Current Research in Pharmacology and Drug Discovery 3 (2022) 100097

Contents lists available at ScienceDirect

Current Research in Pharmacology and Drug Discovery

journal homepage: www.journals.elsevier.com/current-research-in-pharmacology-and-drug-discovery

Ileal and colonic Crohn's disease: Does location makes a difference in therapy efficacy?

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ARTICLE INFO

Keywords:
Crohn's disease
Ileal Crohn's disease
Colonic Crohn's disease
Segment
Therapy

ABSTRACT

Within the IBD entity of Crohn's disease, there is currently no differentiation between ileal and colonic manifestation for recruitment of patients in clinical trials, well-powered analysis of study results or therapeutic decisions in daily clinical practice. However, there is accumulating evidence from epidemiological, genetic, microbial, immunological, and clinical characteristics that clearly indicate that ileal Crohn's disease represents a distinct disease entity, which differentiates itself from colonic Crohn's disease. This is also reflected by lower efficacy of targeted therapies in isolated ileal compared to colonic Crohn's disease. The distinct site-specific mechanisms that drive heightened non-response in ileal disease need to be analysed in-depth in the future, to enable optimized therapy in the individual Crohn's disease patient.

1. Introduction

Inflammatory bowel diseases (IBD) encompass chronic inflammatory disorders of the gastrointestinal tract whose phenotypic entities mainly comprises Crohn's disease and ulcerative colitis (Gomollón et al., 2017; Magro et al., 2017). However, there are several lines of evidence that clearly demonstrate that colonic is dissimilar to ileal Crohn's disease manifestation. This clinically impactful differentiation is already reflected in the Montreal classification of Crohn's disease, which besides age at onset and phenotype also includes stratification by location (terminal ileum (L1), colon (L2), ileocolonic (L3), and upper gastrointestinal location (L4) (Satsangi et al., 2006). This classification has been used to assess the individual risk of disease progression to determine the best possible treatment strategy in the course of disease. Epidemiological, genetic, microbial, immunological and clinical characteristics clearly indicate that ileal Crohn's disease represents a distinct disease entity, which differentiates itself from not only ulcerative colitis, but also colonic Crohn's disease (Atreya and Siegmund, 2021; Dulai et al., 2019; Pierre et al., 2021; Cuthbert et al., 2002; Brant et al., 2003; Naser et al., 2012). These findings indicate that Crohn's disease should in future probably not be defined as one disease anymore that subsumes all type of different manifestations, but should rather be defined by specific biological changes that drive the disease at the respective site of inflammation. This might also have implications for our applied therapeutic strategies, as the location of disease could be based on specific biological processes and would thus also require distinct therapeutic approaches. With the growing armamentarium of available therapies in Crohn's disease, it would be important to find guidance for the selection of the most efficacious therapy, which could also be led by site-specific biological changes to allow individualized treatment with higher response rates and lower levels of toxicity for the patient (Atreya and Neurath, 2018; Atreya et al., 2020). However, such an approach would also have to take into account the rather inconclusive classification of ileocolonic manifestation, where neither bowel segment can be ascribed a predominant influence, resulting in a pathogenic and therapeutic grey zone. Different studies have indicated the potential influence of disease location on the

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https://doi.org/10.1016/j.crphar.2022.100097
Received 6 December 2021; Received in revised form 7 March 2022; Accepted 16 March 2022

therapeutic efficacy of biological therapies in Crohn's disease. In clinical practice there is the perception that our available targeted therapies show less effectiveness in ileal compared to colonic Crohn's disease. In the following, we will present available therapeutic efficacy data of various therapies in relation to ileal compared to colonic disease location. Further insights into the effectiveness of our current therapeutic armamentarium in ileal and colonic Crohn's disease will be needed to optimize our treatment for the individual patient (Digby-Bell et al., 2020).

2. Therapeutic efficacy of therapies in ileal compared to colonic Crohn's disease

Therapeutic effectiveness differences between ileal and colonic disease manifestation have been described for enteral nutrition in a prospective study of 65 pediatric Crohn's disease patients with active disease. Here, the colonic disease group showed the least decline in the Pediatric Crohn's Disease Activity Index (PCDAI) after completing treatment with enteral nutrition, with significantly lower remission rates (50%) in comparison to the ileocolonic (82.1%) and ileal (91.7%) groups. Endoscopic and histologic assessment demonstrated a significant improvement in the ileocolonic, but not in the colonic disease group. Overall, the authors found a better therapeutic response to enteral nutrition if the ileum was also involved (Afzal et al., 2005). Another study reported a statistical significant difference between the remission rates of isolated colonic (51.9%) and a non-isolated colonic (68.3%) Crohn's disease (n = 241) upon exclusive enteral nutrition treatment. Multivariate analyses indicated that isolated colonic involvement was associated with a reduced response to exclusive enteral nutrition treatment (Xu et al., 2019). Clinical study findings indicated that Crohn's disease patients with colonic involvement benefit more likely from antibiotics therapy in comparison to limited ileal disease location (Greenberg, 2004). One study suggested that metronidazole application was more effective in patients with disease confined to the large intestine or affecting both small and large bowel than in those with small bowel disease only (Sutherland et al., 1991). Similarly, application of metronidazole and ciprofloxacin or placebo in combination with budesonide was ineffective for patients with ileal disease but improved the outcome when colonic involvement was present (Steinhart et al., 2002). However, none of the mentioned studies used objective inflammatory outcome measures and were not powered to assess patient subgroups or general efficacy of antibiotics for patients with colonic Crohn's disease (Greenberg, 2004). Results of older studies that investigated the effectiveness of sulfasalazine in the induction of remission in mildly to moderately active Crohn's disease patients could not demonstrate a significant treatment effect in favor of sulfasalazine in comparison to placebo (43% vs. 30%), but found that patients with limited colonic involvement were more likely to respond to the prodrug than placebo (Summers et al., 1979; Levesque and Kane, 2011).

There are several lines of different data that indicate the potential influence of disease location on the therapeutic efficacy of targeted biological therapies in Crohn's disease (Subramanian et al., 2017). It is important to point out that there were no reported subgroup analyses on the efficacy of the anti-TNF antibodies infliximab (Targan et al., 1997; Hanauer et al., 2002) or adalimumab (Hanauer et al., 2006; Colombel et al., 2007; Sandborn et al., 2007) in patients with isolated ileal and colonic Crohn's disease in the respective randomized, controlled trials. However, there was a post hoc analysis of the randomized, controlled trial with the anti-TNF agent certolizumab pegol, where moderate-to-severe Crohn's disease patients were randomized to receive 400 mg subcutaneous certolizumab pegol (n = 223) or placebo (n = 215) at weeks 0, 2, and 4. Patients with colonic (OR 2.39 vs. placebo, 95% CI 0.99 to 5.75, p = 0.052) and ileocolonic disease (OR 2.07, 95% CI 1.01 to 4.28, p = 0.048) were more likely to achieve clinical remission at week 6 compared with isolated ileal disease (OR 0.42, 95% CI 0.18 to 0.99, p = 0.048) (Sandborn et al., 2011). Cohort studies also indicated that treatment with the anti-TNF antibody infliximab led to better efficacy in colonic than in ileal Crohn's disease. In one study, patients with isolated colonic (23/26; 88%) were more likely to respond (HBI reduction by > 3) to infliximab at week 4 than ileal (6/11; 54%) Crohn's disease patients (p = 0.042, OR 3.83) (Arnott et al., 2003). Another study reported that clinical response at week 8 (reduction of CDAI by ≥ 100) to infliximab was reached by 83.3% of patients with colonic Crohn's disease (n = 18) compared to 50% with ileal/ileocolonic (n = 26) disease. Exclusive colonic involvement predicted sustained response to treatment (p = 0.03) (Laharie et al., 2005). Furthermore, another study assessed treatment response in 240 Crohn's disease patients of the Belgian Infliximab Expanded Access Program. Response was assessed at week 4 (reduction CDAI ≥70) or week 10 (50% decrease in draining fistulae). Here, response was recorded in 81% of patients with colonic vs. 55% with ileal vs. 74% with ileocolonic disease (OR 1.905, 95% CI 1.010 to 3.597). Stepwise logistic regression identified isolated ileitis (OR = 0.359, 95% CI = 0.177–0.728, p = 0.004) as inversely correlated with response, whereas isolated colitis (OR = 1.905, 95% CI = 1.010–3.597, p = 0.046) was positively correlated with response to infliximab (Vermeire et al., 2002). However, a retrospective cohort study of patients with pediatric Crohn's disease treated with infliximab (n = 284) found isolated colonic disease (HR 2.72, 95% CI 1.30–5.71, p = 0.008) to be a predictor for loss of response (Dupont-Lucas et al., 2016). Another study reported the need for earlier adalimumab dose escalation in colonic (13.2 weeks) compared to other disease sites (34.6 weeks) with statistical significance (p = 0.0062) (Cohen et al., 2012). However, no trough levels or anti-drug antibodies were measured in the respective studies, limiting interpretation of the data.

There were no formal post hoc analyses of the efficacy of ustekinumab or vedolizumab in the randomized, controlled clinical phase 3 trials. A recently performed meta-analysis of the ustekinumab induction (CERTIFI) (Sandborn et al., 2012), as well as the induction and maintenance (UNITI) (Feagan et al., 2016) trials in patients with moderately to severely active Crohn's disease reported that patients with isolated ileal (n = 170) compared to colonic (n = 136) Crohn's disease were significantly less likely to achieve clinical response or remission (33.5% vs 49.2%; relative risk, 0.68; 95% CI, 0.50–0.92) (Dulai et al., 2019). For vedolizumab, the induction and maintenance trials were included (GEMINI-II/GEMINI-M) (Sandborn et al., 2013). Here, there were no statistical significant differences between isolated ileal (n = 66) compared to colonic (n = 89) Crohn's disease for clinical response or remission (21.2% vs 22.4%; relative risk, 0.82; 95% CI, 0.42–1.60) (Dulai et al., 2018). Meta-analysis of all mentioned randomized, controlled trials with certolizumab pegol, ustekinumab and vedolizumab demonstrated that patients with isolated ileal compared to colonic Crohn's disease were significantly less likely to achieve clinical response or remission (29% vs 38%; relative risk, 0.70; 95% CI, 0.56–0.87; I2 ¼ 0%) (Dulai et al., 2018, 2019). Recently, results from VISIBLE 2, a randomised, double-blind, placebo controlled, phase 3 trial evaluating a novel subcutaneous vedolizumab formulation as maintenance treatment in moderately to severely active Crohn's disease patients was published. All patients received open-label vedolizumab 300 mg intravenous induction therapy at weeks 0 and 2, and at week 6 clinical responders (≥70-point CDAI decrease from baseline) were randomised 2:1 to receive maintenance treatment with vedolizumab 108 mg subcutaneous (SC) (n = 275) or placebo (n = 135) every 2 weeks until week 50. At Week 52, 48% of patients receiving vedolizumab SC versus 34.3% receiving placebo were in clinical remission (p = 0.008). Here, a treatment difference in clinical remission favoring vedolizumab SC over placebo was observed in patients with colonic or ileocolonic disease localisation, but not with localized ileum-only disease. Clinical remission at week 52 was achieved in 49.1% (27/55) of vedolizumab SC compared to 23.1% (6/26) of placebo treated colonic Crohn's disease patients (estimate 26.0; 95% CI, 5.1 to 46.9), whereas only 36.4% (24/66) of vedolizumab SC compared to 42.9% (9/21) of placebo treated ileal Crohn's disease patients (estimate −6.5; 95% CI, −30.6 to 17.6) reached the similar primary endpoint (Vermeire et al., 2021).

A retrospective multi-center cohort study in Crohn's disease patients achieving steroid-free clinical response to ustekinumab induction therapy (n = 104) demonstrated in a multivariate Cox proportional hazards regression analysis that colonic disease (aHR 0.33 (0.11–0.98), and ileocolonic disease (aHR 0.26 (0.10–0.68)) were associated with lower risk for loss of response during maintenance therapy (Ma et al., 2017). In another real-world study in 152 Crohn's disease patients, multivariate analysis showed that only colonic disease (OR: 3.5; 95% CI: 1.34–9.41) was a positive predictor of clinical response one year after ustekinumab initiation (Liefferinckx et al., 2019). However, another report with 407 Crohn's disease patients showed opposite results, as ileocolonic and colonic disease extension were associated with lower clinical response rates at week 26 (OR, 0.56 95% CI, 0.32–0.96, and OR, 0.34 95% CI, 0.16–0.69, respectively). (Iborra et al., 2020).

These data have however to be interpreted very cautiously, as clinical disease activity alone is not a sufficient marker for treatment response in Crohn's disease (Ma et al., 2018). There are scarce studies that have assessed endoscopic disease activity as an outcome parameter for therapeutic effectiveness with inclusion of efficacy in ileal compared to colonic Crohn's disease. The EXTEND trial was a randomized, placebo-controlled study in patients with ileocolonic Crohn's disease, which investigated the effectiveness of adalimumab (n = 49) compared to placebo (n = 21) in patients with Crohn's disease and mucosal ulcerations at baseline. Baseline endoscopic severity was similar across segments. Mean changes after one year in the Crohn's disease index of severity (CDEIS) score were −68.5% to −90.6% from the rectum till the transverse colon, compared to −22.3% to −50.0% in the right colon and ileum. Colonic and Ileal Global Histologic Disease Activity Scores healing was more common in the colon (28.3%) than in the ileum (21.2%) (Reinisch et al., 2017). Another study performed a post-hoc analysis of data from a clinical study of 116 Crohn's disease patients, where 46 had ileal and 70 ileocolonic disease manifestation. All patients were treated with anti-TNF inhibitors at a single Japanese center. Rate of endoscopic healing (Simple endoscopic score for Crohn's disease (SES-CD) $\leq$ 5) was assessed after a median treatment time of 13 months based on findings from balloon-assisted enteroscopy. Upon endoscopic examination during maintenance therapy, 36% (41/114) of patients presented endoscopic healing in the small bowel, while 79% (33/42) demonstrated colonic endoscopic healing. All patients with small bowel endoscopic healing also had accompanying colonic endoscopic healing. Altogether, the proportion of patients with small bowel healing was significantly lower than that of colonic endoscopic healing. Failure to achieve small bowel endoscopic healing was significantly associated with structuring or penetrating disease, lack of concomitant immunosuppressive treatment, and previous treatment with anti-TNF agents. This study strengthened the notion that small bowel ulcerations were harder to heal than respective colonic ulcers (Takenaka et al., 2020). Post hoc analysis of the SONIC trial, where the efficacy of infliximab and azathioprine monotherapy was compared to combination therapy of both substances(Colombel et al., 2010), analysed endoscopic prognostic factors that influenced achievement of endoscopic remission at week 26. It could be shown that endoscopic remission rates for ileal ulcers were significantly lower than remission rates throughout the colon. Furthermore, only larger (>2 cm), and larger and deep ulcers in the rectum and ileum were less likely to reach endoscopic remission at week 26 compared to smaller or superficial ulcers, whereas ulcer size in other colonic segments did not affect the achievement of endoscopic remission at week 26. Noteworthy, overall degree of endoscopic inflammation did not affect the likelihood of achieving endoscopic remission (Narula et al., 2020). The impact of ileal disease location on the probability to achieve endoscopic remission was also found upon post hoc analysis of the TAILORIX randomized controlled trial, which studied biologic-naïve patients with active endoscopic Crohn's disease that received infliximab combination treatment. Endoscopic healing was defined as the absence of ulcers and a CDEIS <3. In the 122 analysed patients, segmental remission rates were lower both at week 12 and 54 in the ileum compared to all respective colonic segments, which also included the rectum. Again, the severity of endoscopic lesions at the baseline did not influence healing rates (Rivière et al., 2021). A retrospective, single-center study assessed endoscopic mucosal healing rates in different ileocolonic segments in infliximab treated Crohn's disease patients. Altogether, 101 patients with similar baseline endoscopic severity across ileocolonic segments were evaluated. The authors were able to demonstrate that complete mucosal healing, defined as a SES-CD of 0 was not uniform in the different ileocolonic regions. The greatest improvements occurred in the transverse colon, where the changes in the SES-CD ulcer size and ulcerated surface subscores were both −94% in the transverse colon, while the smallest changes with −67% and −69% occurred in the terminal ileum at week 30/38 compared with baseline. The highest rate of complete mucosal healing at week 30/38 was again visible in the transverse colon at 81%, while the lowest rate was recorded in the terminal ileum at 45% (Wu et al., 2020). Furthermore, differences upon endoscopic response in ileal and colonic Crohn's disease have also been reported for vedolizumab. An open-label, phase 3b study investigated complete mucosal healing (defined as absence of any ulcers, including aphthae) rates per bowel segment in a 26-week primary study and 52-week substudy upon vedolizumab treatment in Crohn's disease patients with active clinical and endoscopic activity. Here, the proportion of patients that achieved complete mucosal healing was much higher in the rectum (38.5%), descending colon (31.7%), transverse colon (51%), ascending colon (46.1%) than in the ileum (20.6%). Comparable results could also be observed at week 52 in the according subpopulation, where complete mucosal healing rates were again lowest in the ileum. Altogether, endoscopic improvements were generally greater in patients with colonic than with ileal Crohn's disease (Danese et al., 2019). In addition, the specific IL-23p19 antibody risankizumab was tested in a randomized phase II trial with 121 Crohn's disease patients. In the subgroup of patients where mucosal biopsy samples were taken for transcriptomic profiling, risankizumab induced endoscopic response at week 12 in a higher proportion of patients with deep ulcerations in the colon than those with deep ulcerations in the ileum at baseline (Feagan et al., 2017). Further subgroup analyses of the different IL-23 inhibitors (risankizumab, guselkumab, mirikizumab, brazikumab) and their effectiveness in ileal and colonic Crohn's disease are awaited (Schmitt et al., 2019, 2021). Interestingly, a very recent meta-analysis analysed and identified factors that influenced placebo rates across relevant endpoints in Crohn's disease trials. Here, trials enrolling a greater proportion of patients with colonic disease distribution were significantly associated with higher placebo clinical remission rates (OR 1.11, 95% CI 1.02–1.21, p = 0.016). No significant differences were observed for the pooled placebo clinical remission rates based on ileal or ileo-colonic disease distributions. These findings are consistent with the described observations that colonic manifestation was easier to treat than ileal distribution in Crohn's disease (Almradi et al., 2021).

These data suggest that ileal and colonic Crohn's disease may have distinct disease characteristics that influence treatment responsiveness. The exact mechanisms that drive this therapeutic discrepancy is however not clear.

A recent study identified a unique cellular signature in a subset of ileal Crohn's disease patients, which presence correlated with failure to achieve durable corticosteroid-free remission upon initiated anti-TNF therapy. The identified cellular module in the inflamed ileal tissue consisted of IgG-positive plasma cells, inflammatory mononuclear phagocytes, activated T cells, and stromal cells (Martin et al., 2019). Another study described five differentially expressed genes (TNFAIP6, S100A8, IL11, G0S2 and S100A9) that accurately predicted response to infliximab therapy in Crohn's colitis, but not in ileal Crohn's disease patients (Arijs et al., 2010). However, the panel was also able to predict responsiveness of ulcerative colitis patients to infliximab, suggesting that there might be a shared immunological inflammation pathway between Crohn's colitis and ulcerative colitis, but not ileal Crohn's disease patients (Arijs et al., 2009). Impaired effectiveness of vedolizumab in ileal compared to

colonic Crohn's disease may be explained by compensatory homing of effector T cells through the α4β1 integrin upon vedolizumab-mediated inhibition of the α4β7-dependent pathway (Zundler et al., 2017). These data indicate that ileal and colonic Crohn's disease are driven by site-specific mechanisms.

3. Conclusion

Isolated ileal disease occurs in approximately one-third of Crohn's disease patients and various studies have described it as a hallmark for potential complications. Ileal disease location is more often associated

Table 1
Therapeutic efficacy in regard to location in Crohn's disease.

Therapy	Outcome Measure	Number of patients	Results in regard to disease location	Reference
Enteral Nutrition	Clinical remission (PCDAI)	65 (pediatric)	Colonic: 50% Ileocolonic: 82% Ileal: 92%	(13)
Enteral Nutrition	Clinical remission (CDAI <150)	241	Colonic: 52% Non-isolated colonic: 68%	(15)
Metronidazole	Improvement (CDAI)	63	Small intestine +86 (38–134) (n = 24) Small/large intestine +60 (19–101) (n = 31) Large intestine + 145 (26–265) (n = 8)	(16)
Budesonide, Ciprofloxacin, Metronidazole	Clinical remission (CDAI <150)	80	Ileocolonic: 53% Ileal: 26%	(17)
Certolizumab pegol (CZP)	Likeliness to achieve clinical remission (CDAI <150) at week 6	438	Colonic: OR 2.39 vs. placebo (95% CI 0.99–5.75, p = 0.052) Ileocolonic: OR 2.07 (95% CI 1.01–4.28, p = 0.048) Ileal: OR 0.42 (95% CI 0.18–0.99, p = 0.048)	(26)
Infliximab	Clinical response (HBI reduction by > 3) at week 4	37	Colonic: 88% Ileal: 54% (p = 0.042, OR 3.83)	(27)
Infliximab	Clinical response at week 8 (reduction of CDAI by ≥ 100)	44	Colonic: 83.3% Ileal/ileocolonic: 50% (p = 0.03)	(28)
Infliximab	Response at week 4 (reduction CDAI ≥70) or week 10 (50% decrease in draining fistulae)	240	Colonic: 81% Ileocolonic: 74% Ileal: 55% OR 1.905 (95% CI 1.010–3.597)	(29)
Infliximab	Loss of response	284 (pediatric)	Colonic: HR 2.72 (95% CI 1.30–5.71, p = 0.008)	(30)
Adalimumab	Dose escalation (weeks)	75	Colonic: 13.2 Other sites: 34.6 P = 0.0062	(31)
Ustekinumab (UST)	Clinical response or remission (CDAI)	306	Ileal: 33.5% Colonic: 49.2% Relative risk 0.68 (95% CI, 0.50–0.92)	(5)
Vedolizumab (VDZ)	Clinical response or remission (CDAI)	155	Ileal: 21.2% Colonic: 22.4% Relative risk 0.82 (95% CI, 0.42–1.60)	(35)
Meat-analysis RCTs (CZP, UST, VDZ)	Clinical response or remission (CDAI)	288	Ileal: 29% Colonic: 38% Relative risk 0.70 (95% CI, 0.56–0.87; I2 ¼ 0%)	(5)
Vedolizumab	Clinical remission (CDAI <150) at week 52	168	Colonic VDZ: 49.1% Colonic placebo: 23.1% of Estimate 26.0 (95% CI, 5.1–46.9) Ileal VDZ: 36.4% Ileal Placebo: 42.9% Estimate −6.5 (95% CI, −30.6-17.6)	(36)
Ustekinumab	Loss of steroid-free clinical response (CDAI)	104	Colonic: aHR 0.33 (0.11–0.98) Ileocolonic: aHR 0.26 (0.10–0.68)	(37)
Ustekinumab	Clinical response (CDAI)	152	Colonic: OR, 3.5 (95% CI: 1.34–9.41)	(38)
Ustekinumab	Clinical response (CDAI) at week 26	407	Colonic: OR, 0.56 (95% CI, 0.32–0.96) Ileocolonic: OR, 0.34 (95% CI, 0.16–0.69)	(39)
Adalimumab	Mean change (CDEIS); Global Histologic Disease Activity Scores	70	Rectum-transverse colon: −68.5% to −90.6% CDEIS Right colon-ileum: −22.3% to −50.0% CDEIS Colonic: 28.3% GHDAS healing Ileum: 21.2% GHDAS healing	(41)
Anti-TNF	Endoscopic healing (SES-CD) ≤ 5) at a median of 13 months	156	Colonic: 79% Small bowel: 36%	(42)
SONIC-study	Endoscopic remission (ER) at week 26 (CDEIS, SES-CD)	172	ER rate of ileal ulcers significantly lower than colonic ulcers (P < 0.0001)	(44)
TAILORIX-study	Endoscopic remission (CDEIS <3) at week 12 and 54	122	Lower ER rates in the ileum vs. colonic segments (P < 0.01 all comparisons)	(45)
Infliximab	Mucosal healing (SES-CD: 0) and SES-CD change at week 30/38	101	MH transverse colon: 81% MH ileum: 45% SES-CD change (week 30/38) transverse colon: −94%/-94% SES-CD change (week 30/38) ileum: 67%/69%	(46)
Vedolizumab	Mucosal healing (absence of any ulcers, including aphthae) at week 26	101	Rectum 38.5%; descending colon 31.7%; transverse colon 51%; ascending colon 46.1%; ileum 20.6%	(47)

with the development of a penetrating disease phenotype, heightened risk of developing an intestinal complication and raised likelihood to undergo repeated surgeries in comparison to patients with isolated colonic involvement (Atreya and Siegmund, 2021). Optimized anti-inflammatory therapy is therefore essential in the management of these patients to prevent progressive bowel damage and disability. Limited evidence points out better therapeutic efficacy of antibiotics and sulfasalazine in colonic, while enteral nutrition seems to better work in ileal and ileocolonic Crohn's disease manifestations. Current evidence indicates lower efficacy of our targeted therapies in isolated ileal compared to colonic Crohn's disease. Although there are only a limited number of studies available, these observations have been made not only for anti-TNF agents, but for vedolizumab, ustekinumab and risankizumab as well (Table 1). Altogether, further research activities are need to elucidate site-specific mechanisms in ileal and colonic Crohn's disease and correlate them with response to therapies (Atreya and Siegmund, 2021). Furthermore, dedicated clinical trials are needed that specifically investigate the effectiveness of therapies in isolated Crohn's disease patients only. This would of course be challenging (e.g. recruitment of sufficient patients for an adequately powered trial), but would allow us to objectively assess the efficacy of each substance in a sufficiently powered trial. These studies will need to incorporate translational studies, as wells as granular endpoints to reflect therapeutic response. Only advanced understanding of the molecular mechanisms that drive ileal and colonic Crohn's disease will help us to optimize the therapy for the individual patient.

CRediT authorship contribution statement

Raja Atreya: Conceptualization, Writing – review & editing. **Christian Bojarski:** Writing – review & editing. **Anja A. Kühl:** Writing – review & editing. **Zlatko Trajanoski:** Writing – review & editing. **Markus F. Neurath:** Writing – review & editing. **Britta Siegmund:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **RA** has served as a speaker, or consultant, or received research grants from AbbVie, Amgen, Arena Pharmaceuticals, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Cellgene, Celltrion Healthcare, DrFalk Pharma, Ferring, Fresenius Kabi, Galapagos, Gilead, InDex Pharmaceuticals, Janssen-Cilag, Kliniksa Pharmaceuticals, Lilly, MSD Sharp & Dohme, Novartis, Pandion Therapeutics, Pfizer, Roche Pharma, Samsung Bioepsis, Takeda Pharma, Tillotts Pharma AG, Viatris. Research work of RA is funded by the DFG-SFB1181 (Project No. C02) and DFG-SFB/TRR241 (Project No. C02, C03, IBDome). Research work of **CB** is funded by DFG-SFB/TRR241 (Project No. C02). Research work of **AAK**, **ZT** is funded by the DFG-SFB/TRR241 (IBDome), and research work of **AAK** and **BS** is funded by DFG SFB1340-TPB06. **MFN** reports research grants and/or personal fees from Abbvie, MSD, Takeda, Boehringer, Roche, Pfizer, Janssen, Pentax and PPD. **BS** has served as a consultant for Abbvie, Arena, BMS, Boehringer, Celgene, Falk, Galapagos, Janssen, Lilly, Pfizer, Prometheus, Takeda and has received speaker's fees from Abbvie, CED Service GmbH, Falk, Ferring, Janssen, Novartis, Pfizer, and Takeda as a representative of Charité – Universitätsmedizin Berlin.

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