Continuing Medical Education

Treatment Strategies in Inflammatory Bowel Diseases

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Summary

Background: The prevalence of inflammatory bowel disease (IBD) is rising globally. In Germany, these conditions affect 0.7% of the population, or approximately 600 000 patients. Treatment strategies have become more diversified as a result of an improved understanding of disease pathogenesis. It remains unclear how the currently available drugs should best be used in each individual patient.

Methods: This review is based on pertinent publications retrieved by a selective search in PubMed, with special attention to phase III and IV trials and to the German and European guidelines on the treatment of IBD.

Results: An improved understanding of the immunological mechanisms of disease underlies the current treatment strategies in patients with IBD. For those with a complex clinical course, monoclonal antibodies against pro-inflammatory cytokines (TNF, IL-12/IL-23, IL-23) and cell adhesion molecules (α4β7) are of established therapeutic value, along with "small molecules" such as JAK inhibitors and sphingosine-1-phosphate receptor modulators. The numerous studies that have been performed, only a few of which have been head-to-head comparison trials, and the (network) meta-analyses that have been published to date do not imply that any single one of these drugs can be considered the universal, primary treatment for all patients with IBD. In this review, we discuss the available substances and certain important differential-therapeutic aspects of the treatment of IBD.

Conclusion: The treatment of a patient with IBD must take his or her prior treatment(s) and comorbidities into account, along with individual patient characteristics and treatment goals. Rational decision-making is required on the basis of the mechanism of action and the side-effect profile of the various drugs that are now available for use.

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Crohn's disease (CD) and ulcerative colitis (UC) are the two main types of inflammatory bowel disease (IBD). CD is characterized by discontinuous zones of transmural inflammation that can arise in any part of the gastrointestinal tract but are mainly found in the ileocecal junction and the colon. UC, on the other hand, is characterized by a continuous zone of inflammation of the rectal mucosa with variable proximal extension; in rare cases, the terminal ileum is affected as well ("backwash ileitis").

The prevalence of IBD is on the rise around the world. In Europe and North America alone, more than 3.5 million people suffer from IBD (1). Older figures suggest prevalence rates in Germany of 100 to 200 per 100 000 people for CD and 150 per 100,000 people for UC (2). Evaluations of health insurance data from the German federal state of Hesse (an inherently imprecise method) led to an estimated figure of 610 000 persons with IBD in Germany (0.7% of the population); other figures derived from data of

Inflammatory bowel disease

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Prevalence

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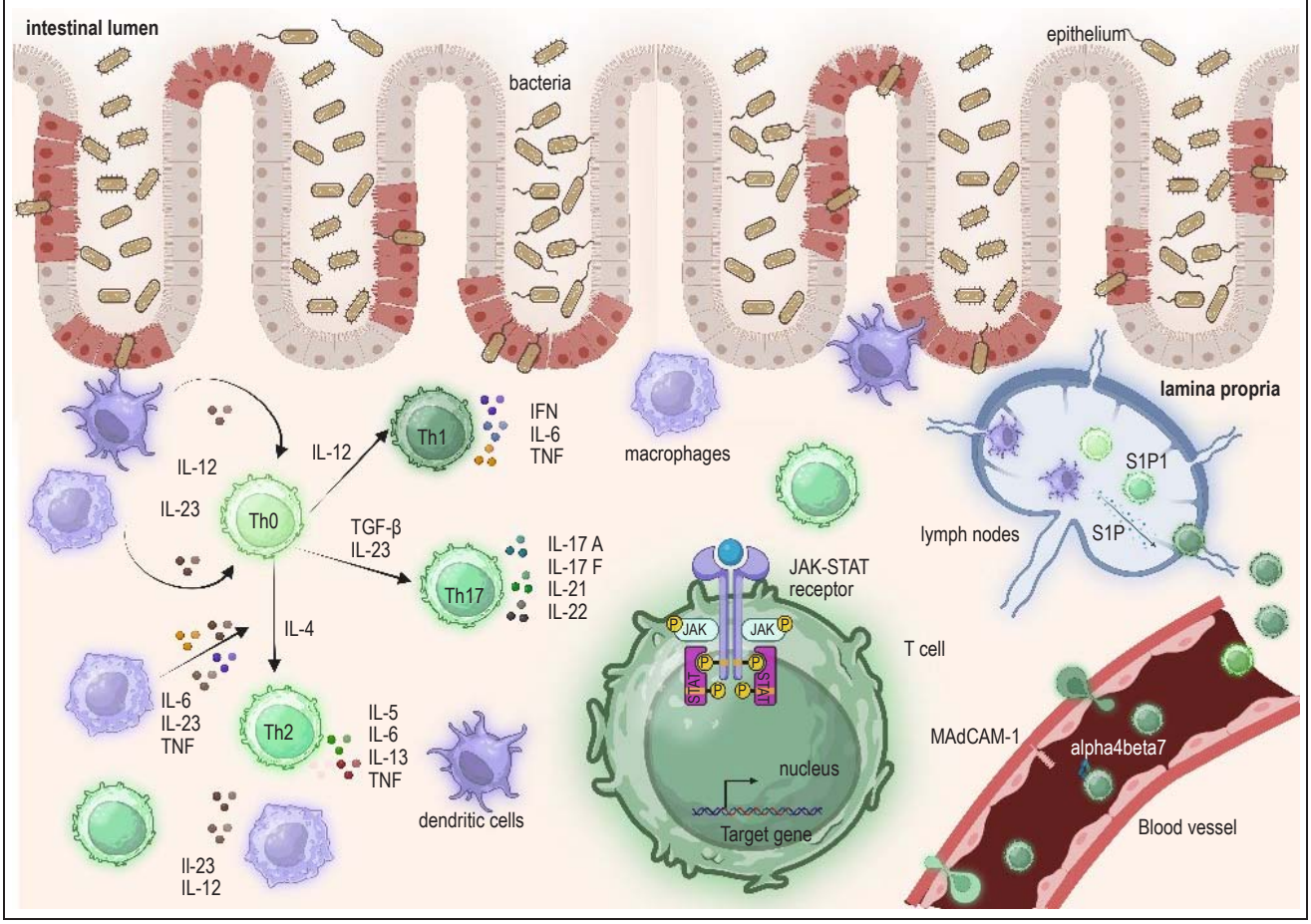
FIGURE



The immune pathogenesis of inflammatory bowel disease

The impaired integrity of the epithelial barrier enables an increased translocation of microorganisms into the intestinal wall. This leads to aberrant activation of innate immune cells, with increased production of pro-inflammatory cytokines by intestinal macrophages and effector T cells (T helper 1 [TH1], TH2 and TH17). After the cytokines bind to their membrane receptor on the corresponding target cells, the intracellular, pro-inflammatory Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway is activated. The excessive immune response is further promoted by the increased migration of immune cells. The recirculation of T cells from the tissue into the blood is mediated by an S1P gradient; T cells migrate from the lymphatic tissue into the efferent lymphatic vessels and onward into the systemic circulation. There, T cells that express integrins (e.g., α4β7) on their surface can interact with ligands expressed on endothelial cells (e.g., mucosal addressin cell adhesion molecule-1" (MAdCAM-1), and this leads to the migration of T cells into the intestine and further perpetuation of inflammation. The illustration was created with BioRender.

the statutory health insurance carriers in Germany reveal a 13% rise in the prevalence of CD and a 29% rise in the prevalence of UC by 2018, compared to 2012 (3). Initial presentations are increasingly seen in persons over age 70. IBD is often thought of as a chronic, progressive disease, with progressive destruction of the intestinal tract and accumulation of various types of damage, yet a study of the Epi-IBD cohort, including persons with a new diagnosis of CD, revealed overall outcomes that were better than expected (4). In 5 years of follow-up, only 22% of patients underwent surgery and 36% were hospitalized for active CD. The disease progressed in 14% of patients with a transition from inflammation without

Rising prevalence

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A chronic progressive disease

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TABLE 1

Nutritional therapy approaches in the treatment of IBD

	Foods not be eaten	Risks in patients with IBD
Ovo-lacto-vegetarian	meat, fish	none
Lactose-reduced	foods containing lactose	none, if sufficient intake of lactose-free products
Gluten-free diet	foods containing gluten	masking celiac disease, constipation, reduced intake of calcium, folic acid, vitamins B and D, iron, zinc, magnesium
Mediterranean diet	reduction of meat and processed foods and moderate consumption of fermented dairy products	none
Vegan	all animal-based foods	low vitamin A, B12, D, zinc, protein intake too low
Paleo diet	potatoes, cereals, meat of domestic animals, juices, sugar, dairy products	low calcium, high fat
Specific carbohydrate diet	disaccharides, potatoes, processed products, cereals, milk, sugar	too little vitamins B and D, calcium, calories
Low FODMAP	mono-, oligo- or disaccharides, fiber, cereals, milk, fruit, and many vegetables	low vitamin B6, thiamine, folic acid and calcium
CD exclusion diet (50 % polymer)	dairy products, gluten, processed foods, soy, corn, potatoes, juices, alcohol, chocolate, coffee	none

CD, Crohn´s disease; FODMAP, fermentable oligo-, di-, and monosaccharides and polyols; IBD, inflammatory bowel disease

penetration or strictures to a complicating penetration or stricture. Among the western European patients in this cohort, 33% were treated with biologic agents, 66% with immunosuppressants, and 56% with 5-acetylsalicylic acid (ASA) preparations, which are no longer recommended in the guidelines.

The data of patients with UC were analyzed analogously (5). Among these patients, only 23% were hospitalized for active UC; 11% were treated with biologic agents, and 29% with immunosuppressants. Thus, the vast majority of patients with IBD whether CD or UC) have a relatively favorable course. The standard drugs (mesalazine and budesonide or steroids) generally suffice.

IBD is a systemic disease whose manifestations can also include inflammatory reactions in the eyes, skin, and joints. Its symptoms include diarrhea, abdominal pain, blood in the stool, weight loss, and fatigue. It can be complicated by intestinal stenosis and fistulization and it elevates the risk of colorectal cancer. Thus, despite the generally good prognosis of IBD, some patients have complex courses with progressively destructive disease. These patients need optimized anti-inflammatory treatment (6, 7).

The etiology of IBD is multifactorial, including genetic, microbial, and environmental factors (e.g., smoking, antibiotic use), ultimately resulting in a heightened intestinal immune response. Impaired barrier function in the gastrointestinal tract promotes the translocation of commensal microorganisms (8), which are, in turn, taken up by immune cells of the innate immune system; this leads to excessive production of pro-inflammatory cytokines (e.g., interferon [INF]-γ, tumor necrosis factor [TNF-α]), and interleukins including IL-12 and IL-23). As a result, more immune cells are recruited into the mucosa, and the intestinal inflammation is perpetuated (9). These mechanisms have provided targets for directed therapies that selectively inhibit major signaling pathways of the inflammatory process *(Figure)*. For a detailed description of the immune pathogenesis of IBD, see the *eBox*.

Lifestyle modification and nutritional interventions

Lifestyle changes, particularly relating to diet, are increasingly being used as treatment for IBD, as they accord well with patients' needs and are safe and easily accessible. In pediatrics, exclusive enteral nutrition (EEN) has been established as the first line of treatment to induce remission in CD (7), after large systematic

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TABLE 2

Efficacy and side effect spectrum of advanced therapeutic agents for inflammatory bowel disease

Substance	Target structure	Indication	(Co-)primary endpoint(s)	Attainment of endpoints			Typical side effects (selected)	Study Reference
				Treatment	Placebo	p-value		
Infliximab	TNF-α	CD	response rate at week 2 clinical remission at week 30	58 % 45 %	– 21 %	– 0.0002	Infections infusion or injection reactions psoriatiform lesions TB reactivation lupus-like syndrome slightly increased risk of melanoma	ACCENTI [e8]
		UC	clinical response at week 8	69 %	37 %	< 0.001		ACT 1. ACT 2 [e9]
Adalimumab	TNF-α	CD	clinical remission at week 4	36 %	12 %	0.001		CLASSIC-I [e10]
		UC	clinical remission at week 8	18.5 % (ULTRA 1) 16.5 % (ULTRA 2)	10 % (ULTRA 1) 9.3 % (ULTRA 2)	0.031 (ULTRA 1) 0.019 (ULTRA 2)		ULTRA 1. ULTRA 2 [e11. e12]
Golimumab	TNF-α	UC	clinical response at week 6	54.9 %	30.3 %	< 0.0001		PURSUIT-SC [e13]
Vedolizumab	α4β7-Integrin	CD	clinical response and clinical remission at week 6	31.4 % (response) 14.5 % (remission)	25.7 % (response) 6.8 % (remission)	0.23 0.02	upper respiratory tract infections headache myalgia	GEMINI 2 [e14]
		UC	clinical response at week 6	47.1 %	25.5 %	< 0.001		GEMINI 1 [e15]
Ustekinumab	IL-12/ IL-23-p40	CD	clinical response at week 6	51.7 % (UNITI-2)	28.7 % (UNITI-2)	< 0.001	upper respiratory tract infections headache dizziness	UNITI-2 [e16]
		UC	clinical remission at week 8	15.6 %	5.3 %	< 0.001		UNIFI [e17]
Risankizumab	IL23-p19	CD	clinical remission, patient-reported outcomes (PRO) and endoscopic response at week 12	45.2 % (cl. remission) 43.5 % (PRO) 40.2 % (endoscopic)	24.6 % (cl. remission) 21.7 % (PRO) 12 % (endoscopic)	< 0.0001	nasopharyngitis headache	ADVANCE [e18]
Tofacitinib	pan-JAK	UC	clinical remission at week 8	18.5 % (OCTAVE 1) 16.6 % (OCTAVE 2)	8.2 % (OCTAVE 1) 3.6 % (OCTAVE 2)	0.007 < 0.001	infections herpes zoster herpes simplex anemia neutropenia lymphopenia hypercholesterolemia cardiovascular events (see esp. Red Hand Letter)	OCTAVE [e19]
Filgotinib	JAK-1	UC	clinical remission at week 10 (biologics-naïve)	26.1 %	15.3 %	0.0157		SELECTION. [e20]
Upadacitinib	JAK-1	UC	clinical remission at week 8	26 %	5 %	< 0.0001		U-ACHIEVE [e21]
		CD	clinical remission and endoscopic response at week 12	49 % (cl. remission) 46 % (endoscopic)	29 % (cl. remission) 13 % (endoscopic)	< 0.0001 < 0.0001		U-EXCEL. unpublished [e22]*
Ozanimod	S1P1/5	UC	clinical remission at week 10	18.4 %	6 %	< 0.001	bradycardia hypotension infections leukopenia	True North [e23]

Phase III induction studies. The primary endpoint is stated as specified. In studies with different dosages, the results of the most effective dosage are presented.
Because of differing patient populations with different proportion of biologic-naïve patients and different endpoint criteria, the trial findings are only comparable to a limited extent.
CD, Crohn's disease; JAK, Janus kinase inhibitors; TNF, tumor necrosis factor; UC, ulcerative colitis

reviews repeatedly showed its non-inferiority to systemic steroid treatment. The obvious limitations of EEN are the difficulty of adhering to it and its incompatibility with normal social life beyond the short term (11). Concepts have been introduced to circumvent the acceptance problems and to mimic the assumed mechanisms of action, in particular, by avoiding potentially pro-inflammatory food components that can damage to the intestinal mucosa (12) and making use of the modulatory effect on the microbiome to lessen the burden of pro-inflammatory microorganisms (13). One such concept is the Crohn's Disease Exclusion Diet (CDED), in which potentially pro-inflammatory foods (gluten, dairy products, animal fats, processed meat, and all highly processed foods) are excluded. This diet combined with 50% PEN (partial enteral nutrition) (CDED + PEN) led to remission at 6 weeks in 70% of participating children and adolescents and meets with greater acceptance among patients than EEN (14). In a pilot study in adults with CD, CDED + PEN and CDED alone yielded clinical remission rates of 68% and 57%, respectively, at six weeks, with 80% still in remission at the end of the 24-week observation period (15). The low FODMAP diet (FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides and polyols), which has been used successfully in the symptomatic treatment of irritable bowel syndrome, with response rates of 50–80%, has also lessened the symptom burden of IBD in clinical studies, but without endoscopically demonstrated reduction of disease activity (16). The details of these diets are shown in *Table 1*. It should be noted that targeted nutritional therapy for patients with IBD must be closely supervised by a specially trained nutritionist and accompanied by strict medical monitoring and guidance; its risks include macro- and micronutrient deficiencies, nutritional and eating disorders, and psychosocial dysfunction.

The current treatment of IBD

The treatments that are now approved for IBD *(Table 2)* help many patients, yet there remain sizeable subgroups of patients in which they are insufficiently effective or must be discontinued because of adverse side effects. The central goal of treatment for patients with CD and UC is steroid-free remission, because repetitive or long-term steroid treatment can have serious adverse effects, both acute and chronic. The principles of therapeutic decision-making are summarized in the guidelines of the DGVS (7, 17) and the European Crohn's Colitis Organization (ECCO) (18, 19). The German guidelines deliberately refrain from assigning ranks or priorities to drugs in such a way as to dictate specific decisions in certain cases. Rather, emphasis is placed on individualized treatment, in consideration of personal treatment goals and in view of the potential complications or contraindications. Nonetheless, in this review, we report the strength of each drug recommendation in the German guidelines, in order to give our readers the broadest possible informational basis for decision-making. These reported strengths reflect the strength of the evidence underlying each recommendation, including the consistency of the study findings, the clinical relevance of the endpoints and their importance to patients, the risk-benefit ratio, patient preferences, and ease of implementation. Recommendation grade A (RG A) corresponds to a strong recommendation, recommendation grade B (RG B) to an otherwise not qualified recommendation, and recommendation grade 0 (RG 0) to an open recommendation ("may be considered/may be omitted").

Ulcerative colitis

Aminosalicylates (5-ASA) are the cornerstone of conventional drug treatment for uncomplicated UC. Many patients can be successfully treated with them over the long term. The optimal form of application depends on the pattern of involvement; it should generally include treatment per rectum (≥ 1 g/d), as this yields high local concentrations of the drug. While isolated proctitis can be treated with suppositories alone (RG A), foams and enemas are suitable for proctosigmoiditis, as they enable more proximal application of the active substance. Additional oral 5-ASA therapy (once per day) at a sufficiently high dosage above 3 g/d, in granule or pellet form, is standard treatment for left-sided colitis and pancolitis (RG A).

If there is an insufficient response to induction therapy with 5-ASA, systemic steroid bolus therapy is indicated at an initial dose of 0.5–1 mg/kg bw/d prednisolone equivalent, regardless of the pattern of involvement (RG A). It is important to aim for a steady dose taper leading to discontinuation within 10–12 weeks; repeated steroid treatments (e.g., twice a year) should be avoided, and a need for them indicates rather that more complex therapies should be initiated. For mild to moderate disease activity, budesonide MMX (9 mg/d) can be used as an alternative, particularly in left-sided colitis (RG B), with fewer systemic side effects. Once remission has been achieved (RG A), 5-ASA monotherapy with steroids should be continued for at least two years (RC B) and can be used over the long term (RC B) to prevent colon cancer. In maintenance therapy, the oral 5-ASA dose can be reduced, although

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Ulcerative colitis

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TABLE 3

Aspects to be considered in determining the optimal individualized treatment*

	Anti-TNF-AB	Integrin-AB	IL12/IL-23-AB	JAK inhibitor	S1PRM	Calcineurin inhib.
CD/UC	+ / +	+ / +	+ / +	+ / +	n. a. / +	– / + (n. a.)
Very high activity (CD/UC)	+ / +	– / –	(+) / (+)	(+) / (+)	– / –	– / +
Maintenance of remission (CD/UC)	+ / +	+ / +	+ / +	+ / +	– / +	– / –
Postoperative recurrence prophylaxis (CD)	+	(+)	(+)	n. a.	n. a.	–
Extraintestinal manifestations (EIM) CD/UC	+ / +	– / –	(+)	+ / +	–	n. a.
Psoriasis	+	–	+	+	–	–
Comorbidities, especially prior neoplasia	(+)	+	+	–	(+)	–
Cardiovascular comorbidities (e.g. heart failure)	–	+	+	–	–	–
Pregnancy/desire to become pregnant	+	(+)	(+)	–	–	(+)

*This table provides no more than a rough assessment of the use of various therapeutic agents in IBD.
The characteristics of the individual patient in the specific situation at hand are always an important consideration.
+ effective in this situation in large-scale studies and suitable according to the authors' assessment, (+) second-choice treatment approach,
– less suitable or not suitable in this situation.
AB, antibody; CD, Crohn's disease; IL, interleukin; JAK, Janus kinase; n.a., not approved;
S1PRM, sphingosine-1-phosphate receptor modulators; TNF, tumor necrosis factor; UC, ulcerative colitis

a dose of ≥ 2 g/d has been shown to be more effective in maintaining remission. In the event of a steroid-refractory or steroid-dependent course (i.e., absence of response to steroids or inability to get off steroids), further treatment can be with TNF antibodies (adalimumab, golimumab, infliximab; the last is preferably combined with a thiopurine), mirikizumab, ustekinumab or vedolizumab, calcineurin inhibitors (ciclosporin, tacrolimus [off-label]), JAK inhibitors (filgotinib, tofacitinib, upadacitinib [not yet included in the guideline, because only recently approved (20)]), or the sphingosine-1-phosphate receptor (S1P) modulator ozanimod (EG B). With the exception of calcineurin inhibitors, all of these drugs are also suitable for maintaining remission (EG B). Etrasimod is expected to be approved as an S1P modulator (21) for the treatment of UC in late 2023.

A special situation arises for azathioprine/6-mercaptopurine. This immunosuppressant can be used as monotherapy to maintain remission in patients with UC and steroid-dependent disease course, possibly enabling the discontinuation of steroids.

In fulminant, steroid-refractory acute, severe UC, only infliximab or ciclosporin (or tacrolimus) are recommended in the guidelines. In such cases, proctocolectomy must be considered at an early stage in interdisciplinary discussion with a surgeon who has experience in the treatment of IBD.

Crohn's disease

In contrast to UC, 5-ASA preparations have no proven value in CD (RG 0) (7, 18). They are not recommended for induction therapy or for maintenance of remission, yet they are nevertheless often used. The standard treatment for mild ileocecal or right-sided colonic involvement is budesonide (9 mg/d) (RG A). In cases of high inflammatory activity and extensive small bowel involvement, systemic steroid bolus treatment is necessary at an initial dose of 1 mg/kg bw with a maximum of 75 mg prednisolone equivalent/day (RG A). Just as in UC, the repetitive use of steroids should be avoided (RG A); in case of frequent relapses, newer drugs should be used to maintain remission. For steroid-dependent or steroid-refractory courses, anti-TNF antibodies (infliximab and adalimumab), ustekinumab, and vedolizumab

Steroid bolus therapy for ulcerative colitis

If there is an insufficient response to induction therapy with 5-ASA, systemic steroid bolus therapy is indicated at an initial dose of 0.5–1 mg/kg bw/d prednisolone equivalent, regardless of the pattern of involvement (RG A).

5-ASA preparations in Crohn's disease

In contrast to ulcerative colitis, 5-ASA preparations have no proven value in Crohn's disease (RG 0) (7, 18). They are not recommended for induction therapy or for maintenance of remission.

are available; all of these drugs can also be used to maintain remission (RG B). Extensive small bowel involvement may also be a reason for early use of these drugs (RG 0). The JAK inhibitor upadacitinib and the interleukin-23 antibody risankizumab have only recently been approved and have not yet found their way into the guidelines. Upadacitinib may have therapeutic potential for patients in which various biologic agents have lost their efficacy (22); however, its potential side effects must be considered, particularly in patients at high risk.

The drug of first choice for fistulizing Crohn's disease is infliximab, as this is the only drug whose use is supported by the findings of a prospective, randomized trial in which the primary endpoint was fistula closure (RG B) (23). Combining infliximab with a thiopurine should always be considered in a young patient, as the combination enhances the therapeutic effect and helps prevent the development of neutralizing autoantibodies against infliximab, which is otherwise very frequent; these benefits, must be weighed against the risk of lymphoma after prolonged treatment, which must be mentioned when discussing this potential combined treatment with the patient. For isolated ileocecal involvement without response to steroids, the so-called LIR!C study has convincingly shown that surgical ileocecal resection is at least as effective as treatment with infliximab, and this is why a recommendation for early elective ileocecal resection in this situation has been included in the German CD guideline. Smoking cessation is especially important for maintaining remission in patients with CD who smoke (EG A), as it halves the recurrence rate.

The relative utility of various drugs in the first-line treatment of IBD

In addition to the classic anti-inflammatory drugs (mesalazine, steroids) and immunosuppressants (mainly thiopurines and methotrexate), six further classes of drugs are now available for the first-line treatment of IBD: namely, antibodies against TNF-α, α4β7 integrins, IL-12/23 and IL-23, and small molecules. Briefly put, these drugs have been approved for use in the event of the inefficacy or intolerability of treatment with conventional drugs or biological agents. This immediately raises the question which patients stand to benefit most from which drug.

The selection of an active drug or substance class should be based on the findings of clinical trials and on patient-specific factors. Results from randomized, controlled clinical trials (RCTs; these are often approval studies) with homogeneous patient groups that are characterized in detail yield valid data in relation to well-defined criteria of inclusion and exclusion. Nonetheless, patients in clinical practice can differ from patients in RCTs in many ways, and observational studies from clinical practice are thus important as well. Head-to-head (H2H) trials are the best way to compare one substance against another. In recent years, for example, such trials have demonstrated the superior clinical efficacy of the α4β7 integrin inhibitor vedolizumab compared to the TNF-alpha inhibitor adalimumab in the treatment of UC (clinical remission, 31.3 % versus 22.5 % at 52 weeks) (24), and the comparable efficacy of the IL12/IL23 antibody ustekinumab and adalimumab in CD (clinical remission, 64.9 % versus 61.0 % at 52 weeks) (25). Further H2H trials will be reported in the years ahead (e.g., risankizumab [IL23-AK] or mirikizumab [IL23-AK] versus ustekinumab [IL12/23-AK] in CD, or brazikumab [IL23 receptor-AK] versus vedolizumab, or else tofacitinib versus cyclosporine A, in UC). As only a limited number of direct comparisons can be made, indirect comparisons of clinical trials in (network) meta-analyses are important as well, but these must be interpreted cautiously, as important differences (e.g., between patient populations and prior treatments) cannot be fully compensated for, even with complex statistical procedures such as propensity scores.

According to a recent network meta-analysis, infliximab followed by risankizumab and upadacitinib appears to be most effective in inducing remission in complex CD. For maintaining remission, upadacitinib followed by adalimumab and infliximab was rated as the most effective treatment (26). Again according to network meta-analyses, upadacitinib appears to be the most effective drug for inducing clinical remission in UC, but also had the most adverse effects. Vedolizumab has the most favorable side effect profile, while ozanimod has the worst (27). The Red Hand Letter issued on March 17, 2023 with the joint participation of the European Medicines Agency (EMA) and the German Federal Institute for Drugs and Medical Devices (BfArM) contains the recommendation that JAK inhibitors should only be used as reserve drugs, and not as first- or second-line treatment, in patients at high risk (i.e., patients who are aged 65 and above, have an increased risk of severe cardiovascular disease, are current or long-term previous smokers, or have an increased risk of cancer). In other patients, however, side effects were rarely seen. The use of these drugs in selected patients after a risk assessment seems reasonable (28, 29).

Crohn's disease and repetitive steroid use

Just as in ulcerative colitis, the repetitive use of steroids should be avoided (RG A); in case of frequent relapses, newer drugs should be used to maintain remission.

Smoking cessation in Crohn's disease

Smoking cessation is especially important for maintaining remission in patients with Crohn's disease who smoke (EG A), as it halves the recurrence rate.

All of these trials included large groups of patients, but were not based on individual characteristics and needs, which are of great importance for the selection of a drug. The list in *Table 3* provides guidance for the selection of an individualized treatment. For example, the rapidity of response to treatment with JAK inhibitors in CD and UC may be an important reason to use these drugs. A history of severe infections, particularly in older patients, limits the use of TNF antibodies (30). As for postoperative maintenance of remission in CD, the best efficacy data are currently available for anti-TNF antibodies. Extraintestinal manifestations of IBD can be treated with anti-TNF antibodies, but also with JAK inhibitors and (depending on the extraintestinal manifestation [EIM]) with IL-12/IL-23 antibodies. Specific EIM should always be considered as well; the indications for it are highly specific. Vedolizumab and IL-12/IL-23 antibodies have favorable safety profiles, e.g. with regard to complicating infections, and can thus be given preferentially to patients with the corresponding pre-existing conditions and risk factors. Infections have been found to be less common with ustekinumab as well, but this drug is not without undesirable side effects (31). Latent tuberculosis must be ruled out before the initiation of treatment with any of these drugs except ozanimod. Before TNF antibodies are given, patients must be tested for a hepatitis B infection. Integrin and IL-12/IL-23 antibodies can presumably be used relatively safely in patients with preexisting cardiovascular disease or an increased tumor risk. TNF antibodies are contraindicated in patients with NYHA stage III/IV heart failure. JAK inhibitors should also only be used in exceptional cases in patients with cardiovascular risk factors, and ozanimod should not be given to patients with arrhythmias or a history of a cardiovascular event in the last six months. Moderate to severe renal insufficiency requires a dose reduction of JAK inhibitors; no studies are available for biologic agents or ozanimod in this situation, and decisions must be made case by cases, as needed. For women desiring to become pregnant, TNF antibodies are again the preferred choice, being supported by the fullest safety data for use during pregnancy and breastfeeding. Experience with the use of vedolizumab or ustekinumab in pregnancy is still limited. To date, however, no unfavorable courses of pregnancy have been reported. It is thus recommended that these drugs can be continued during pregnancy up to delivery, while JAK inhibitors and S1P modulators must not be used.

Along with providing the well-established types of nutritional therapy, pediatric gastroenterologists face the additional challenges presented by the child or adolescent patient, such as the goal of age-appropriate growth and development. Moreover, the use of suitable new drugs in this age group must often be off label because of a lack of data or delays in approval (32).

It would also be very important to be able to predict the individual treatment response with the aid of objective criteria. Many different approaches for this purpose (imaging, serological, histological, immunological, genetic, microbiological) have already been developed in the past. These include a scoring system for predicting the response to vedolizumab in CD (33), molecular imaging with labeled antibodies to predict the response to TNF-AK (34), and the prediction of the development of anti- infliximab antibodies in the presence of the *HLADQA1*05* genotype (35). None of these predictive methods have yet been used in the clinical setting.

Perspectives

In the future, precision medicine (PM) will involve individually selected treatment and individual prediction of the treatment response. PM will need to be based on advanced bioinformatic tools, such as systems biology, that integrate all components of the disease process into a network-medicine approach. The ultimate goal is to be able to treat patients with IBD with highly specific, customized PM drugs (36). Current studies are also addressing the safety and efficacy of combinations of two biologic agents; this is a potentially promising approach utilizing combined effects at more than one point in the inflammatory cascade. Until these prospects have been realized, the difficult choice of treatment for patients with IBD will still have to be based on the critical evaluation of study findings, the physician's personal experience, and, above all, the individual characteristics and needs of the patient.

Conflict of interest statement

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Complex Crohn's disease and the induction of remission

Infliximab followed by risankizumab and upadacitinib appears to be most effective in inducing remission in complex Crohn's disease. For maintaining remission, upadacitinib followed by adalimumab and infliximab was rated as the most effective treatment.

Inflammatory bowel diseases and the desire to become pregnant

For women desiring to become pregnant, TNF antibodies are the preferred choice, being supported by the fullest safety data for use during pregnancy and breastfeeding.

Pharma, Tillotts Pharma, and Viatris. He also has received research funding from the DFG for TRR241 (IBDome) and SFB1181 (C02).

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► **Supplementary Material**

eReferences, eBox:
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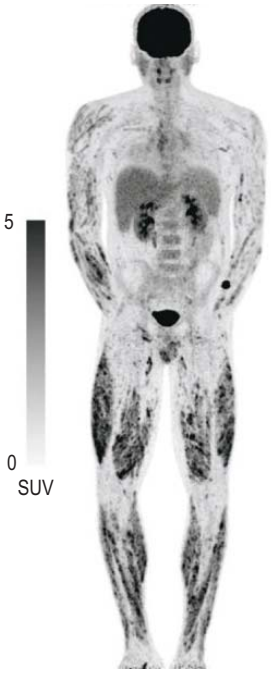
Further information on CME

- Participation in the CME certification program is possible only over the Internet: cme.aerzteblatt.de. This unit can be accessed until 9 November 2024. Submissions by letter, e-mail or fax cannot be considered.
- The completion time for all newly started CME units is 12 months. The results can be accessed 4 weeks following the start of the CME unit. Please note the respective submission deadline at: cme.aerzteblatt.de.
- This article has been certified by the North Rhine Academy for Continuing Medical Education. CME points can be managed using the "uniform CME number" (*einheitliche Fortbildungsnummer,* EFN). The EFN must be stated during registration on www.aerzteblatt.de (*"Mein DÄ"*) or entered in *"Meine Daten,"* and consent must be given for results to be communicated. The 15-digit EFN can be found on the CME card (8027XXXXXXXXXX)

CLINICAL SNAPSHOT



The Tiger Man Sign in Systemic Sarcoidosis

A 33-year-old man was admitted to the hospital for investigation of acute kidney injury (creatinine 2.35 mg/dL) with hypercalcemia (3.12 mmol/L). He reported a history of nodular lesions on the skin of his lower arms accompanied by bilateral swellings of his hands and feet with a feeling of tightness. The production and excretion of urine were unchanged. Laboratory tests showed increased levels of soluble interleukin-2 receptor, angiotensin-converting enzyme, and 1,25(OH)$_2$ vitamin D$_3$. 2-[^{18}F]FDG-PET/CT demonstrated bipulmonary nodules with a perilymphatic distribution pattern accompanied by mediastinal and bihilar lymphadenopathy with elevated glucose metabolism. Furthermore, the muscles of the extremities showed lesions indicating myositis (the tiger man sign; *Figure*). Magnetic resonance imaging of the lower legs revealed correlating intramuscular edema. Histological examination demonstrated interstitial nephritis. Systemic sarcoidosis was diagnosed. Treatment with prednisolone (starting at 1 mg/kg) and azathioprine (2 mg/kg) restored the creatinine and calcium levels to normal within 2 weeks. The tiger man sign, first described in 2012, is considered a characteristic finding in sarcoidosis.

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Participation is possible at cme.aerzteblatt.de. The submission deadline is 9 November 2024.

Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

Which of the following are typical side effects of filgotinib, tofacitinib and upadacitinib?

a) psoriatiform lesions
b) lupus-like syndrome
c) joint pain
d) hypercholesterolemia
e) bradycardia

Question 2

Which of the following statements about small molecules in the treatment of CIBD is incorrect?

a) They can usually be administered orally.
b) They are not limited in their long-term effectiveness by the formation of anti-drug antibodies.
c) They can interact with other drugs.
d) They have a relatively long half-life.
e) They include JAK inhibitors and S1P receptor modulators.

Question 3

What is the prevalence of ulcerative colitis in Germany?

a) 30 per 100 000 people
b) 60 per 100 000 people
c) 90 per 100 000 people
d) 120 per 100 000 people
e) 150 per 100 000 people

Question 4

What type of nutrition is first-line treatment to induce remission in children with Crohn's disease?

a) exclusive enteral nutrition
b) a gluten-free diet
c) a vegan diet
d) the paleo diet
e) the specific carbohydrate diet

Question 5

Which of the following statements about patients with inflammatory bowel disease (IBD) is correct?

a) Most patients with Crohn's disease need surgery.
b) The prevalence of IBD is falling in Germany.
c) IBD has a single, genetic cause.
d) Extraintestinal manifestations in IBD illustrate its systemic nature.
e) The initial presentation of IBD is never in an elderly patient.

Question 6

What does the Crohn's disease exclusion diet consist of?

a) the avoidance of potentially pro-inflammatory foods
b) fermented plant foods and protein shakes
c) foods containing gluten and vegetable oils
d) steamed vegetables and fish
e) raw vegetables and animal protein

Question 7

What is the central goal of treatment in Crohn's disease and ulcerative colitis?

a) steroid-free remission
b) steady weight gain up to a BMI of 25
c) improved blood count
d) the strict adherence of patients to a lifelong diet
e) patient acceptance of their disease

Question 8

Which statement about the effects of specific drugs is incorrect?

a) In a randomized controlled trial, vedolizumab was superior to adalimumab for inducing remission in ulcerative colitis.
b) Infliximab plus azathioprine is an effective combination therapy.
c) Vedolizumab has more severe side effects in patients with ulcerative colitis.
d) Tofacitinib is rapidly effective drug against ulcerative colitis.
e) Ustekinumab and adalimumab were found to be comparably effective in an RCT in patients with Crohn's disease.

Question 9

In which patient population should JAK inhibitors not be used s first- or second-line therapy?

a) patients with an increased risk of cancer
b) patients under age 40
c) premenopausal women
d) patients with a BMI above 30 kg/m^2
e) patients with extraintestinal manifestations

Question 10

What is the target structure on which adalimumab exerts its effect?

a) α4β7-integrin
b) TNF-α
c) interleukin 23
d) JAK-1
e) interleukin 12

► **Participation is only possible online: cme.aerzteblatt.de**

Supplementary material to:

Treatment Strategies in Inflammatory Bowel Diseases

by Andreas Stallmach, Raja Atreya, Philip Christian Grunert, Johannes Stallhofer, Jan de Laffolie, and Carsten Schmidt

Dtsch Arztebl Int 2023; 120: 768–78. DOI: 10.3238/arztebl.m2023.014

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eBOX

The immune pathogenesis of IBD as a rational basis for new therapeutic approaches

Advances in the understanding of the immune pathogenesis of IBD led to the early development and approval of the TNFα antibody class (infliximab, adalimumab, golimumab) and another antibody (ustekinumab) that inhibits the common p40 subunit of IL-12 and IL-23. Data from murine models suggest, however, that IL-23 in particular is essential for the development of chronic intestinal inflammation (e1), and that an antibody that neutralizes the p19 subunit of the heterodimer IL-23 strongly inhibits this inflammation (e2). Thus the selective blockade of IL-23 via neutralization the p19 subunit might be an even more finely targeted therapeutic approach. In the treatment of psoriasis, which is pathophysiologically related to IBD, the specific IL-23p19 antibody riskankizumab has also been found more effective than the IL-12/IL-23 antibody ustekinumab; these findings, of course, cannot be directly transferred to IBD (e3). IL-23 inhibition seems particularly attractive in patients with IBD who have not responded to anti-TNF therapy or in whom a secondary loss of efficacy was observed. These patients exhibit increased IL-23 production in CD14-positive macrophages, leading to the expansion of apoptosis-resistant IL23R+/TNFR2+/CD4+ T cells that mediate anti-TNF therapy resistance (e4).

In parallel with the development of the anti-cytokine strategy, the intracellular Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway, which is responsible for cytokine signaling, was identified as a target structure for treatment. There are four intracellular tyrosine kinases in the JAK family (JAK1, JAK2, JAK3 and TYK2). Once cytokines become bound to their membrane receptor on the target cells, the effect occurs via Janus kinases in pairs with the recruitment of STAT molecules. The subsequent phosphorylation leads to translocation into the cell nucleus and transcription of the target genes. JAK inhibitors (filgotinib, tofacitinib, upadacitinib) inhibit intracellular signal transduction in these pro-inflammatory signaling pathways (e5). The excessive immune response is further promoted by the increased migration of immune cells: this process involves adhesion molecules and receptors expressed on the surface of immune cells and blood vessels, as well as signaling pathways modulated by sphingosine-1-phosphate (S1P). The recirculation of T cells from the tissue into the blood is mediated by a constantly present S1P gradient with high concentrations in the blood. S1P is sensed by the S1P receptors (S1PR)1–5, which are expressed on lymphocytes, and leads to the efflux of T cells from the lymphoid tissue into the efferent lymphatic vessels and the systemic circulation. S1P modulation by an appropriate S1P1 and S1P5 agonist (e.g., ozanimod) is intended to keep the naïve and central memory T cells in the lymphoid tissue and prevent their migration into the inflamed mucosa (e6). The migration of immune cells, including T lymphocytes, into the gut is a tightly regulated, multistep process that helps sustain the inflammatory response. After recirculation, T cells can interact with molecules expressed by endothelial cells. The binding of integrins expressed on T cells (e.g. α4β7, α4β1) to their ligands expressed on endothelial cells (e.g. „mucosal addressin cell adhesion molecule-1“ [MAdCAM-1]) leads to migration into the intestine through a multi-stage extravasation process. An antibody directed against the adhesion molecule α4β7 (vedolizumab) inhibits the interaction of T cells with the corresponding ligand MAdCAM-1 and thus blocks the migration of inflammatory cells from the blood into the intestine (e7).