currently approved medical treatment for patients with UC.

tional effect by combining a thiopurine with infliximab when compared to either treatment alone [13]. If the medical strategies do not result in a reasonable life quality due to uncontrolled disease activity or due to side effects, surgery should be offered [7, 8].

Figure 1 summarizes the currently approved therapeutic options for UC.

Recent Developments

Methotrexate has been proven effective for patients with Crohn's disease but was never evaluated in patients with UC. The recent METEOR trial by the GETAID group fills this gap [14]. Here, patients with steroid-dependent UC were randomly assigned to receive either placebo or methotrexate (25 mg/weekly) for 24 weeks. The primary endpoint achieved was steroid-free remission as defined by a Mayo score ≤ 2 with no item > 1 , hence including clinical as well as endoscopic features, and complete withdrawal of steroids at week 16. In this trial, methotrexate was not superior to placebo in terms of the primary endpoint of the study [14]. Notably, one secondary endpoint was attained, namely, methotrexate-induced clinical remission without steroids at week 16. However, all other 8 secondary endpoints were not achieved; hence, the overall results of this study underline that methotrexate is not efficacious in UC [15].

As already introduced above, the anti-integrin-strategy vedolizumab targeting $\alpha 4\beta 7$ was introduced 2 years ago and is about to enter the next generation of guidelines in UC as well as with regard to Crohn's disease [16, 17]. The integrin $\alpha 4\beta 7$ enables the infiltration of immune cells into the intestinal wall and so represents an almost gut-specific approach [18]. By blocking $\alpha 4\beta 7$ the therapeutic effect observed is mediated by the inhibition of the infiltration of inflammatory cells into the tissue; however, all inflammatory cells that had entered this site before can still mediate inflamma-

Table 1. Summary of relevant studies

Trial name	Aim	Number of patients	Primary endpoint	Results	p value	Author, year
Meteor	Evaluate efficacy of parenteral methotrexate (MTX) in steroid-dependent UC	111	Steroid-free remission week 16 (Mayo ≤ 2 , no item >1) and complete steroid withdrawal	31.7% MTX versus 19.6% placebo (95% CI -4.0 to 28.1%)	0.15	Carbonnel et al. [14], 2016
UC success	Evaluate the comparative efficacy and safety of infliximab and azathioprine therapy alone or in combination for UC	239	Corticosteroid-free clinical remission at week 16	39.7% infliximab + azathioprine versus 22.1% infliximab versus 23.7% azathioprine	0.017 combo versus Infliximab 0.032 combo versus azathioprine	Panaccione et al. [13], 2014
–	Compare the efficacy and safety of infliximab and ciclosporin in patients with acute severe UC	115	Treatment failure defined by the absence of clinical response at day 7	60% ciclosporin versus 54% infliximab (absolute risk difference 6%; 95% CI -7 to 19)	0.52	Laharie et al. [11], 2012
Gemini 1	Efficacy of vedolizumab in induction therapy	374	Reduction of Mayo score of at least 3 points and a decrease of at least 30% from baseline; decrease in rectal bleeding score of at least 1 point or an absolute rectal bleeding subscore of 0 or 1	47.1% vedolizumab versus 25.5% placebo (95% CI 11.6 – 31.7)	<0.001	Feagan et al. [16], 2013

tion. The lifespan of these cells averages up to 60 days and this is the reason for a delayed onset of disease amelioration. Nevertheless, this strategy is highly specific and entirely different with regard to the mechanism of action when compared, for example, to TNF-antibodies. Hence, this strategy is a valuable addition to the toolbox of IBD therapy. In line with this, the GEMINI trials indicate therapeutic efficacy for UC as well as Crohn's disease [16, 17]. Although a different strategy, vedolizumab has been proven to be more effective in the treatment of TNF-antibody-naïve patients [16, 17]. The main studies discussed above are summarized in table 1. In addition, figure 3 provides a gradual progression from health to severe inflammation in UC.

Future Perspective for Novel Therapies

What novel strategies are on the horizon for UC? Within the class of vedolizumab, etrolizumab, which is a sole $\beta 7$ antagonist, has shown efficacy in phase II trials and is currently being investigated in a broad phase III study program [19]. Etrolizumab represents just one out of numerous strategies pointing to this direction. There is no doubt that vedolizumab will get additional members to this class over the next years.

Additionally, an entirely new class for UC is in view – the Janus kinase (Jak) inhibitors. Tofacitinib has been investigated in 2 phase III randomized-controlled trials (OCTAVE) in UC. Here, tofacitinib (10 mg b.i.d.) was tested in a 4:1 randomization against placebo. The primary endpoint was remission in week 8. The primary endpoint in these trials was achieved and it showed again, similar to vedolizumab, that tofacitinib is more efficacious in patients who had not previously received TNF-antibodies [20].

Lastly, over a year ago, biosimilars for infliximab entered the market in Europe and therefore into clinical practice. The biosimilar CT-P13 has been proven to exert similar efficacy in 2 randomized controlled trials for rheumatoid arthritis and ankylosing spondylitis [21, 22] and was subsequently approved for all other indications that infliximab had been previously approved. It is beyond the scope of this article to enter the complex discussion of how to handle biosimilars in clinical practice. For CT-P13, data obtained from real life are now available for UC, indicating, in fact, similar efficacy when compared to the original product [23]. Several questions yet remain unresolved as, for example, how we proceed with the next biosimilar for infliximab that already has received approval by the European authorities. Can we switch in between different biosimilars in a patient frequently or should we rather

Fig. 2. Future perspective on individualized therapeutic algorithms for patients with UC.

Fig. 3. Colon mucosa – health and inflammation. **a** Healthy mucosa, **b** mild inflammation, **c** severe inflammation.

stick on to one product? Who will be able to dictate as to which biosimilar we will have to prescribe in the future? With all these open questions, the physicians should better adhere to the facts; we need scientific proof and hence studies to answer these questions. If answered, as it has been for the first biosimilar, there is no reason not to use it in clinical practice. However, in our opinion, at this point one should stay with one product in a patient and avoid changing, since there is the fear of inducing neutralizing antibodies, thereby limiting clinical efficacy.

Perspective

The content above indicates that after decades of stagnancy, several novel therapeutic strategies have either already entered clinical practice or are likely to enter in the foreseeable future. This is posing novel challenges, since a broader variety of possibilities raise the question as to in which clinical situation and in which patient we should introduce which strategy. A future therapeutic algorithm is shown in figure 2. Preliminary and rather experimental proof-of-concept studies for adalimumab

and etrolizumab indicate that this is feasible. The main task for the next years will be to restructure clinical algorithms and provide predictive markers that will guide the choice for each individual patient.

Key Points

- (1) Environmental factors that are yet to be defined contribute to the pathogenesis of UC.
- (2) An accelerated step-up therapy represents the current standard in UC.
- (3) Anti-integrins represent the most recently introduced pharmacological class in the therapy of UC.
- (4) Novel strategies including Jak inhibitors are in the process of making a difference in the near future.

Disclosure Statement

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