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Review

New and Old Therapeutic Options for Luminal Crohn's Disease - An Overview of Current Literature

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Special Issue: New and Old Therapeutic Options for Crohn's Disease

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Abstract

Crohn's Disease (CD) is a chronic inflammatory, relapsing and remitting condition that leads to structural damage of the bowel wall. It can be located in any part of the gastrointestinal tract with associated extra-intestinal manifestations. It varies in severity having many complications resulting in significant morbidity. In the past decade medical management of CD has evolved rapidly and with ongoing research it continues to show promising novel therapies. In this article we aim to give an overview of current literature on old and new therapy options for luminal CD looking at data including their efficacy and safety. With new oral biologic therapies such as the Janus Kinase inhibitor and gut specific targeted therapies developing their place in this ever growing marketplace treatment options for physicians are going to become even more challenging.

Keywords

Crohn's Disease; therapy; remission; induction

1. Introduction

Inflammatory bowel diseases (IBD), Ulcerative Colitis (UC) and Crohn's Disease (CD), are chronic, intermittent and, debilitating conditions. The prevalence of IBD in the UK is 0.5-1% with an estimated 600,000 people thought to be affected [1]. The aetiology remains unknown but it is thought to be a combination of genetic susceptibility with an environment trigger leading to an inappropriate up regulated mucosal immune response [2]. In addition CD has an increased mortality of up to 50% when compared to the background population [3].

Up until the 1960s, when studies reported the efficacy of steroids in CD, the fundamental treatment was supportive care and surgery [4]. Since then treatment has radically evolved. Current treatment involves glucocorticosteroids, 5-aminosalicylates, immunomodulators and biologics, of which includes, anti-tumour necrosis factor (anti-TNF) agents, interleukin-12/23 inhibitor (ustekinumab) and α4β7 integrin inhibitor (vedolizumab) and potential novel oral therapies.

Current treatment for CD is directed at inducing and maintaining clinical response and remission, with the ultimate aim of improvement in patient reported symptoms, prevention of disability, biomarker remission and complete endoscopic mucosal healing [5]. The wide variability in disease extent, and severity, alongside an ever-growing range of therapies can make decisions regarding treatment challenging. With developing therapies targeting lymphocyte trafficking, direct interleukin 23 inhibition and the specific janus kinase inhibitors this decision will undoubtedly become more complicated. In this article we provide an overview of existing data on old and new therapies for CD to help clinicians evaluate their current and potential future role in management.

2. Materials and Methods

A comprehensive evidence based electronic search in English using the PubMed database between 1965 to January 2019 was conducted. Key terms used included "inflammatory bowel disease", "Crohn's Disease", “therapies”, “treatments”, "5- aminosalicylic acid, 5-ASA", “corticosteroids”, “prednisolone”, ”azathioprine”, ”thiopurines “, ” methotrexate“, "anti TNF”, "infliximab", "adalimumab", "certolizumab pegol", " natalizumab", "vedolizumab", "ustekinumab", "tofacitinib", "upadacitinib" and "autologous haematopoietic stem cell therapy"

To include most up-to-date data a further search was conducted via the Congress of the European Crohn's and Colitis Organisation (ECCO), United European Gastroenterology Week (UEGW) and Digestive Disease Week (DDW) abstract database. Key terms used include "Crohn's" and "phase". Reference lists from retrieved articles were also examined to identify any additional studies of relevance.

3. Old and New Therapies

3.1 Anti-Inflammatory Therapies

3.1.1 5- Aminosalicylic Acid, 5-ASA

5- aminosalicylic acid (5-ASA), is first line therapy in patients with mild-moderate UC and is widely used in standard treatment for mild to moderate-severe UC. The actual benefits of 5-ASA in CD are controversial. Its role in maintenance therapy as well as post-surgical resection has been reviewed.

In 1993 a GETAID study divided patients into two groups, presumed high risk for early relapse or lower risk. Patients were given Pentasa, ® Ferring pharmaceuticals, 2g/day for 2 years. In the high risk of relapse group Pentasa reduced the relapse rate compared with placebo (29% versus 45%, p = < 0.003) [6]. A further study found that mesalazine reduced clinical relapse rates overall compared with placebo (25% versus 36%) but not reaching statistical significance [7]. A meta-analysis in 2011 reported that both sulfasalazine and mesalamine were ineffective in preventing relapse in patients with quiescent CD, but in a per protocol analysis mesalamine appeared to reduce the risk of relapse (RR=0.79; 95% CI=0.66-0.95, NNT=13) [8].

In regards to its role in the prevention of post-surgical relapse one study (after three years follow up) reported that 31% of patients treated with mesalazine 3g/day post resection had clinical recurrence compared with 41% in the control group (p = 0.031) [9]. Another showed mesalazine (asacol) 2.4g/day reduced clinical and endoscopic recurrence rates at 24 months but the significance of these results are questionable as the study was not double blinded and the control group did not receive placebo [10].

5- ASA are well tolerated and show low toxicity but with the conflicting and mixed results their role in CD is limited and not recommended by ECCO [11].

3.1.2 Glucocorticosteroids

Glucocorticosteroids (GCS) have an important role in active CD to induce clinical remission although their use often becomes limited due to their numerous side effects [12] and risk of dependence. Studies as early as the 1950's have shown benefit of GCS in CD. The National Cooperative CD Study, a randomised, prospective, double blind, placebo controlled trial reported prednisone (0.25–0.75 mg/kg/day) lead to a reduction in disease activity in 60% of patients versus 30% in the placebo group; improvement was based on the Crohn's Disease Activity Index (CDAI) [13].

Furthermore, GETAID's studies reported the ability of tapered GCS dosing to induce clinical remission in active colonic or ileocolonic CD. A prospective multicentre study of 142 patients showed more than 90% of patients achieved remission. Oral prednisolone (1 mg/kg/day) was administered for 3–7 weeks then reduced in steps of 5-10 mg per 10 days to discontinue. It should be noted, however, that only 29% of patients in clinical remission also achieved endoscopic remission [14]. The length of GCS treatment, did not appear to affect remission rate after cessation (85% after 7 weeks versus 87% after 15 weeks), however, multiple courses of GCS in the previous 3 years and short time period between treatments appear to be risk factors for relapse [15].

With the numerous side effects related to GCS newer studies have been developed to assess non-systemic GCS in the treatment of IBD such as budesonide and beclomethasone dipropionate. Budesonide is rapidly effective in its controlled ileal release (CIR) formulation [16, 17]. *Campieri et al* compared budesonide 9 mg once daily with budesonide 4.5 mg twice daily or prednisolone 40 mg/day in mild to moderate active CD. After eight weeks, remission was achieved in 60% treated with budesonide 9 mg once daily or prednisolone, and 42% treated with budesonide twice daily ($p = 0.062$) [16]. This was supported by another study by *Rutgeerts et al 1994* [17]. The properties of this gastric resistant formulation, together with its high GCS potency, rapid absorption and extensive first pass liver metabolism, reduce the risk of steroid associated side effects [12, 17].

Budesonide CIR has also been compared to mesalazine in mild to moderate active CD reporting that after 16 weeks, 62% of patients were in remission compared to 36% of those treated with mesalazine ($p < 0.001$) [18]. There may also be a role in maintenance therapy, budesonide 6 mg/day has shown to be significantly more effective than placebo in prolonging time to relapse in CD, and in switching steroid dependent patients from systemic steroids [12].

The British Society of Gastroenterology (BSG) (2019) and ECCO (2017) guidelines recommend steroids to induce remission but they have no role in maintaining remission [11, 19].

3.2 Immunomodulator Therapy

3.2.1 Thiopurines

Thiopurines (namely mercaptopurine, azathioprine and 6-thioguanine) are purine antagonists which inhibit DNA and RNA synthesis. They were introduced in the treatment of CD based on their effectiveness in treating other autoimmune conditions. Given the lengthy time until clinical response is observed in most patients (commonly response rates between 12-17 weeks) their main role is in maintenance therapy, as steroid sparing agents or in addition to biologics to prevent antibody production [20].

A meta-analysis reported that 73% of patients treated with azathioprine were able to maintain remission over 6–18 months, compared to 62% in the placebo group (RR 1.19, 95% CI, 1.05-1.34) [21].

A meta-analysis to assess the effectiveness of thiopurines for the induction of remission in active CD concluded that azathioprine and 6-mercaptopurine offer no advantage over placebo for induction of remission or clinical improvement. In this study 48% of patients achieved remission compared to 37% of placebo patients (5 studies, 380 patients; RR 1.23, 95% CI 0.97 to 1.55) [22]. However, this analysis reported statistically a significant difference in steroid sparing (defined as prednisone dose < 10 mg/day while maintaining remission) between azathioprine and placebo. In addition, 64% of azathioprine patients were able to reduce their prednisone dose to < 10 mg/day compared to 46% of placebo patients (RR 1.34, 95% CI 1.02 to 1.77) [22].

Both the AZTEC [23] and GETAID [24] study evaluated early use of azathioprine in CD. They concluded that azathioprine is no more effective than placebo or conventional therapy in increasing time of clinical or steroid free remission. Post-hoc analysis of the AZTEC study reported lower relapse rates in the azathioprine group than in the placebo group (11.8% vs 30.2%; $P = 0.01$) [23].

The landmark SONIC (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease), was a randomised, double-blind trial, evaluating the efficacy of infliximab monotherapy, azathioprine monotherapy, and infliximab and azathioprine combination therapy in immunomodulator and biologic naive patients with moderate-to-severe CD. The authors reported that combination therapy or infliximab monotherapy was more likely to induce a corticosteroid-free clinical remission than azathioprine monotherapy. For combination therapy 57% were in corticosteroid-free clinical remission at week 26 (the primary end point), as compared with 44% receiving infliximab alone (p=0.02) and 30% receiving azathioprine alone (p<0.001 for the comparison with combination therapy and p=0.006 for the comparison with infliximab) [25]. This is further supported by a meta-analysis by *Chande et al* [22]. One major factor for the increased efficacy is thought to be a lower incidence of infliximab antibody production and higher infliximab trough levels. This is supported by a post-hoc analysis of the SONIC study by *Reinisch et al* who found that higher infliximab trough levels were associated with steroid free remission and mucosal healing [26].

Despite well-established evidence that thiopurines are effective in CD there is some concern regarding their use due to rates of adverse reactions with up to 60% of IBD patients discontinuing therapy during their disease course [27]. Common adverse events include pancreatitis, leukopenia, nausea, allergic reaction and infection [21]. The increase risk of opportunistic infection has been shown to be increased 2-3 fold [28]. Several studies demonstrate an associated 1.3 to 1.7 overall relative risk of cancer such as lymphomas, myeloid disorders and skin cancers [27]. It is important to note that although the relative risk is increased, the absolute risk still remains small, and evidence shows that the treatment benefit outweighs the risk [29].

3.2.2 Methotrexate

Methotrexate is a folic acid antagonist with anti-interleukin properties. Two pivotal trials conducted by the North American Crohn's Study Group Investigators established the role for methotrexate in steroid dependence and maintaining remission. The first was a double-blind, placebo-controlled multicentre study of weekly 25mg injections of methotrexate in patients who had chronically active CD despite a minimum of three months of prednisone therapy. Results concluded that 39.4 % were in clinical remission in the methotrexate group, compared with 19.1 % in the placebo group (p = 0.025). The methotrexate group received less prednisone overall than those in the placebo group (p = 0.026) [30]. Their second study showed low dose methotrexate (15mg intramuscular once weekly) induced remission in 65% of patients at 40 weeks, compared with 39% in the placebo group (p=0.04). Also noted was that there were fewer patients in the methotrexate group than in the placebo group required prednisone for relapse (28% vs. 58 %, p=0.01) [31].

Despite this evidence there is a low clinical usage of methotrexate in CD. This may be due to the route of administration, high incidence of nausea when anti-emetics are not utilised (20%) or concerns regarding long term safety, especially regarding liver toxicity, given the lack of studies beyond 1 year [32].

The few long term studies show clinical benefit and ability to maintain remission substantially reduces over time. A meta- analysis by *Hausmann et al*, including 267 CD patients with long-term

follow-up, highlighted the cumulative probability to maintain remission on methotrexate monotherapy decreases by approximately 30% over a 3-year time period [33].

Since the first report of hepatosplenic T-cell lymphoma, with combined thiopurine and anti-TNF therapy, the use of methotrexate as choice of first line immunomodulator in paediatric CD has grown [34]. As these patients transition into adult services long term safety will need to be further evaluated.

The Combination of Maintenance Methotrexate-Infliximab Trial (COMMIT) aimed to evaluate the potential superiority of combination therapy over infliximab monotherapy. The addition of methotrexate to infliximab was well tolerated and lead to antibody suppression with higher trough levels. Unlike the SONIC trial these results did not correlate with an improvement in clinical outcome compared to infliximab monotherapy during the 50 weeks duration of the trial [35]. These results may have been due to several factors such as the study's inclusion criteria, concurrent steroid therapy or lack of synergistic effect of methotrexate and infliximab [35, 36]. Further studies are needed to evaluate this unanswered question.

In clinical practice The BSG and ECCO recommend immunomodulator therapy as steroid sparing agents [11, 19]. They are recommended for maintenance of remission but are not established therapy for induction of remission given their slow onset of action.

3.3 Calcineurin Inhibitors

Calcineurin inhibitors, Tacrolimus and Cyclosporine, suppress the production of inflammatory cytokines and T-cell activation. They have a narrow therapeutic window with side effects ranging from nausea to severe renal failure.

3.3.1 Tacrolimus

Tacrolimus is used as rescue therapy in refractory UC and has been used in fistulating CD. It does appear to be well tolerated and should be considered as an alternative therapy in refractory CD or those intolerant to conventional therapy. There are scarce and small studies evaluating its long term benefit and safety [37].

3.3.2 Cyclosporine

The first published randomised, control trial of oral cyclosporine in CD by *Brynskov et al* suggested 12 weeks of high dose cyclosporine (median 7.6 mg/kg/day) had beneficial therapeutic effect for induction of remission compared to placebo [38]. At the end of the treatment period 59% had improvement in the treatment group, compared with 32 % in the placebo ($p = 0.032$) [38]. A systemic review article by *McDonald et al* reported that further studies have failed to show any statistically significant benefit for clinical improvement or induction of remission for low dose cyclosporine treatment (5 mg/kg/day) [39]. Furthermore the primary trial by *Brynskov et al* had a small study number, lack of validated clinical grading scale and on review there are no statistically significant differences in the mean CDAI score at 12 weeks demonstrating it is no more effective than placebo for induction of remission in CD [39]. Higher doses have not been adequately evaluated. Current evidence indicates cyclosporine treatment has no role in CD.

3.4 Antibiotic Therapy in CD

Research has been published on the use of broad spectrum antibiotics in CD on the assumption and rationale that intestinal bacteria are involved in the pathogenesis of the disease.

A prospective study to report the effects of metronidazole and co-trimoxazole to induce remission in CD was published. Metronidazole was used as a single agent or in combination with co-trimoxazole, and compared with co-trimoxazole alone and a double placebo. After 4 weeks' there was no difference in response among the four groups [40]. In another study metronidazole (250mg four times daily) in combination with ciprofloxacin (500mg twice daily) was compared to a standard steroid treatment for 12 weeks. Both treatments showed similar rates of remission; suggesting a potential alternative to steroid treatment [41]. Unfortunately, systemic metronidazole is associated with significant side effects. Topical metronidazole 10% ointment has some benefit for peri-anal CD. This was associated with a reduction in Paediatric CDAI (PCDAI) of at least five points compared with the placebo group. It was well tolerated, with minimal adverse effects suggesting its use as a potential treatment for peri-anal pain and discharge [42].

A 6 month preliminary study by *Arnold et al* compared adding ciprofloxacin (500mg twice daily) versus placebo to the treatment of moderately active, but resistant cases of CD. The results reported a significant reduction in CDAI score compared to placebo group ($p < 0.001$) suggesting that it may be an effective agent [43].

An open-label study evaluating rifaximin 600 mg/day for 16 weeks in mild-moderately active CD concluded that 59% of patients achieved remission, with a significant reduction of the mean CDAI score compared with baseline [44]. This finding was not supported by a multicentre, double-blind, randomised, placebo-controlled trial that concluded rifaximin 800 mg twice daily was superior to placebo in inducing clinical remission but this was not statistically significant [45].

A 4 week study of 25 patients with active CD receiving ornidazole 500 mg/day showed that the CDAI score fell gradually from week 0 to week 4 ($p < 0.001$), the percentage of patients achieving remission increased progressively from week 0 to week 4 (75%) [46].

Anti-TB treatment was assessed in a 2 year placebo-controlled, double-blinded, randomised trial. Paratuberculosis, a mycobacterium avium subspecies, has been suspected as a cause of CD. Combination therapy with clarithromycin, rifabutin, and clofazimine was assessed in active CD, with a further year of follow-up. No evidence of a continued benefit was seen; some short-term improvement occurred at week 16 with significantly more patients achieving remission in the antibiotic arm (66%) than the placebo arm (50%) likely because of non-specific antibacterial effects [47].

The results suggest that antibiotics have a potential beneficial role in CD, however, further high quality studies are needed.

3.5 Probiotic Therapy

Probiotics have shown efficacy and promise in UC, however, none of those tested have shown effectiveness in inducing or maintaining remission in CD [48].

3.6 Anti-Tumour Necrosis Factor (TNF) Therapy

TNF cytokines play a vital role in the inflammatory process in CD hence targeted therapy with anti-TNF blockage. Infliximab, adalimumab and certolizumab pegol are anti-TNF antibodies approved for the treatment of moderate to severe CD, in those refractory or intolerant of conventional therapy. Certolizumab is not licensed for use in the UK. A meta-analysis in 2012 concluded that infliximab, adalimumab and certolizumab were effective as induction and maintenance therapy, including in those with fistulating disease [49]. Furthermore anti-TNF treatment has also been shown to be a strong inducer of mucosal healing [50].

3.6.1 Infliximab

Infliximab is an immunoglobulin G1 (IgG1) chimeric monoclonal antibody and is delivered intravenously. The ACCENT-I randomised control trial assessed the benefit of maintenance infliximab treatment in those with active CD who had responded to a single infusion of infliximab. The authors reported that those who responded to an initial dose of infliximab had a higher probability of remission at weeks 30 and 54, if infliximab therapy was maintained every 8 weeks. They were also more likely to stop glucocorticosteroids and to maintain their response for a longer period of time, with a similar incidence of infection across all groups [51]. Not only did this study highlight the efficacy of infliximab in maintenance therapy but it also concluded fewer hospital stays, higher rates of mucosal healing and less development of antibodies, it also provided a rationale for dose escalation in those losing response [52].

The ACCENT-II trial was then published 2 years later to evaluate infliximab effectiveness as maintenance therapy in fistulating CD. The trial included 306 patients with one or more draining abdominal or perianal fistulas of at least three month duration. At week 54, 19% in the placebo group had a complete absence of draining fistulas, as compared with 36% in the infliximab group ($p=0.009$) [53]. Two recent studies strongly suggest that optimal treatment of peri-anal fistulating CD requires significantly higher target infliximab levels in both induction and maintenance therapy [54, 55].

As previously discussed the SONIC trial in 2010 demonstrated the superiority of infliximab over azathioprine as well as the advantage of combination therapy [25].

3.6.2 Adalimumab

Adalimumab was the first designed fully human IgG1 monoclonal antibody against TNF. The CLASSIC-I trial established adalimumab as induction therapy. In this study 299 anti-TNF therapy naive patients were randomized to 4 dosing groups and received subcutaneous injections at weeks 0 and 2. The highest rate of remission was seen at the highest dose studied (160 mg at week 0, 80 mg at week 2) with a remission rate of 36% versus 12% in the placebo group ($p= 0.001$) [56]. There was a linear dose response curve with a ceiling effect not achieved therefore it is unclear if higher dosing would be more effective [57]. The GAIN trial further evaluated adalimumab as an induction agent but this time as second line therapy in those who failed infliximab therapy. In this study 301 patients completed the trial with 21% in the adalimumab group versus 7% in the placebo group achieving remission at week 4 ($p < 0.001$) [58].

Both the CLASSIC-II and CHARM studies evaluated the efficacy and safety of adalimumab as maintenance therapy. CLASSIC-II followed up 276 patients from CLASSIC-I study. In this study 55 patients in remission at both weeks 0 and 4 were re-randomised to adalimumab 40 mg every other week, 40 mg weekly, or placebo for 56 weeks. Patients not in remission were enrolled in an open-label arm and received adalimumab 40 mg every other week. For those patients randomised at week 4, 79% who received adalimumab 40 mg every other week and 83% who received 40 mg weekly were in remission at week 56, versus 44% for placebo (p = 0.05). In the open-labelled arm 46% patients were in clinical remission at week 56. [59] The larger open-label CHARM study enrolled 854 patients who did not responding to alternative immunosuppression including infliximab. The percentage of randomised responders in remission was significantly greater in the adalimumab group compared to placebo. At week 56, every other week and weekly dosing of adalimumab 40mg, was similarly effective, 36% and 41%, and superior to placebo 12% (p < .001) [60].

The DIAMOND study, an open-labelled prospective study of 177 patients, compared adalimumab monotherapy with adalimumab combination therapy with azathioprine (25-200mg daily), in biologic and thiopurine naive patients [61]. The primary end point was clinical remission at 26 weeks (CDAI $\leq$150) and Simple Endoscopy Score for CD (SES-CD) was assessed at week 26 and 52. The results reveal that clinical remission rate at week 26 was not significantly different between the two groups (71.8% versus 68.1%; p = 0.63). However, the rate of endoscopic improvement at week 26 was significantly higher in the combination group than in the monotherapy group (84% versus 64%; p = 0.019) [61].

A phase III trial by *Colombel et al* has reported that adalimumab therapy induces healing of draining fistulas in patients with active CD. The mean number of draining fistulas per day was significantly decreased compared with placebo treated patients. In most patients complete fistula healing was sustained for up to 2 years [62].

Adalimumab was well tolerated in all studies with similar adverse events in all groups except injection site reactions were more common with adalimumab [56, 59]. In the CHARM trial a greater percentage of patients receiving placebo discontinued treatment because of an adverse event (13.4%) than those receiving adalimumab (6.9% and 4.7% in the every other week and weekly dosing groups, respectively) [60] This highlights the importance and benefit of disease control.

3.6.3 Certolizumab Pegol

Certolizumab pegol is an antigen-binding fragment (Fab') of an IgG antibody attached to polyethylene glycol that has a high affinity for anti-TNF [48].

A large phase II trial reported its efficacy in moderate to severe CD. The clinical response rates were highest for certolizumab 400 mg, greatest at week 10 (certolizumab 52.8%; placebo 30.1%; p = .006) but this significance was lost at week 12 (certolizumab 44.4%; placebo 35.6%; p = 0.278) presumed due to high placebo rates in patients with low serum CRP [63]. This was then followed up by the PRECiSE-I, II and III trials which reported certolizumabs benefit in induction and maintenance therapy in moderate to severe CD. PRECiSE-I reported modest improvement in response rates at week 6 and 26, as compared with placebo, but with no significant improvement in remission rates [64]. PRECiSE-II and III went on to successfully demonstrate maintenance of

remission [65, 66]. In PRECiSE-II patients who responded to induction therapy at week 6, remission (defined by a CDAI score of ≤150) at week 26 was achieved in 48% of patients in the certolizumab group and 29% of those in the placebo group ($p<0.001$) [65]. Furthermore the MUSIC trial reported evidence of mucosal healing with certolizumab therapy as early as week 10 and maintained through week 54 [67]. In addition post-hoc analysis of the PRECiSE-II study reported improved likelihood of sustained fistula closure [68].

The PRECiSE-III study followed patient on certolizumab for up to 7 years. During 1920 patient-years of exposure no new safety signals were experienced. Regarding serious infection and malignancies, incidence rates (new cases/100 patient-years) were 4.37 and 1.06 respectively. Lymphoproliferative malignancies were not reported [66].

With lack of direct comparative studies the choice of initial or subsequent CD therapies can be challenging. *Hazlewood et al* performed a meta-analysis of 39 randomised controlled trials comparing methotrexate, azathioprine/6-mercaptopurine, infliximab, adalimumab, certolizumab, vedolizumab, or combined therapies with placebo or an active agent for induction and maintenance of remission in patients with CD. They concluded that adalimumab and infliximab plus azathioprine show superior efficacy [69]. Again, highlighting the important therapeutic role of anti-TNF therapy.

With all anti-TNF therapy the most significant adverse effects are opportunistic infections, malignancies, injection/infusion reactions and autoantibody formation. A meta-analysis evaluated 21 studies concluding that there were no differences in the frequency of death, malignancies or severe infections. There was however noted to be an increased frequency of hepatosplenic T-cell lymphoma in young patients [70]. A further meta-analysis by *Kawalec et al* evaluated 19 studies. This reported no statistically significant difference in the incidence of any adverse effects during long-term maintenance therapy with the anti-TNF agents when compared with placebo (RR = 0.99, 95% CI: 0.93–1.05, p = 0.72) [49].

ECCO recommend anti-TNF therapy for moderate to severe CD which is steroid dependent despite immunomodulator use, or, in widespread active disease particularly with adverse prognostic factors [11]. The BSG also support this recommendation with a further statement that combination infliximab and thiopurine therapy should be used rather than monotherapy [19]. Furthermore the consensus from both BSG and ECCO is that all anti-TNF therapies have similar efficacy in luminal CD and similar reported adverse effects therefore therapy choice is situation dependent e.g availability, patient preference, cost [11, 19].

3.7 Anti-Integrin Based Therapy

3.7.1 Natalizumab

Studies of natalizumab, a monoclonal antibody that modulates gut and brain lymphocyte migration by antagonising $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin, showed promising results in CD including modest induction benefits, rising response and remission rates over 12 weeks and maintenance effects [71]. However its use has been limited by the development in some patients of progressive multifocal leukoencephalopathy (PML), an opportunistic brain infection that is caused by reactivation of latent JC polyomavirus and can be fatal [72, 73].

3.7.2 Vedolizumab

Vedolizumab is a "gut-selective" humanised IgG1 monoclonal antibody that binds to $\alpha_4\beta_7$ integrin expressed on the surface of lymphocytes [74]. It is gut selective, hence theoretically less likely to cause PML but may have similar kinetic characteristics to Natalizumab [71].

The GEMINI trials, demonstrated vedolizumab's efficacy as induction and maintenance therapy in patients with moderately to severely active UC or CD who were naive to, or had prior exposure to, TNF antagonists [71, 75]. Post-hoc analysis of the GEMINI trials report vedolizumab has increased efficacy over placebo in CD regardless of previous anti-TNF status. Overall, however, rates of response and remission were higher when vedolizumab was used as a first line biologic. Responders to vedolizumab induction at week 6 (48.9% of TNF-naive and 27.7% of TNF-failure patients) were in remission with vedolizumab at week 52 (versus 26.8% and 12.8% with placebo). Efficacy appeared to be similar between the different types of anti-TNF failure or number of previous failed, and the safety profile was similar in both subgroups [75].

Furthermore post-hoc analysis of GEMINI-2 reported beneficial effects in fistulating CD [76]. Exploratory analyses were conducted in 461 responders to 6 week vedolizumab induction therapy who received maintenance placebo (VDZ/PBO, n = 153) or vedolizumab (VDZ/VDZ, n = 308).Data from 153 (33%) patients with a history of fistulating CD and 57 (12%) patients with ≥1 actively draining fistula was evaluated. Fistula closure rates at week 14 were higher in VDZ/VDZ treated patients compared VDZ/PBO (28% versus 11%, 95% CI-11.4-43.9). Also patients in the VDZ/VDZ group had faster time to fistula closure and were more likely to have fistula closer at week 52 [76].

Vedolizumab is thought to have a slow onset of action. A post-hoc analysis of GEMINI phase 3 trials reported significantly improved patient-reported symptoms (abdominal pain and stool frequency) as early as week 2 and this continued to improve through the first 6 weeks, particularly when vedolizumab was used as first-line biologic therapy [74].

Vedolizumab is thought to have a favourable safety profile and this was supported in a review evaluating the safety data from six trials of vedolizumab, this included 2830 patients with 4811 persons-years of vedolizumab exposure [77]. There was no increased risk of any infection or serious infection. Serious clostridium infections, sepsis and tuberculosis were reported infrequently (≤0.6% of patients). No cases of PML were observed. <1% (18) patients treated with vedolizumab were diagnosed with a malignancy [77].

ECCO consensus recommend vedolizumab as therapy for moderate to severe CD who have failed anti-TNF or immunomodulator therapy, or those refractory to corticosteroids [11]. The BSG also recommend vedolizumab in both anti-TNF naive patients and in those where anti-TNF treatment has failed [19].

3.7.3 Etrolizumab

Etrolizumab is a humanised anti-β7 monoclonal antibody which has been evaluated in moderate to severe CD as an induction agent. The phase III BERGAMOT study included 300 patients with moderate to severe CD (refractory/intolerant to anti–TNF agents, immunosuppressants, and/or corticosteroids) [78]. Patients were assigned to 3 groups (2:2:1) etrolizumab 105 mg subcutaneously every 4 weeks, etrolizumab 210 mg at weeks 0, 2, 4, 8, and 12, or placebo for 14 weeks.

Symptomatic remission was achieved in a greater proportion of patients who received ertolizumab at both doses compared with placebo from week 6 through to 14. At week 14 endoscopic improvement (≥50% reduction from baseline SES-CD was achieved in 21% and 17.4% of patients who received ertolizumab (105mg and 210mg respectively) compared to 3.4% who received placebo. Etrolizumab was well tolerated and there were no reports of PML [78].

3.7.4 Alicaforsen

Targeted inhibition of the endothelial ligands intercellular adhesion molecule-1 (ICAM-1) and mucosal addressin cell adhesion molecule (MAdCAM) has been recognised in IBD. These two molecules are involved in leukocyte recruitment and are over expressed in inflamed mucosa hence targeted therapy [79].

Alicaforsen is an ICAM-1 anti-sense oligonucleotide and highly selective ICAM-1 inhibitor. Intravenous therapy in CD showed no significant efficacy compared to placebo [80]. Promising results where however seen in pouchitis.

3.7.5 SHP647

SHP647 is an anti-MAdCAM-1 monoclonal antibody. In the OPERA study patients were randomised to SHP647 22.5 mg, 75 mg, 225 mg or placebo [81]. The phase 2 study reported the clinical end-point of a 70 CDAI point decrease from baseline at week 8 or 12 was not significantly different between SHP647 and placebo. Despite this finding SHP647 showed a continued dose related decrease in soluble MAdCAM and a dose related increase in circulating β_7+ central memory T cells showing active pharmacology [82].

The 72 week OPERA-II phase 2 extension study was designed to assess the long-term safety and efficacy of SHP647 [83]. Patients were enrolled who had completed the 12 week induction phase of OPERA-I or had a clinical response to 225 mg SHP647 in the open-label TOSCA study [81, 84]. In total 268 patients entered the treatment period with 149 completing the study. All patients received 75mg of SHP647 subcutaneous every 4 weeks; dose de-escalation to 22.5 mg or escalation to 225 mg could be performed. Over the course of the study no patient required dose reduction. However 157 patients required dose escalation with these patients appearing to have higher inflammatory indicators. Furthermore 19.8% of patients in the treatment period discontinued therapy due to adverse events, the most common being a CD flare. In total, 92.9% of patients experienced an adverse event, but these were deemed to be treatment related in only 46.3% of patients. The most common treatment related adverse event were nasopharyngitis (5.6%), arthralgia (6.0%), and headache (5.2%). Furthermore, results reported a sustained Harvery Bradshaw Index response rate suggesting efficacy of SHP647 over 72 weeks of treatment. No reports of PML were demonstrated [83].

3.7.6 Andecaliximab

Matrix metalloproteinase-9 (MMP9) plays a role in the underlying pathogenesis of CD. The efficacy of andecaliximab, a MMP9 inhibitor, as induction therapy in moderate to severe CD has been reported in a phase 2 randomised, placebo-control trial [85]. In this study 187 patients were randomised to receive subcutaneous injections of placebo weekly, andecaliximab 150mg every 2

weeks, andecaliximab 150mg weekly or andecaliximab 300mg weekly, for 8 weeks. The primary endpoint of patient-reported clinical response and endoscopic response failed to show a meaningful difference between the andecaliximab group and placebo group. Andecaliximab was well tolerated [85].

3.7.7 E6011

E6011 is a humanised anti-fractalkine monoclonal antibody which could provide a potentially novel therapy for CD. Fractalkine/CX3CL1 has been demonstrated as new type of leukocyte trafficking regulator. It signals via its leukocyte receptor CX3CR1 allowing them to migrate directly to inflammatory sites [86].

A phase 1/2 study was conducted in patients with mild to moderate CD who had failed conventional therapy [86]. In this study 28 patients were allocated to one of four dosing groups (2, 5, 10, and 15 mg/kg). E6011 was administered intravenously every 2 weeks for 12 weeks. At week 12, CDAI decrease ≥ 70, CDAI decrease ≥ 100 and clinical remission (CDAI $\leq$ 150) were seen in 10/25 (40%), 9/25 (36%) and 4/25 (16%) patients who had baseline CDAI ≥ 220, respectively. In total 9 patients had a clinical response/remission at week 12 then entered an extension period were they received the same dosing. Results report 4/7 (57%) of these patients had a sustained CDAI decrease ≥ 70 or clinical remission at week 52.

This drug appears safe and well tolerated; the most common adverse event reported was a viral upper respiratory tract infection. Serious adverse events were not considered to be related to the study drug [86].

3.8 Anti-Interleukin Therapy

3.8.1 Ustekinumab

Ustekinumab is a human IgG kappa monoclonal antibody that blocks interleukin-12 and interleukin-23.

The UNITI trials established ustekinumab's role in both induction and maintenance. UNITI-1 and UNITI-2 were 8 week induction trials, UNITI-1 in 741 patients who failed anti-TNF α therapy and UNITI-2 in 628 patients who failed conventional therapy. Both established that ustekinumab was more effective than placebo at inducing remission, with statistically significant clinical response (CDAI decrease ≥100points) seen at week 6. In UNITI-1 33.7% and 34.3% (6 mg/kg and 130 mg dosing group, respectively) achieved clinical response versus 21.5% in the placebo group [87]. In UNITI-2 at week 6, 55.5% and 51.7% achieved clinical response versus 28.7% in the placebo group [88].

Similar results were seen for clinical remission at week 8. In UNITI-1 clinical remission was seen in 20.9% and 15.9% (6 mg/kg and 130mg dosing group, respectively) versus 7.3% in the placebo group ($p < 0.001$, $p = 0.003$, respectively) [87]. In UNITI-2 at week 8, 40.2% and 30.6% were in clinical remission versus 19.6% in the placebo group ($p \leq 0.009$) [88]. Secondary analysis did conclude that there was a non-significance in CDAI score compared to placebo in UNITI-1 compared to UNITI-2, however, the results still favour ustekinumab treatment [89].

IM-UNITI highlighted ustekinumab as maintenance therapy. In this study 397 patients who completed the induction trials were randomised to maintenance subcutaneous injections of either

90 mg every 8 weeks, 90mg every 12 weeks or placebo. A significantly greater proportions of patients maintained clinical response at week 44; 59.4% in the 8 weekly group and 58.1% in the 12 weekly group versus 44.3% administered placebo (p=0.05 for both) [89]. A further study of 140 patients, of which >90% failed anti-TNF therapy, reported the role in maintenance therapy with clinical, endoscopic and radiological response. In total 71.8% maintained clinical response at 52 weeks, with 64.4% maintaining endoscopic or radiological response [90].

There have been retrospective reports of ustekinumab in peri-anal CD. Post-hoc analysis including data from the UNITI trials reported complete fistula resolution was obtained in 14.1% in the placebo group, 24.2% in the 130mg dosing group, 27.7% with 6mg/kg dosing and 24.7% of all ustekinumab at week 8. The IM-UNITI study also reported a higher percentage of patients in the ustekinumab group had fistula response compared to placebo (80% versus 45.5%). Although none of these results show statistical significance it shows ustekinumab may have some role in peri-anal disease with more studies needed to conclude its significance [91].

Ustekinumab safety has been well established in the treatment of psoriasis and in CD clinical trials the serious adverse event rate is similar to placebo [90]. There were no reported cases of death, malignancy, lymphoma or serious infections during a long-term maintenance study [90]. Biologics have not been extensively evaluated in pregnancy. A recent case study highlighted that, when checked in a woman treated with ustekinumab until week 30 of pregnancy, the cord blood ustekinumab level was markedly higher than the maternal blood level. There were no adverse effects noted on the baby in the follow up period of one year [92].

The BSG advise that ustekinumab can be used as induction and maintenance therapy for CD, both in anti-TNF naive patients and in those where anti-TNF treatment has failed [19]. There is no updated consensus from ECCO.

3.8.2 Brodalumab

Brodalumab is a humanised monoclonal antibody that targets interleukin-17. A phase 2 randomised, double-blinded, placebo-controlled study was conducted in those with moderate to severe CD. The study reported disappointing results with a disproportionate incident of cases of worsening CD in active treatment groups and no evidence of significant effectiveness. The study was terminated early [93].

3.8.3 Risankizumab

Risankizumab is a humanised monoclonal antibody that targets the p19 subunit of interleukin 23. In a phase 2 study by *Feagan et al* it was superior over placebo in inducing clinical and endoscopic remission [94]. In this study 121 patients with moderate to severe CD were randomised to receive risankizumab 200mg, 600mg or placebo at week 0, 4 and 8. At week 12 31% of risankizumab patients compared to 15% of placebo were in clinical remission (p=0.0489). In the 200mg dosing group 24% had clinical remission compared to 37% in the 600mg dosing group [94]. A follow up open-label extension study found that extended induction therapy was effective at increasing clinical response and remission at week 26. Furthermore at week 52 71% of these people had maintained clinical remission; 81% had clinical response, 35% showed endoscopic remission and 55% and endoscopic response [95].

Risankizumab was well tolerated with most adverse events deemed mild or moderate and considered unrelated to treatment. The most frequent adverse events were arthralgia (22%), headache (20%), abdominal pain (18%), nasopharyngitis (16%), nausea (16%), and pyrexia (13%) [95].

3.8.4 Brazikumab (MEDI2070)

Brazikumab, similar to Risankizumab, is a humanised monoclonal antibody that selectively targets p19 on the subunit of interleukin 23. A phase 2a induction study demonstrated clinical effectiveness in 121 patients with moderate to severe CD, who previously had failed anti-TNF therapy. At week eight, clinical response (> 100 drop from baseline CDAI score or CDAI < 150) was achieved in 49.2% of patients in receiving brazikumab, compared to 26.7% of patients receiving placebo (p = 0.010) [96]. Brazikumab appeared to be well tolerated with similar adverse events as Risankizumab, most commonly headache and nasopharyngitis [96].

The role of selective blockage of interleukin 23 in the treatment of CD needs further evaluation. Other early studies are undergoing for guselkumab (CNTO1959), tildrakizumab (MK3222), and mirikizumab (LY3074828) [97].

3.9 Janus Kinase (JAK) Inhibitor Therapy

3.9.1 Tofacitinib

In August 2018 Tofacitinib, an oral non-selective JAK inhibitor, received European approval for the treatment of moderate to severe UC. It's efficacy has been shown in UC by the OCTAVE trials. Phase 2b studies evaluating tofacitinib in CD were conducted by Panés et al [98]. After week 8 of induction therapy, the percentage of patients with clinical remission (CDAI <150) was 43.5% and 43.0% with 5 and 10 mg twice daily dosing, compared with 36.7% in the placebo group (p=0.325 and p=0.392 for 5 and 10 mg twice daily versus placebo). In the 26-week maintenance phase, the primary endpoint (clinical response-100 or clinical remission) was seen in a higher proportion of patients in the tofacitinib 10 mg dosing group than placebo (55.8% versus 38.1%, p=0.130) Despite this evidence of minor efficacy these findings did not reach statistically significance [98]. Tofacitinib has yet to demonstrate its efficacy in CD.

3.9.2 Upadacitinib

Unlike tofacitinib, upadacitinib, is a selective oral JAK 1 inhibitor. Data from the CELEST study reported upadacitinib as induction and maintenance therapy in CD [99, 100]. A sub analysis of a 16 week induction study of 220 patients reported that a significantly greater number of patients treated with upadacitinib (6, 12 and 24mg twice daily) achieved modified clinical remission as early as week 4 compared with placebo [99].

A phase 2 CELEST extension trial reported outcomes after 52 weeks of therapy [100]. Patients who completed the 16 week induction phase were re-randomised to receive upadacitinib 3mg twice daily, 12mg twice daily, or 24mg daily for 36 weeks. The 24mg group was subsequently stopped, with a 6mg twice daily dosing group initiated to evaluate an intermediate maintenance dose. Dose dependent results were observed, and increased rates of modified clinical remission

and endoscopic remission were overall greater in the 6mg and 12mg groups. In those who achieved clinical and endoscopic response at week 16 modified clinical remission was seen in 41.2%, 62.5%, 73.3% and 40% of the 3mg, 6mg, 12mg and 24mg group respectively at 52 weeks. Furthermore endoscopic remission was achieved in 25%, 25%, 37.5% and 10% in the 3mg, 6mg, 12mg and 24mg group respectively [100].

The general safety profile was similar to other studies in rheumatoid arthritis. There were no dose dependent adverse events. One case of Hodgkin's disease and one case of malignant neoplasm of thymus occurred in the 12mg dosing group [100].

3.9.3 Filgotinib

Filgotinib is another selective JAK 1 inhibitor administered orally once daily. The phase 2 FITZROY study enrolled 174 patients with active CD randomised to 2 groups, 200mg Filgotinib once daily or placebo, for 10 weeks. 47% of patients treated with filgotinib achieved clinical remission compared to 23% treated with placebo (p= 0.0077) [101]. An analysis of all periods of filgotinib and placebo exposure over 20 weeks found serious treatment related adverse effects were reported in 9% (14/152) of filgotinib treated patients compared to 4% (3/67) of placebo [101].

Further phase 3 studies on selected JAK inhibition are awaited.

3.10 Sphingosine-1-Phosphate (S1P) Therapy

3.10.1 Ozanimod

Studies have shown Ozanimod, an oral immunomodulator that selectively targets $S1P_1$ and $S1P_5$, is effective and safe in the treatment of UC. The STEPSTONE trial further questions its role and efficacy in CD [102]. This phase 2, open-label study evaluated endoscopic improvement and clinical outcomes following treatment with ozanimod 1mg daily for 12 weeks in 69 patients with moderate to severe CD. Patients with available data at baseline and week 12 were included in the analysis of the SES-CD matched intestinal segments (n=60) and the analysis of CDAI (n=59). SES-CD score reductions from baseline of ≥50% were seen in 27% of patients and of ≥25% in 43% of patients. Patients who had shorter disease duration and lower disease severity had a greater endoscopic response. At week 12, in 66% of patients a CDAI response (CDAI decrease ≥100) was seen, and CDAI remission (CDAI < 150) in 46% [102].

Through the study most reported adverse events appeared to be related to underlying CD [102]. Another S1P modulator Etrasimod is showing promising results in phase 2 trials for UC but trials for CD are awaited [103].

3.10.2 Laquinimod

Laquinimod is also an oral novel S1P receptor immunomodulator. A phase 2 study by *D'Haens et al* suggests a treatment benefit in induction therapy in moderate to severe CD. Laquinimod 0.5 mg showed consistent effects on remission, 48.3% versus 15.9% in the placebo group at week 8. Furthermore 55.2% in the treatment group achieved a reduction in CDAI >100 versus 31.7% in the placebo while 62.1% achieved a CDAI reduction >70 versus 34.9% in the placebo. It appeared safe and well tolerated [104]. Further phase 3 studies have not taken place.

3.11 Autologous Haematopoietic Stem Cell Therapy

Autologous haematopoietic stem cell transplantation (AHSCT) as treatment for refractory CD has been investigated in a limited number of small volume studies. Currently the ASTIC study is the only randomised control trial of AHSCT in CD [105]. Included were patients with refractory CD not amenable to surgery despite treatment with ≥3 immunosuppressive/biologic therapies. 23 patients underwent AHSCT. The control group was comprised of 22 patients who received standard CD treatment. The primary aim was sustained disease remission at 1 year; CDAI <150, no active treatment for at least 3 months, and no endoscopic/radiological evidence of active disease. The results were not statistically significant with only 2 patients (8.7%) achieving the primary outcome versus 1 control patient (4.5%) (p =0 .60). AHSCT was also associated with significant toxicity with 76 reported serious adverse events versus 38 in the control group [105].

The primary outcomes in ASTIC have been criticized for being too stringent. A further 1 year follow up study, including pooled data from ASTIC, showed clinical benefit in 40 transplant patients [106]. Evidence of efficacy with complete endoscopic healing in 50% of patients, and 47% were assessed as free of disease on endoscopy and radiology imaging at 1 year. Additionally those who relapsed were re-sensitised to anti-TNF therapy to which they had previously been refractory. Of the 23 patients with available data 76 serious adverse events occurred, most commonly treatment related infection. Smoking and per-anal disease were associated with increased serious adverse events [106].

A recent Retrospective Survey of Long-term Outcomes from the European Society for Blood and Marrow Transplantation found 68% post AHSCT patients experienced complete remission/significant improvement in symptoms at a median follow-up of 41 months. It again highlighted re-sensitivity with 57% (24/42) patients responsive to therapies of which they had previously been refractory, and similar to ASTIC perianal disease was associated with adverse treatment free survival [107].

These show the potential treatment benefit of AHSCT in a specific cohort of patients.

3.12 Bispecific Antibodies

A bispecific antibody is an antibody containing two different antigen-binding sites in one molecule. The main use of these currently is in oncology with catumaxomab and blinatumomab approved for clinical use. Further novel bispecific antibodies are being evaluated in pre-clinical and clinical trials for the treatment of inflammatory conditions, such as psoriatic arthritis [108]. These bispecific antibodies target cytokines and integrins involved in IBD pathogenesis. Given the complexity of the pathogenesis of CD bispecific antibodies targeting multiple cytokine pathways is proposed as a potential future alternative therapy [109].

4. 'Treat-to Target' Approach in Crohn's Disease

The risk of colorectal and small bowel cancer is increased two to eightfold among IBD patients with various factors such as persistent inflammation contributing to this increased risk [3]. The 'Treat to target' strategy in CD has changed the primary aim of treatment with a focus on absolute control of inflammation.

The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) programme was undertaken by the International Organisation for the Study of Inflammatory Bowel Diseases [5]. The programme used evidence-based expert consensus to set targets for monitoring and adjusting treatment to achieve that target. The recommendations for treating to target in CD are clinical and patient-reported remission, and endoscopic remission. Clinical and patient reported remission is defined as resolution of abdominal pain and diarrhoea or altered bowel habit (assessed at least every 3 months until resolution, then every 6 to 12 months). Endoscopic remission is defined as resolution of ulceration at ileocolonoscopy, or resolution of inflammation on cross-sectional imaging in patients who cannot be assessed adequately by ileocolonoscopy (assessed at least every 6 to 9 months during active disease). Biomarker, C-reactive protein (CRP) and faecal calprotectin are considered an adjunctive target [5].

The CALM study supports this approach [110]. The CALM Study was the first study to demonstrate that the decision to escalation therapy using combined clinical symptoms and biomarkers, faecal calprotectin and CRP, results in better clinical and endoscopic outcomes. In this study 244 CD patients were randomised into 2 groups. A significantly greater proportion of patients in the group combining biomarkers and clinical symptoms achieved mucosal healing at 48 weeks compared to those using clinical symptoms alone; 46% versus 30% [110]. The REACT study also highlighted the importance of evidence of mucosal healing as objective measures and clinical remission appear to correlate poorly with disease activity [111].

The 'Treat to Target' approach is quickly becoming gold standard in most practise. Full implementation of this approach will be challenging due to numerous factors such as resources and patient compliance.

5. Conclusion

CD has significant morbidity associated with lack of disease control. With old therapies showing significant potential toxicity and unclear efficacy the new targeted therapies are becoming more attractive choices in the management of CD to induce deep clinical remission. With lack of direct comparative or combination studies the choice of initial or subsequent therapies can be challenging. Anti- TNF therapy remains an important treatment option with the most clinical evidence and analysis of cost-effectiveness shows infliximab domination over both adalimumab and ustekinumab in terms of net monetary benefit [112]. The addition of selective JAK inhibition, targeted interleukin-23 blockage and potential bispecific antibodies are exciting prospective therapies for future clinical therapy. Furthermore potential oral therapies have numerous benefits, including, the lack of requirement for hospital attendance and equipment for injection, no autoantibody formation and short half-life. Future trials will help conclude their place in the management of this complex and debilitating condition.

Author Contributions

Rachel Rutherford wrote the manuscript with additional guidance in drafting and editing from Patrick B Allen.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012; 142: 46-54. Available from: https://doi.org/10.1053/j.gastro.2011.10.001.
2. Baumgart DC, Sandborn WJ. Crohn's disease. Lancet (London, England). 2012; 380: 1590-1605.
3. Burisch J, Munkholm P. The epidemiology of inflammatory bowel disease. Scand J Gastroenterol. 2015; 50: 942-951.
4. Jones JH, Lennard-Jones JE. Corticosteroids and corticotrophin in the treatment of Crohn's disease. Gut. 1966; 7: 181-187.
5. Peyrin-Biroulet L, Sandborn W, Sands BE, Reinisch W, Bemelman W, Bryant RV, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining therapeutic goals for treat-to-target. Am J Gastroenterol. 2015; 110: 1324-1338.
6. Gendre JP, Mary JY, Florent C, Modigliani R, Colombel JF, Soule JC, et al. Oral mesalamine (Pentasa) as maintenance treatment in Crohn's disease: A multicenter placebo-controlled study. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID). Gastroenterology. 1993; 104: 435-439.
7. Sutherland LR, Martin F, Bailey RJ, Fedorak RN, Poleski M, Dallaire C, et al. A randomized, placebo-controlled, double-blind trial of mesalamine in the maintenance of remission of Crohn's disease. The Canadian Mesalamine for Remission of Crohn's Disease Study Group. Gastroenterology. 1997; 112: 1069-1077.
8. Ford AC, Kane S V, Khan KJ, Achkar J-P, Talley NJ, Marshall JK, et al. Efficacy of 5-aminosalicylates in Crohn's disease: Systematic review and meta-analysis. Am J Gastroenterol. 2011; 106: 617-629.
9. Mcleod RS, Wolff BG, Steinhart AH, Carryer PW, Rourke KO, Andrews DF, et al. Prophylactic mesalamine treatment decreases postoperative recurrence of Crohn 's disease. Gastroenterology. 1995; 109: 404-413.
10. Caprilli R, Andreoli A, Capurso L, Corrao G, D'Albasio G, Gioieni A, et al. Oral mesalazine (5-aminosalicylic acid+ADs- Asacol) for the prevention of post-operative recurrence of Crohn's disease. Gruppo Italiano per lo Studio del Colon e del Retto (GISC). Aliment Pharmacol +ACY-Ther. 1994; 8: 35-43.
11. Gomollón F, Dignass A, Annese V, Tilg H, Assche G Van, Lindsay JO, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 1: Diagnosis and medical management. J Crohn's Colitis. 2017; 11: 3-25.
12. Campieri M. New steroids and new salicylates in inflammatory bowel disease: A critical appraisal. Gut. 2002; 50 Suppl 3: III43-46.
13. Summers RW, Switz DM, Sessions JTJ, Becktel JM, Best WR, Kern FJ, et al. National Cooperative Crohn's Disease Study: Results of drug treatment. Gastroenterology. 1979; 77: 847-869.

14. Modigliani R, Mary JY, Simon JF, Cortot A, Soule JC, Gendre JP, et al. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives. Gastroenterology. 1990; 98: 811-818.
15. Brignola C, De Simone G, Belloli C, Iannone P, Belluzzi A, Gionchetti P, et al. Steroid treatment in active Crohn's disease: A comparison between two regimens of different duration. Aliment Pharmacol Ther. 1994; 8: 465-468.
16. Campieri M, Ferguson A, Doe W, Persson T, Nilsson L, Budesonide G. Oral budesonide is as e V ective as oral prednisolone in active Crohn 's disease. Gut. 1997; 41: 209-214.
17. Rutgeerts P, Lofberg R, Malchow H, Lamers C, Olaison G, Jewell D, et al. A comparison of budesonide with prednisolone for active Crohn's disease. N Engl J Med. 1994; 331: 842-845.
18. Thomsen OO, Cortot A, Jewell D, Wright JP, Winter T, Veloso FT, et al. A comparison of budesonide and mesalamine for active Crohn's disease. International Budesonide-Mesalamine Study Group. N Engl J Med. 1998; 339: 370-374.
19. Lamb CA, Kennedy NA, Raine T, Hendy P, Smith PJ, Jimmy K. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019.
20. Lim SZ, Chua EW. Revisiting the role of thiopurines in inflammatory bowel disease through pharmacogenomics and use of novel methods for therapeutic drug monitoring. Front Pharmacol. 2018; 9: 1107.
21. Chande N, Patton PH, Tsoulis DJ, Thomas BS, MacDonald JK. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Cochrane database Syst Rev. 2015; (10):CD000067.
22. Chande N, Tsoulis DJ, MacDonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane database Syst Rev. 2013; (4): CD000545.
23. Panes J, Lopez-Sanroman A, Bermejo F, Garcia-Sanchez V, Esteve M, Torres Y, et al. Early azathioprine therapy is no more effective than placebo for newly diagnosed Crohn's disease. Gastroenterology. 2013; 145: 766-774.
24. Cosnes J, Bourrier A, Laharie D, Nahon S, Bouhnik Y, Carbonnel F, et al. Early administration of azathioprine vs conventional management of Crohn's Disease: A randomized controlled trial. Gastroenterology. 2013; 145: 755-758.
25. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010; 362: 1383-1395.
26. Reinisch W, Colombel J-F, Sandborn WJ, Mantzaris GJ, Kornbluth A, Adedokun OJ, et al. Factors associated with short- and long-term outcomes of therapy for Crohn's disease. Clin Gastroenterol Hepatol. 2015; 13: 539-547.
27. Axelrad JE, Roy A, Lawlor G, Korelitz B, Lichtiger S. Thiopurines and inflammatory bowel disease: Current evidence and a historical perspective. World J Gastroenterol. 2016; 22: 10103-10117.
28. Toruner M, Loftus EVJ, Harmsen WS, Zinsmeister AR, Orenstein R, Sandborn WJ, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. Gastroenterology. 2008; 134: 929-936.

29. Armstrong RG, West J, Card TR. Risk of cancer in inflammatory bowel disease treated with azathioprine: A UK population-based case-control study. Am J Gastroenterol. 2010; 105: 1604-1609.
30. Feagan BG, Rochon J, Fedorak RN, Irvine EJ, Wild G, Sutherland L, et al. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. N Engl J Med. 1995; 332: 292-297.
31. Feagan BG, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, et al. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. N Engl J Med. 2000; 342: 1627-1632.
32. Herfarth HH. Methotrexate for inflammatory bowel diseases – new developments. 2016; 27599: 140-146.
33. Hausmann J, Zabel K, Herrmann E, Schröder O. Methotrexate for maintenance of remission in chronic active Crohn's diseaseLong-term single-center experience and meta-analysis of observational studies. Inflamm Bowel Dis. 2010; 16: 1195-1202. Available from: http://dx.doi.org/10.1002/ibd.21166.
34. Sunseri W, Hyams JS, Lerer T, Mack DR, Griffiths AM, Otley AR, et al. Retrospective cohort study of methotrexate use in the treatment of pediatric Crohn's disease. Inflamm Bowel Dis. 2014; 20: 1341-1345.
35. Feagan BG, McDonald JWD, Panaccione R, Enns RA, Bernstein CN, Ponich TP, et al. Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. Gastroenterology. 2014; 146: 681-688.
36. Narula N, Peyrin-Biroulet L, Colombel JF. Combination therapy with methotrexate in inflammatory bowel disease: Time to commit? Gastroenterology. 2014; 146: 608-611. Available from: https://doi.org/10.1053/j.gastro.2014.01.040.
37. Baumgart DC, Pintoffl JP, Sturm A, Wiedenmann B, Dignass AU. Tacrolimus is safe and effective in patients with severe steroid-refractory or steroid-dependent inflammatory bowel disease-a long-term follow-up. Am J Gastroenterol. 2006; 101: 1048-1056.
38. Brynskov J, Freund L, Rasmussen SN, Lauritsen K, de Muckadell OS, Williams N, et al. A placebo-controlled, double-blind, randomized trial of cyclosporine therapy in active chronic Crohn's disease. N Engl J Med. 1989; 321: 845-850.
39. McDonald JWD, Feagan BG, Jewell D, Brynskov J, Stange EF, Macdonald JK. Cyclosporine for induction of remission in Crohn's disease. Cochrane database Syst Rev. 2005; (2): CD000297.
40. Ambrose NS, Allan RN, Keighley MR, Burdon DW, Youngs D, Barnes P, et al. Antibiotic therapy for treatment in relapse of intestinal Crohn's disease. A prospective randomized study. Dis Colon Rectum. 1985; 28: 81-85.
41. Prantera C, Zannoni F, Scribano ML, Berto E, Andreoli A, Kohn A, et al. An antibiotic regimen for the treatment of active Crohn's disease: A randomized, controlled clinical trial of metronidazole plus ciprofloxacin. Am J Gastroenterol. 1996; 91: 328-332.
42. Maeda Y, Ng SC, Durdey P, Burt C, Torkington J, Rao PKD, et al. Randomized clinical trial of metronidazole ointment versus placebo in perianal Crohn's disease. Br J Surg. 2010; 97: 1340--1347.
43. Arnold GL, Beaves MR, Pryjdun VO, Mook WJ. Preliminary study of ciprofloxacin in active Crohn's disease. Inflamm Bowel Dis. 2002; 8: 10-15.

44. Shafran I, Johnson LK. An open-label evaluation of rifaximin in the treatment of active Crohn's disease. Curr Med Res Opin. 2005; 21: 1165-1169.
45. Prantera C, Lochs H, Campieri M, Scribano ML, Sturniolo GC, Castiglione F, et al. Antibiotic treatment of Crohn's disease: Results of a multicentre, double blind, randomized, placebo-controlled trial with rifaximin. Aliment Pharmacol Ther. 2006; 23: 1117-1125.
46. Triantafillidis JK, Nicolakis D, Emmanoullidis A, Antoniou A, Papatheodorou K, Cheracakis P. Ornidazole in the treatment of active Crohn's disease: Short-term results. Ital J Gastroenterol. 1996; 28: 10-14.
47. Selby W, Pavli P, Crotty B, Florin T, Radford-Smith G, Gibson P, et al. Two-year combination antibiotic therapy with clarithromycin, rifabutin, and clofazimine for Crohn's disease. Gastroenterology. 2007; 132: 2313-2319.
48. Triantafillidis JK, Merikas E, Georgopoulos F. Current and emerging drugs for the treatment of inflammatory bowel disease. Drug Des Devel Ther. 2011; 5: 185-210.
49. Kawalec P, Mikrut A, Wiśniewska N, Pilc A. Meta-analysis Tumor necrosis factor- α antibodies (infliximab, adalimumab and certolizumab) in Crohn's disease : Systematic review and meta-analysis. Arch Med Sci. 2013; 9: 765-779.
50. Fidder HH, Hommes DW. Anti-TNF and Crohn's disease: When should we start? Curr Drug Targets. 2010; 11: 143-147.
51. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: The ACCENT I randomised trial. Lancet (London, England). 2002; 359: 1541-1549.
52. Rutgeerts P, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology. 2004; 126: 402-413.
53. Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med. 2004; 350: 876-885.
54. Davidov Y, Ungar B, Bar-Yoseph H, Carter D, Haj-Natour O, Yavzori M, et al. Association of induction infliximab levels with clinical response in perianal Crohn's Disease. J Crohns Colitis. 2017; 11: 549-555.
55. Yarur AJ, Kanagala V, Stein DJ, Czul F, Quintero MA, Agrawal D, et al. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. Aliment Pharmacol Ther. 2017; 45: 933-940.
56. Hanauer SB, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: The CLASSIC-I trial. Gastroenterology. 2006; 130: 323-333.
57. Reinglas J, Gonczi L, Kurt Z, Bessissow T, Lakatos PL. Positioning of old and new biologicals and small molecules in the treatment of inflammatory bowel diseases. World J Gastroenterol. 2018; 24: 3567-3582.
58. Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Colombel JF, Panaccione R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: A randomized trial. Ann Intern Med. 2007; 146: 829-838.
59. Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG, et al. Adalimumab for maintenance treatment of Crohn's disease: Results of the CLASSIC II trial. 2007; 1232-1239.

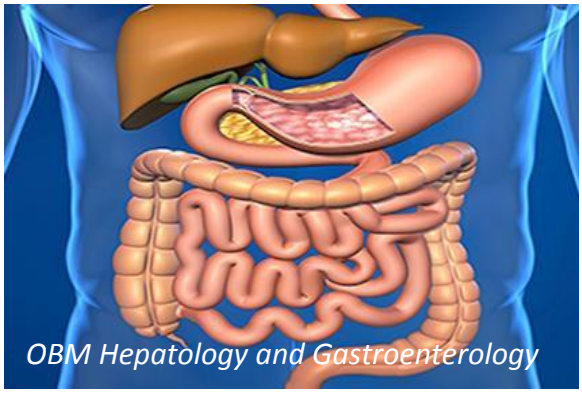
60. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: The CHARM trial. Gastroenterology. 2007; 132: 52-65.
61. Matsumoto T, Motoya S, Watanabe K, Hisamatsu T, Nakase H, Yoshimura N, et al. Adalimumab monotherapy and a combination with azathioprine for Crohn's disease: A prospective, randomized trial. J Crohns Colitis. 2016; 10: 1259-1266.
62. Colombel JF, Schwartz DA, Sandborn WJ, Kamm MA, D'Haens G, Rutgeerts P, et al. Adalimumab for the treatment of fistulas in patients with Crohn's disease. Gut. 2009; 58: 940-948.
63. Schreiber S, Rutgeerts P, Fedorak RN, Khaliq-Kareemi M, Kamm MA, Boivin M, et al. A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. Gastroenterology. 2005; 129: 807-818.
64. Sandborn WJ, Feagan BG, Stoinov S, Honiball PJ, Rutgeerts P, Mason D, et al. Certolizumab Pegol for the treatment of Crohn's disease. New Engl J Med Med. 2007; 357: 228-238.
65. Schreiber S, Khaliq-Kareemi M, Lawrance IC, Thomsen OO, Hanauer SB, McColm J, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. N Engl J Med. 2007; 357: 239-250.
66. Sandborn WJ, Lee SD, Randall C, Gutierrez A, Schwartz DA, Ambarkhane S, et al. Long-term safety and efficacy of certolizumab pegol in the treatment of Crohn's disease: 7-year results from the PRECiSE 3 study. Aliment Pharmacol Ther. 2014; 40: 903-916.
67. Hebuterne X, Lemann M, Bouhnik Y, Dewit O, Dupas J-L, Mross M, et al. Endoscopic improvement of mucosal lesions in patients with moderate to severe ileocolonic Crohn's disease following treatment with certolizumab pegol. Gut. 2013; 62: 201-208.
68. Schreiber S, Lawrance IC, Thomsen OO, Hanauer SB, Bloomfield R, Sandborn WJ. Randomised clinical trial: Certolizumab pegol for fistulas in Crohn's disease - subgroup results from a placebo-controlled study. Aliment Pharmacol Ther. 2011; 33: 185-193.
69. Hazlewood GS, Rezaie A, Borman M, Panaccione R, Ghosh S, Seow CH, et al. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: A network meta-analysis. Gastroenterology. 2015; 148: 344-345.
70. Peyrin-Biroulet L, Deltenre P, de Suray N, Branche J, Sandborn WJ, Colombel JF. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: Meta-analysis of placebo-controlled trials. Clin Gastroenterol Hepatol. 2008; 6: 644-653.
71. Sandborn WJ, Feagan BG, Hanauer S, Colombel J, Sands BE, Lukas M, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013; 369: 711-721.
72. Bloomgren G, Richman S, Hotermans C, Subramanyam M, Goelz S, Natarajan A, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N Engl J Med. 2012; 366: 1870-1880.
73. Yousry TA, Major EO, Ryschkewitsch C, Fahle G, Fischer S, Hou J, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. N Engl J Med. 2006; 354: 924-933.
74. Feagan BG, Lasch K, Lissoos T, Cao C, Wojtowicz AM, Khalid JM, et al. Rapid response to vedolizumab therapy in biologic-naive patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2019; 17: 130-138.e7.

75. Sands BE, Sandborn WJ, Van Assche G, Lukas M, Xu J, James A, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease in patients naive to or who have failed tumor necrosis factor antagonist therapy. Inflamm Bowel Dis. 2017; 23: 97-106.
76. Feagan BG, Schwartz D, Danese S, Rubin DT, Lissoos TW, Xu J, et al. Efficacy of vedolizumab in fistulising Crohn's disease: Exploratory analyses of data from GEMINI 2. J Crohns Colitis. 2018; 12: 621-626.
77. Colombel J-F, Sands BE, Rutgeerts P, Sandborn W, Danese S, D'Haens G, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. Gut. 2017; 66: 839-851.
78. Selinger C, Sandborn W, Panes J, Jones J, Hassanali A, Jacob R, et al. OTU-003 Etrolizumab as induction therapy in moderate to severe crohn's disease: Results from bergamot cohort 1. Gut [Internet]. 2018; 67: A53. Available from: http://gut.bmj.com/content/67/Suppl_1/A53.1.abstract.
79. Reinisch W, Hung K, Hassan-Zahraee M, Cataldi F. Targeting Endothelial Ligands: ICAM-1/alicaforsen, MAdCAM-1. J Crohns Colitis. 2018; 12: S669-677.
80. Jairath V, Khanna R, Feagan BG. Alicaforsen for the treatment of inflammatory bowel disease. Expert Opin Investig Drugs. 2017; 26: 991-997.
81. D'Haens G, Lee S, Tarabar D, LOUIS E, Klopocka M, Park DI, et al. OP022 Anti-MAdCAM-1 antibody (PF-00547659) for active refractory Crohn's disease: Results of the OPERA study. In: 10th Congress of the European Crohn's and Colitis Organisation. 2015; 9: S14.
82. Sandborn WJ, Lee SD, Tarabar D, Louis E, Klopocka M, Klaus J, et al. Phase II evaluation of anti-MAdCAM antibody PF-00547659 in the treatment of Crohn's disease: Report of the OPERA study. Gut. 2018; 67: 1824-1835.
83. D'Haens GR, Reinisch W, Lee SD, Tarabar D, Louis E, Kłopocka M, et al. OP024 Long-term safety and efficacy of the anti-MAdCAM monoclonal antibody SHP647 for the treatment of Crohn's disease: The OPERA II study. J Crohns Colitis. 2018; 12: S017-S018.
84. D'Haens G, Vermeire S, Cataldi F, Vogelsang H, Allez M, Desreumaux P, et al. OP007 Anti-MAdCAM monoclonal antibody PF-00547659 does not affect immune surveillance in the central nervous system of anti-TNF and immunosuppressant experienced Crohn's disease patients who are anti-TNF inadequate responders: Results from the TOSCA study. J Crohns Colitis. 2014; 8: S4-S5.
85. Schreiber S, Siegel CA, Friedenberg KA, Younes ZH, Seidler U, Bhandari BR, et al. A phase 2, randomized, placebo-controlled study evaluating matrix metalloproteinase-9 inhibitor, andecaliximab, in patients with moderately to severely active Crohn's disease. J Crohns Colitis. 2018; 12: 1014-1020.
86. Matsuoka K, Naganuma M, Tanida S, Kitamura K, Matsui T, Arai M, et al. DOP056 Efficacy and safety of anti-fractalkine monoclonal antibody, E6011, in patients with Crohn's disease who had lost response to anti-TNFα agents: A multicentre, open-label, Phase 1/2 study. In: 13th Congress of the European Crohn's and Colitis Organisation. 2018; 12: S070.
87. Sandborn W, Gasink C, Blank M, Lang Y, Johanns J, Sands B, et al. Placebo-Controlled Phase3 Study of in Moderate-Service Crohn ' s Disease Refractory to Anti-TFNα : UNITI-1. Inflamm Bowel Dis. 2016; 22: S1.
88. Feagan B, Gasink C, Lang Y, Friedman JR, Johanns J, Gao L-L, et al. OC-007 A multicenter, double-blind, Placebo (PBO)-controlled Ph3 study of Ustekinumab (UST), A human MAB to IL-12/23P40, IN PTS with moderately-severely active Crohn's Disease (CD) who are naïve or not

refractory to anti-TNFA: UNITI-2. Gut [Internet]. 2016; 65: A6 LP-A7. Available from: http://gut.bmj.com/content/65/Suppl_1/A6.abstract.

89. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2016; 375: 1946-1960.
90. Ma C, Fedorak RN, Kaplan GG, Dieleman LA, Devlin SM, Stern N, et al. Long-term maintenance of clinical, endoscopic, and radiographic response to ustekinumab in moderate-to-severe Crohn's disease: Real-world experience from a multicenter cohort study. Inflamm Bowel Dis. 2017; 23: 833-839.
91. Rackovsky O, Hirten R, Ungaro R, Colombel JF. Clinical updates on perianal fistulas in Crohn's disease. Expert Rev Gastroenterol Hepatol. 2018; 12: 597-605.
92. Klenske E, Osaba L, Nagore D, Rath T, Neurath MF, Atreya R. Drug levels in the maternal serum, cord blood and breast milk of a ustekinumab-treated patient with Crohn's disease. J Crohns Colitis. 2019; 13: 267-269.
93. Targan SR, Feagan B, Vermeire S, Panaccione R, Melmed GY, Landers C, et al. A randomized, double-blind, placebo-controlled phase 2 study of brodalumab in patients with moderate-to-severe Crohn's disease. Am J Gastroenterol. 2016; 111: 1599-1607.
94. Feagan BG, Sandborn WJ, D'Haens G, Panes J, Kaser A, Ferrante M, et al. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: A randomised, double-blind, placebo-controlled phase 2 study. Lancet (London, England). 2017; 389: 1699-1709.
95. Feagan BG, Panes J, Ferrante M, Kaser A, D'Haens GR, Sandborn WJ, et al. Risankizumab in patients with moderate to severe Crohn's disease: An open-label extension study. Lancet Gastroenterol Hepatol. 2018; 3: 671-680.
96. Sands BE, Chen J, Feagan BG, Penney M, Rees WA, Danese S, et al. Efficacy and safety of MEDI2070, an antibody against Interleukin 23, in patients with moderate to severe Crohn's Disease: A phase 2a study. Gastroenterology. 2017; 153: 77-86.e6.
97. Ma C, Jairath V, Khanna R, Feagan BG. Investigational drugs in phase I and phase II clinical trials targeting interleukin 23 (IL23) for the treatment of Crohn's disease. Expert Opin Investig Drugs. 2018; 1-12.
98. Panes J, Sandborn WJ, Schreiber S, Sands BE, Vermeire S, D'Haens G, et al. Tofacitinib for induction and maintenance therapy of Crohn's disease: Results of two phase IIb randomised placebo-controlled trials. Gut. 2017; 66: 1049-1059.
99. Schreiber S, Peyrin-Biroulet L, Boland B, Higgins P., Armuzzi A, Terdiman J, et al. OP022 Rapidity of clinical and laboratory improvements following upadacitinib induction treatment: Data from the CELEST study. In: 13th Congress of the European Crohn's and Colitis Organisation. 2018; 12: S015.
100. Panes J, Sandborn W., Jr E. L, Assche G Van, Ghosh S, Zhou Q, et al. P273 Efficacy and safety of upadacitinib maintenance treatment for moderate to severe Crohn's disease: Results from the CELEST study. In: 13th Congress of the European Crohn's and Colitis Organisation. 2018; 12: S238-S239.
101. Vermeire S, Schreiber S, Petryka R, Kuehbacher T, Hebuterne X, Roblin X, et al. Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): Results from a phase 2, double-blind, randomised, placebo-controlled trial. Lancet (London, England). 2017; 389: 266-275.

102. Feagan BG, D'Haens G, Usiskin K, Liu J, Paul D, Pai RK. P661 Early histological improvement demonstrated with oral ozanimod in patients with moderately to severely active Crohn's disease in the STEPSTONE trial. J Crohn's Colitis. 2019; 13: S450.
103. Peyrin-Biroulet L, Panés J, Chiorean M V, Zhang J, Vermeire S, Jairath V, et al. Histologic remission and mucosal healing in a randomized, placebo-controlled, phase 2 study of etrasimod in patients with moderately to severely active ulcerative colitis. Gastroenterology [Internet]. 2019; 156: S217. Available from: https://doi.org/10.1016/S0016-5085(19)37338-X.
104. D'Haens G, Sandborn WJ, Colombel JF, Rutgeerts P, Brown K, Barkay H, et al. A phase II study of laquinimod in Crohn's disease. Gut. 2015; 64: 1227-1235.
105. Hawkey CJ, Allez M, Clark MM, Labopin M, Lindsay JO, Ricart E, et al. Autologous hematopoetic stem cell transplantation for refractory Crohn disease: A randomized clinical trial. JAMA. 2015; 314: 2524-2534.
106. Lindsay JO, Allez M, Clark M, Labopin M, Ricart E, Rogler G, et al. Autologous stem-cell transplantation in treatment-refractory Crohn's disease: An analysis of pooled data from the ASTIC trial. Lancet Gastroenterol Hepatol. 2017; 2: 399-406.
107. Brierley CK, Castilla-Llorente C, Labopin M, Badoglio M, Rovira M, Ricart E, et al. Autologous haematopoietic stem cell transplantation for Crohn's disease: A retrospective survey of long-term outcomes from the European Society for Blood and Marrow Transplantation. J Crohns Colitis. 2018; 12: 1097-1103.
108. Sedykh SE, Prinz VV, Buneva VN, Nevinsky GA. Bispecific antibodies: Design, therapy, perspectives. Drug Des Devel Ther. 2018; 12: 195-208.
109. Peyrin-Biroulet L, Demarest S, Nirula A. Bispecific antibodies: The next generation of targeted inflammatory bowel disease therapies. Autoimmun Rev. 2019; 18: 123-128.
110. Colombel JF, Panaccione R, Bossuyt P, Lukas M, Baert F, Vanasek T, et al. Effect of tight control management on Crohn's disease (CALM): A multicentre, randomised, controlled phase 3 trial. Lancet (London, England). 2018; 390: 2779-2789.
111. Khanna R, Bressler B, Levesque BG, Zou G, Stitt LW, Greenberg GR, et al. Early combined immunosuppression for the management of Crohn's disease (REACT): A cluster randomised controlled trial. Lancet (London, England). 2015; 386: 1825-1834.
112. Aliyev ER, Hay JW, Hwang C. Cost-effectiveness comparison of ustekinumab, infliximab, or adalimumab for the treatment of moderate-severe Crohn's disease in biologic-naive patients. Pharmacotherapy. 2019; 39: 118-128.



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