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Inflammatory Bowel Diseases: Current Medical and Surgical Therapy

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Question 1: There is great promise in new therapeutic strategies that prevent recurrence of Crohn's disease after surgical resection. Does this change the indication to operate – for instance at an earlier time point for stenotic disease?

Siegmund: The availability of novel therapeutic strategies is at this point mainly restricted to the timely management of Crohn's disease patients after surgery. Hence, this is not changing the European Crohn's and Colitis Organisation (ECCO) guideline statement 'Localised ileocaecal Crohn's disease with obstructive symptoms, but not significant evidence of active inflammation, should be treated by surgery'. Thus, the time point of surgery does not change.

Stallmach: Relapse prevention has no influence on the indication for resection. The indication for surgery has to be timely and must not be understood as a failure of therapy. Surgery represents a part of the therapeutic spectrum; e.g., young patients with a short segment of stenosing ileitis may benefit to a higher degree from surgery than from immunosuppression.

Atreya: Recently published clinical trials have evaluated different therapeutic strategies in Crohn's disease patients to prevent postoperative recurrence of mucosal inflammation. It could for instance be shown that application of an anti-TNF (tumor necrosis factor) antibody was able to prevent recurrent mucosal disease in almost all high-risk patients, and was moreover more efficient than thiopurines. It is nevertheless important to individualize the postoperative therapy for every single patient, as an intensified postoperative therapy is only justified in a certain subgroup of patients with poor postoperative disease prognosis, while other patients do not necessarily need any postoperative treatment at all.

In my opinion, these postoperative treatment strategies do not alter the indication to operate, as in that setting irreversible structural damage has already taken place that would not benefit from any therapeutic application. It is important that the indication for operation in these patients is not delayed by a futile therapeutic initiative. For example, fibrotic stenotic disease does not benefit from any of the currently available therapies and should therefore be evaluated regarding an immediate surgical therapy instead.

Kreis: No, there is no evidence for a need to change the indication to operate or to suggest that stenosis should be operated earlier.

Question 2: What is your current definition of 'deep remission' and how do you determine deep remission in an individual patient?

Siegmund: The term 'deep remission' is in several respects more confusing than helpful and should be avoided. One could state that deep remission implies endoscopic as well as histologic healing. However, as indicated by several clinical trials, clinical activity indices are often still increased in the presence of mucosal healing, which can be explained by the fact that in most trials even mild signs of inflammation are considered as mucosal healing. Furthermore, histologic remission may be patchy and hence not be representative. In particular in Crohn's disease inflammation might be absent in the luminal layers accessible to the biopsy; however, deeper layers might still be inflamed. In addition, histologic evaluation remains a subjec-

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tive criterion strongly depending on a single pathologist. Last changes of the microbiota in the intestine have been described in patients with inflammatory bowel disease (IBD) despite the absence of detectable inflammation. Consequently, patients with clinical and endoscopic remission in the absence of histologic signs of inflammation are in remission. The subclassification of remission into deep remission is not adding further information.

Stallmach: A patient with arterial hypertension is not treated according to the degree of headache. Therefore, remission includes amelioration of clinical symptoms, improvement of the quality of life, normalization of laboratory parameters (e.g. anemia), and mucosal healing.

Atreya: My current definition of 'deep remission' is clinical, laboratory, and endoscopic remission at the same time. Clinical remission is primarily defined by patient-reported outcomes like absence of blood in stool, normalization of stool frequency (ulcerative colitis, Crohn's disease), and absence of abdominal pain (Crohn's disease). It is moreover complemented by laboratory findings such as normalization of calprotectin (ulcerative colitis) and CRP (Crohn's disease). Furthermore, endoscopic remission (mucosal healing) is defined by the absence of mucosal ulcerations (Crohn's disease) and Mayo Score 0/1 (ulcerative colitis). Currently, I do not include histological or molecular parameters to define deep remission.

Kreis: As a surgeon, I cannot really comment on this.

Question 3: Are mucosal healing and deep remission therapeutic goals for all of your patients or only for (a) certain subgroup(s)?

Siegmund: The induction of remission including mucosal healing is the optimal response situation in a given patient. However, this aim cannot be reached in every patient. In case a patient still has signs of mucosal inflammation under immunosuppressive therapy in the absence of clinical symptoms, one has to consider the risk-benefit ratio in this individual patient.

Stallmach: Mucosal healing and deep remission are therapeutic goals for all patients. However, it is unclear whether therapy should be intensified if the patient is in clinical remission but endoscopic inflammatory changes persist.

Atreya: Mucosal healing and deep remission cannot be defined as global therapeutic goals for all patients. It has currently not been prospectively shown that an achievement of these therapeutic aims enables a change of the natural disease course in all patients. From my point of view, there is a difference in the individual therapeutic aims for each patient as these are also dependent on many factors, such as age, comorbidities, previous disease course, and quality of life, which have to be taken into account. Deep remission is therefore not a global therapeutic goal for all patients.

Kreis: Generally these are therapeutic goals for all patients. However, some patients may not tolerate or accept medications that are necessary to achieve these goals. In these patients different goals may need to be defined.

Question 4: Are there individual patient characteristics that determine which biologic you use first?

Siegmund: Two classes of biologics are available for both diseases: several TNFα antibodies as well as vedolizumab. No head-to-head comparison of both strategies is available yet. The various TNFα antibodies share their mode of action and differ by their route of application. Patient characteristics, compliance, disease phenotype as well as disease severity contribute to the selection of one specific TNFα antibody in a defined situation. Considering the mode of action, vedolizumab is blocking the entry of inflammatory cells to the mucosal site. Consequently, inflammatory cells that previously entered the tissue are still exerting their inflammatory capacity, leading to the conclusion that in severe disease this prolonged response time might exclude a monotherapy with vedolizumab.

Stallmach: Young patients with high inflammatory activity, severe disease, and extraintestinal manifestations, such as pyoderma gangrenosum, or patients with a toxic megacolon as a first manifestation of ulcerative colitis should be treated with infliximab.

Atreya: There are certain individual criteria which influence the decision regarding the use of anti-TNF antibodies or vedolizumab as a first biologic treatment. The presence of extraintestinal manifestations (especially arthritis) or complicated fistula lead to the application of an anti-TNF antibody, as there are currently no prospective data for vedolizumab in this regard. In severe, steroid-refractory ulcerative colitis, anti-TNF antibodies are also the first biologic treatment to be chosen, as there are no data for vedolizumab. The same also applies to pregnant IBD patients.

In contrast, vedolizumab is more favored in patients with a history of recurrent opportunistic infections (especially of the upper airway, pneumonia).

Kreis: In fistulizing disease my preference is infliximab. Vedolizumab comes last due to an unknown profile at present. Otherwise I have no preference.

Question 5: How and when will new endoscopic techniques change the recommendations for surveillance endoscopy and random biopsies?

Siegmund: New endoscopic techniques have already entered clinical guidelines and practice. The guidelines state that 'Pan-colonic methylene blue or indigo carmine chromoendoscopy should be performed during surveillance colonoscopy, with targeted biop-

sies of any visible lesions'. Random biopsies are an alternative option in case there is no expertise in chromoendoscopy.

Stallmach: A recently published paper by Leifeld et al. revealed that stepwise biopsies (4 biopsies every 10 cm) are indispensable in white-light (WL) colonoscopy. The combination of targeted and segmental biopsies in narrow-band imaging (NBI) technique is as sensitive as targeted together with stepwise biopsies in WL. The highest sensitivity for dysplasia detection could be reached by combining the WL and NBI technique by switching between the modes. However, reimbursement of chromoendoscopy or confocal laser endoscopy will improve acceptance.

Atreya: From my point of view, chromoendoscopy has already changed the current recommendations for surveillance endoscopy and random biopsies. It should be clearly favored (also by the guidelines) for surveillance colonoscopies in patients with long-standing IBD as higher dysplasia detection rates have been proven by many studies. Studies with virtual chromoendoscopy may offer comparable advantages but results of repeated prospective, multicentered trials have to be obtained.

Kreis: When new endoscopic techniques are shown in randomized studies, they survey patients with ulcerative colitis as good as standard surveillance with adequate random biopsies.

Question 6: How should we define irreversible structural damage that is not amenable to medical therapy in ulcerative colitis?

Siegmund: Endoscopic signs of scarring tissue and loss of haustration in the absence of inflammation should be defined as irreversible structural damage.

Stallmach: Difficult question, short answer: unresponsiveness to consistent anti-inflammatory medical therapies, such as steroids or anti-TNF agents, together with low fecal inflammation markers.

Atreya: Crohn's disease patients progress from inflammatory lesions that are often amenable to therapy towards irreversible structural disease (strictures and penetrating disease). In ulcerative colitis, there is no comparable progress of inflammation. The occurrence of pseudopolyps can be defined as structural damage which is not reversible by anti-inflammatory therapy. Irreversible structural damage can also be defined by the occurrence of intraepithelial mucosal neoplasia in ulcerative colitis, as this is not amenable to medical therapy and can only be approached by endoscopic or more often surgical procedures.

Kreis: Structural alteration in ulcerative colitis that has no relevant inflammatory component.

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