Aminosalicylates

Class of Drug: 5-ASA

Generic name: Mesalamine

Brand Name: Apriso, Asacol HD, Delzicol, Lialda, Pentasa

Mechanism of Action: Mesalamine has several anti-inflammatory effects. Mesalamine can block the production of interleukin-1. It can also inhibit cyclooxygenase and it is potent antioxidant. Beyond this, mesalamine can inhibit antibody production and it hinders macrophage and neutrophil function by impairing chemotaxis (52).

Efficacy: In a trial with 80 patients with Crohn's disease, it was seen that those that received 4 grams of mesalamine a day had a remission rate of 43% after 16 weeks (8). Another trial with 20 patients receiving 3.2 grams of mesalamine per day found that 45% of the patients either achieved partial or complete remission after 16 weeks (9). In another trial that was comparing the efficacy of mesalamine and budesonide, it was seen that in 89 patients receiving 4 grams of mesalamine a day, 45% of them went into remission (10). In patients with distal ulcerative colitis, it was seen that topical mesalamine was superior to placebo and as effective as oral mesalamine in maintaining remission (1).

Side Effects: Headache, nausea, dyspepsia, constipation, sore throat, gas, diarrhea, and skin rash.

Class of Drug: 5-ASA

Generic name: Olsalazine

Brand Name: Dipentum

Mechanism of Action: Olsalazine is converted and delivered in its active form, mesalazine, to the large intestine. Mesalazine blocks the production of interleukin-1, it impairs chemotaxis of macrophages and neutrophils, and it inhibits cyclooxygenase, which decreases the production of prostaglandins (52).

Efficacy: In a multicenter, randomized, double-blind study, 91 patients with mild to moderate Crohn's disease received either olsalazine (1 gram twice a day) or a placebo. It was seen that only 8 out of 46 patients (17%) achieved remission or improved their symptoms, compared to the 22 out of 45 in the placebo group (49%) that achieved remission or improved their symptoms (29).

Side Effects: Nausea, heartburn, stomach pain, loss of appetite, skin rash, and itching.

Class of Drug: 5-ASA

Generic name: Sulfasalazine

Brand Name: Sulfazine, Azulfidine, Azulfidine EN-tabs

Mechanism of Action: Sulfasalazine exhibits similar effects to olsalazine. Sulfsalazine inhibits activation and expression of adhesion molecules on endothelial cells. This results in a decrease in the number of leukocytes that can reach sites of inflammation. Sulfasalazine also inhibits TNF-α binding to its receptor,

preventing it from propagating its pro-inflammatory effects. Sulfasalazine also inhibits cyclooxygenase, which decreases the production of prostaglandins (52).

Efficacy: In a clinical trial containing 74 patients with Crohn's disease, it was seen that 43% of patients receiving 1 gram/day of sulfasalazine went into remission after 17 weeks. In another clinical trial with 54 patients, 50% of the patients went into remission after 16 weeks (7).

Side Effects: Headache, nausea, vomiting, skin rash, fever, dizziness, and loss of appetite.

Class of Drug: 5-ASA

Generic name: Balsalazide

Brand Name: Giazo, Colazal

Mechanism of Action: Balsalazide is converted into 5-ASA and released into the large intestine. It exhibits the same activities as mesalamine, such as inhibition of cyclooxygenase. It also impairs chemotaxis of macrophages and neutrophils (52).

Efficacy: One study found that balsalazide induced remission in a greater number of patients than mesalamine over a 12-week period. It was found that 62% of the patients with moderate to severe ulcerative colitis went into remission, compared to the 37% of patients that were on mesalamine (1).

Side Effects: Headache, nausea, vomiting, joint pain, abdominal pain, and loss of appetite.

Corticosteroids

Class of Drug: Steroid

Generic name: Budesonide

Brand Name: Uceris, Pulmicort, Entocort, Symbicort

Mechanism of Action: Budesonide is a corticosteroid that exhibits glucocorticoid activity. It binds to intracellular glucocorticoid receptors. This binding activates glucocorticoid-responsive elements, which can inhibit and suppress immune system elements. One example of suppression would be preventing the recruitment and proliferation of macrophages. It can also inhibit the migration of neutrophils to areas of inflammation. Since it is a non-systemic steroid, its activity is limited to within the intestinal lumen (1).

Efficacy: In a randomized, double-blind trial with 176 patients with Crohn's disease, it was seen that 53% of the patients treated Budesonide went into remission after 10 weeks (5). In another randomized, double-blind study with 200 patients with Crohn's disease, 48% of patient's receiving 9 mg once a day went into remission. It was also found that 53% of patients receiving 4.5 mg twice a day went into remission (6). Another randomized trial on Crohn's disease that treated 93 patients with 9 mg/day of budesonide found that after 16 weeks, 69% of those patients went into remission (10).

Side Effects: Chills, fever, sore throat, sneezing, headache, rash, indigestion, and vomiting.

Class of Drug: Steroid

Generic name: Prednisone

Brand Name: RAYOS, Deltasone, Predone, Sterapred, Sterapred DS

Mechanism of Action: Prednisone is a glucocorticoid receptor agonist, which is involved in suppressing inflammation. Once ingested, it is metabolized in the liver, generating prednisolone. Once in its active form, prednisolone crosses the cell membrane and binds to glucocorticoid receptors in the cytoplasm. This binding results in a downregulation of the expression of inflammatory cytokines, which leads to a reduction in the activity of the immune system.

Efficacy: In a trial of patients with Crohn's Disease, 60% of patients treated with prednisone went in to remission after 17 weeks. In a retrospective study, patients maintained favorable responses for approximately 6.6 years, but the data did not support the use of corticosteroids to maintain remission (1).

Side Effects: Nausea, vomiting, heartburn, headache, dizziness, blurred vision, shortness of breath, weight gain, irregular heartbeat, and agitation.

Class of Drug: Steroid

Generic name: Methylprednisolone

Brand Name: Medrol, Medrol Dosepak

Mechanism of Action: Methylprednisolone behaves similarly to prednisone. Once it has crossed the cellular membrane, it binds to a glucocorticoid receptor. This binding activates glucocorticoid-responsive elements, which have many activities. These elements can inhibit the recruitment and generation of lymphocytes, monocytes, and macrophages in response to inflammation (1). These elements can also decrease the number of prostaglandins and cytokines that are produced (5).

Efficacy: In a trial of 452 patients with Crohn's disease, 80% of patients treated with methylprednisolone achieved remission within 18 weeks (3). In another randomized trial with 176 patients with Crohn's disease, it was found that 66% of patients receiving prednisolone went into remission (4).

Side Effects: Nausea, vomiting, heartburn, headache, dizziness, blurred vision, shortness of breath, weight gain, irregular heartbeat, and agitation.

Immunomodulators

Class of Drug: Immunomodulator

Generic name: Cyclosporine

Brand Name: Neoral, Gengraf, Sanmdimmune

Mechanism of Action: Cyclosporine exhibits several anti-inflammatory effects, such as inhibiting calcineurin. The inhibition of calcineurin results in a downregulation of IL-2, which is involved in the differentiation of T-cells (42).

Efficacy: In a randomized study of 30 patients with ulcerative colitis, 9 out of 14 patients (64%) responded to the cyclosporine after 8 days. After 12 months, 7 out of 9 patients (78%) remained in

remission. Another randomized study with 30 patients with ulcerative colitis found that individuals that received cyclosporine monotherapy (1 mg/kg/day) for 7 days had a remission rate of 67% (10/15 patients) (28).

Side Effects: Abdominal pain, cough, dizziness, chest pain, blurred vision, drowsiness, fever, headache, itching, loss of appetite, swollen glands, shortness of breath, and sore throat.

Class of Drug: Immunomodulator

Generic name: Thalidomide

Brand Name: Immunoprin

Mechanism of Action: Thalidomide has several inhibitory effects on the immune system. It decreases integrin beta-chain production, which inhibits leukocyte chemotaxis. It also suppresses expression of endothelial cell adhesion molecules, which are involved in the emigration of leukocytes to sites of inflammation (51).

Efficacy: It was noted that because of this drug's well-documented teratogenicity, its use is severely restricted. In a small trial of 11 patients with Crohn's disease (2 patients withdrew after 3 weeks because of mood disturbances), individuals were given a daily dose of thalidomide for 12 weeks. The mean Crohn's disease activity index score (CDAI) decreased from 117 points to 48 points ($p = 0.0012$) (27).

Side Effects: Tiredness, dizziness, fever, chills, diarrhea, muscle pain, and difficulty breathing

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Class of Drug: Immunosuppressant

Generic name: Mycophenolate mofetil

Brand Name: CellCept

Mechanism of Action: Mycophenolate mofetil is metabolized in the liver, generating mycophenolic acid (MPA). MPA inhibits inosine monophosphate dehydrogenase (IMPDH), which is involved in *de novo* synthesis of guanosine nucleotides. The pathway by which these nucleotides are generated is crucial for T- and B-lymphocyte proliferation. Inhibition of this pathway has a cytostatic effect on lymphocytes (40).

Efficacy: In a randomized trial with 70 patients with Crohn's disease, 35 received mofetil and corticosteroids, while another 35 received azathioprine and corticosteroids. It was found that the patients that received the mofetil had a greater decrease in their CDAI score than the patients treated with azathioprine. It was also seen that the mofetil group had more patients entering remission over a 6-month period than the azathioprine group (17).

Side Effects: Abdominal pain, irregular pulse, chest pain, loss of appetite, muscle pain and cramps, sore throat, dizziness, cough, blurred vision, fever, chill, fainting, trembling, nausea, and vomiting.

Class of Drug: Antimetabolite

Generic name: Methotrexate

Brand Name: Trexall, Rasuvo, Otrexup

Mechanism of Action: Several mechanisms of action have been proposed for methotrexate. It is believed that methotrexate prevents purine and pyrimidine synthesis in lymphocytes, inhibiting their proliferation and hampering the inflammatory response. It has also been suggested that methotrexate induces apoptosis in leukocytes and activated T-cells. A proposed mechanism is that methotrexate inhibits polyamine-producing enzymes. Lower polyamine enzyme levels result in higher amounts of intracellular reactive oxygen species, which are harmful to DNA and can lead to apoptosis (39).

Efficacy: One study that focused on treating 141 steroid-refractory Crohn's disease patients found that after 4 months, 39.4% of patients in the methotrexate group achieved remission, while 19.1% in the placebo group achieved remission (14). Another Crohn's disease study containing 84 patients divided into 3 groups (26 received methotrexate, 32 received 6-mercaptopurine, and 26 were placebo) found no statistically significant difference in remission rates between the groups. They did note that the methotrexate group did improve more than the other two, however (15). In another Crohn's disease study, it was found that patients that achieved remission with methotrexate were able to maintain remission longer than those in a placebo group and those in a group receiving prednisone (16). Randomized controlled trials have only shown benefit in Crohn's disease (1).

Side Effects: black and tarry stools, bloody vomit, reddening of the skin, stomach pain, joint pain, and diarrhea.

Class of Drug: Antimetabolite

Generic name: Azathioprine

Brand Name: Imuran, Azasan

Mechanism of Action: Azathioprine inhibits purine synthesis in leukocytes and lymphocytes. Once metabolized, azathioprine incorporates into replicating DNA, blocking the synthesis of purines. Lymphocytes do not have a salvage pathway that can generate new purines *de novo*, which is why they are specifically affected by this drug. Without new purines, the DNA cannot be replicated, leading to lower levels of immune cells (38).

Efficacy: A meta-analysis comprised of 13 randomized controlled trials, totaling 1211 patients with Crohn's disease, found that patients treated with either azathioprine or 6-mercaptopurine showed no statistically significant difference in remission rates, when compared to placebo patients (13).

Side Effects: Bloody stools, sore throat, swollen glands, tiredness, weakness, shortness of breath, fever, chills, and painful urination.

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https://www.gastrojournal.org/article/S0016-5085(19)39719-7/pdf

Class of Drug: Immunomodulator

Generic name: Ozanimod

Brand Name:

Mechanism of Action: Ozanimod is an oral immunomodulator that selectively targets sphingosine 1-phosphate receptors 1 and 5. They regulate the number of lymphocytes that are released into the blood stream. Ozanimod targets these receptors to be broken down, resulting in fewer lymphocytes available to buildup in the GI tract, reducing or stopping the inflammatory response (55).

Efficacy: In a double-blind, placebo-controlled phase 2 trial of ozanimod in 197 adults with moderate-to-severe ulcerative colitis, patients were randomly assigned, in a 1:1:1 ratio, to receive ozanimod at a dose of 0.5 mg or 1 mg or placebo daily for up to 32 weeks(56). At week 32, the rate of clinical remission was 21% in the group that received 1 mg of ozanimod, 26% in the group that received 0.5 mg of ozanimod, and 6% in the group that received placebo; the rate of clinical response was 51%, 35%, and 20%, respectively. At week 8, absolute lymphocyte counts declined 49% from baseline in the group that received 1 mg of ozanimod and 32% from baseline in the group that received 0.5 mg (55).

Side Effects: anemia and headache.

Biologic Therapies

Class of Drug: Biologic, antibody

Generic name: Ustekinumab (Anti IL-12 antibody)

Brand Name: Stelara

Mechanism of Action: Interleukin-12 (IL-12) is produced by dendritic cells, macrophages, neutrophils, and B cells. It has several activities, such as enhancing cytotoxic activity of natural killer cells and inducing cytokine production from natural killer and T-cells (50). Anti-IL antibodies target IL-12, preventing it from binding to receptors (1).

Efficacy: In a randomized, double-blind trial consisting of 79 patients with active Crohn's disease, it was seen that patients that received treatment (3 mg/kg) after seven weeks had a higher response rate (75%) than the placebo group's response rate (25%). This trial defined clinical response as a reduction of CDAI score by at least 100 points (26).

Side Effects: Headache, dizziness, nausea, diarrhea, and skin rash.

Class of Drug: Biologic, antibody

Generic name: Anti IL-6 receptor antibody (MRA)

Brand Name: Actemra

Mechanism of Action: Interleukin-6 (IL-6) is involved in a variety of immune processes. IL-6 promotes the differentiation of naïve CD4 T cells. It also stimulates the production of antibodies (49). MRA binds to the IL-6 receptor, preventing IL-6 from binding (1).

Efficacy: In a randomized study with 36 patients with active Crohn's disease, it was found that those that received a biweekly infusion of MRA (8 mg/kg) for 12 weeks had a clinical response rate of 80%, compared to the placebo response rate of 31%. The clinical response rate was defined as a reduction in their CDAI by 70 or more (25).

Side Effects: Chest pain, dizziness, difficulty breathing, difficulty swallowing, fever, chills, headache, skin rash, loss of appetite, stomach pain, tightness of chest, tiredness, nausea, pale skin, and nasal congestion.

Class of Drug: Biologic Antibody

Generic name: Visilizumab

Brand Name: Nuvion

Mechanism of Action: Visilizumab is a monoclonal antibody that is designed to target the CD3ε chain of the T-cell receptor on T-cells. The CD3 complex is involved in intracellular signaling and activating cytotoxic T-cells (48). Visilizumab binds to the CD3ε chain, preventing it from forming the complex (1).

Efficacy: A small open-label trial with medically-refractory Crohn's patients found that out of 14 patients that were given 2 doses of visilizumab (10 μg/kg) over the course of two days, 58% had a response to it and 33% achieved remission after 89 days. In an open-label trial of 24 patients with steroid-refractory ulcerative colitis, it was shown that patients receiving 10 mcg/kg for two consecutive days had a response rate of 79% and a remission rate of 54% after 30 days (1).

Side Effects: Fever, weakness, skin flushing, nausea, chills, and headache.

Class of Drug: Selective Adhesion Molecule Inhibitor

Generic name: Vedolizumab (MLN02)

Brand Name: Entyvio

Mechanism of Action: Vedolizumab is a monoclonal antibody that targets α4β7 integrin heterodimers. The ligand for this integrin heterodimer is mucosal addressin cell adhesion molecule-1, which is expressed on the endothelium of Peyer's patches and gut-associated lymphoid tissues. This integrin heterodimer is involved in the adhesion of white blood cells to activated endothelium. By targeting this heterodimer, vedolizumab inhibits the emigration of leukocytes to sites of inflammation (1).

Efficacy: In a trial containing 185 patients with mild to moderate Crohn's disease, individuals that received 2.0 mg/kg of MLN02 for 2 months had a remission rate of 36.9%, compared to the 20.7% remission rate of the placebo group. In another trial with 181 patients with ulcerative colitis, it was seen that patients that received 0.5 mg/kg or 2.0 mg/kg for one month had remission rates of 33% and 32%, respectively. The placebo group had remission rates of 14% (1).

Side Effects: Headache, fever, sore throat, sneezing, ear congestion, chills, difficulty breathing, body aches, tiredness.

Class of Drug: Selective Adhesion Molecule Inhibitor

Generic name: Natalizumab

Brand Name: Tysabri

Mechanism of Action: Natalizumab is a monoclonal antibody that targets the α4 subunit of α4β1 or α4β7 integrins. These integrins are expressed on the surface of leukocytes and they interact with endothelial ligands, such as vascular cell adhesion molecules (expressed at sites of inflammation) and mucosal addressin cell adhesion molecules (expressed on the endothelium of Peyer's patches and gut-associated lymphoid tissues). These cell adhesion molecules mediate leukocytes adhering to the endothelium. Natalizumab prevents the formation of the integrin complex, which inhibits the emigration of leukocytes to areas of inflammation (1).

Efficacy: In a trial with 905 patients with Crohn's disease that were treated with natalizumab, no significant difference in the response or remission rates was seen after 10 weeks between patients receiving the drug and the placebo group. In a second trial, patients that had a response to natalizumab (339 patients) were randomly reassigned and given either 300 mg of natalizumab or placebo every 4 weeks for 56 weeks. It was seen that the patients that continued natalizumab in the second trial had a higher rate of remission (44%) than the placebo group (26%) (24).

Side Effects: Cough, tiredness, skin rash, tightness in the chest, fast heartbeat, dizziness, and difficulty swallowing.

Class of Drug: TNF-a inhibitor

Generic name: Certolizumab

Brand Name: Cimzia

Mechanism of Action: Certolizumab is a monoclonal antibody that binds to and neutralizes TNF-α. Unlike other TNF-α inhibitors, certolizumab does not induce apoptosis in monocytes (45).

Efficacy: A randomized trial examined remission rates in 92 patients with moderate to severe Crohn's disease. Patient's received a single intravenous dose of either certolizumab or the placebo. Patient's receiving the drug received one of the following doses: 1.25 mg/kg, 5 mg/kg, 10 mg/kg, or 20 mg/kg. At 2 weeks, the remission rate in the patients that received the 10 mg/kg dosage was 47%, which was the highest out of the dosages (22).

Side Effects: Stuffy nose, constipation, diarrhea, stomach pain, sinus pain, and skin rash.

Class of Drug: IFN-y Inhibitor

Generic name: Fontolizumab

Brand Name: HuZAF

Mechanism of Action: Interferon-y (IFN-y) is involved in a variety of immunoregulatory roles. IFN-y can activate macrophages and lymphocytes. IFN-y also induces the expression of class II major histocompatibility complex molecules, which are involved in presenting antigens to immune cells for activation (46). Fontolizumab binds to IFN-y, effectively neutralizing it so that it cannot induce inflammation (47).

Efficacy: A trial of 133 patients with moderate to severe Crohn's disease examined the efficacy of fontolizumab in treating the disease. Patients received either one or two doses (separated by 28 days) of

the following amounts: 4 mg/kg, 10 mg/kg, or a placebo. There was no noticeable difference in the response from individuals that were given a single dose. In individual's that were given two doses, the response rate after 56 days was 69% (4 mg/kg group) and 67% (10mg/kg group), compared to the placebo group which was 32% (23).

Side Effects: Diarrhea, bloating, fatigue, fever, and bloody stool.

Class of Drug: TNF-a inhibitor

Generic name: Adalimumab

Brand Name: Humira, Amjevita, Cyltezo

Mechanism of Action: Adalimumab behaves similarly to infliximab, as both are antibodies that directly bind to and inhibit TNF-α. This inhibition results in a reduction of TNF-induced inflammation. Adalimumab can also induce apoptosis in monocytes, leading to a reduction in inflammation (44).

Efficacy: A randomized, double-blind, placebo trial examined the rates of remission of Crohn's disease in 299 patients that were divided into 4 groups. Three of the groups received different dosages of adalimumab (40 mg, 80 mg, or 160 mg) and the last group received a placebo. The following remission rates were observed at week 4: 18% (40 mg), 24% (80 mg), 36% (160 mg), and 12% (placebo) (21).

Side Effects: Headache, stuff nose, stomach pain, and sinus pain.

Class of Drug: TNF-a inhibitor

Generic name: Infliximab

Brand Name: Remicade, Renflexis, Inflectra, Ixifi

Mechanism of Action: Infliximab is an artificial antibody that directly binds to TNF-α. By doing so, it effectively neutralizes TNF-α by preventing it from binding to its receptors. Beyond this, it has been seen that infliximab also inhibits the production of granulocyte-macrophage colony-stimulating factor (GM-CSF) by mucosal T cells. This cytokine is involved in stimulating the production of monocytes and granulocytes. In IBD, it has been shown that there are higher levels of GM-CSF than normal. By inhibiting the production of GM-CSF, the inflammatory response is lessened (43). Another proposed mechanism of reducing inflammation is that infliximab can bind to and induce apoptosis in TNF-producing cells (44).

Efficacy: In a study comprised of 108 randomized patients with active Crohn's disease, it was seen that 33% of patients achieved remission after 4 weeks from one dose of infliximab. After 12 weeks, 37% of those patients relapsed (19). The patients that responded to the first dose were randomized and then received 10 mg/kg every 8 weeks, or they received a placebo. After 44 weeks, it was found that 53% of the patients receiving infliximab achieved remission, while 20% of the placebo group achieved remission (20). In a clinical trial with 364 patients with ulcerative colitis, each patient received either a placebo or infliximab (5 or 10 mg/kg) at 0 weeks, 2 weeks, 6 weeks, and then every 8 weeks after that. It was found that after 54 weeks, over two thirds of the infliximab group achieved clinical response and one third achieved clinical remission (1).

Side Effects: Headache, nausea, stuffy nose, sinus pain, skin rash, and flushing.

https://gut.bmj.com/content/67/Suppl_1/A102.2

Class of Drug: Biologic Antibody

Generic name: Etrolizumab

Brand Name:

Mechanism of Action: Etrolizumab has a dual mechanism of action, inhibiting both α4β7:MAdCAM-1-mediated lymphocyte trafficking to the gut mucosa and αEβ7:E-cadherin-mediated lymphocyte retention in the intraepithelial space (57).

Efficacy: TNF antagonist-experienced pts with moderate-severe UC and high disease burden treated with open label Etrolizumab for 14 weeks achieved clinically meaningful clinical response and remission and endoscopic improvement. In a study of 130 UC patients, at week 14, Etrolizumab treatment was associated with clinical response in 50.8% of patients; remission in 12.3% of patients; rectal bleeding remission in 52.3% of patients; and stool frequncy remission in 35.4% of patients (58).

Side Effects: headache, fatigue, abdominal pain, dizziness, nasopharyngitis, nausea, arthralgia.

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https://www.gastrojournal.org/article/S0016-5085(18)31581-6/fulltext

Class of Drug: JAK1 inhibitor

Generic name: Filgotinib

Brand Name:

Mechanism of Action: Filgotinib is a specific inhibitor of JAK 1 (59).

Efficacy: In a random control trial including 174 patients, filgotinib efficacy and safety was examined for the treatment of moderate-to-severe CD. Sixty (47%) of 128 patients in the filgotinib group achieved the primary endpoint (clinical remission at week 10) compared to 10 (23%) of 44 patients in the placebo group. There was a greater proportion of patients achieving endoscopic remission at week 10 in the filgotinib versus the placebo group, but that difference did not reach statistical significance (60).

Side Effects: headache, sleepiness and fatigue, nausea, upper abdominal discomfort, and abnormal taste in mouth.

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https://www.thelancet.com/journals/langas/article/PIIS2468-1253(18)30233-4/fulltext

Class of Drug: anti interleukin 23A antibody

Generic name: Risankizumab

Brand Name:

Mechanism of Action: Risankizumab is a monoclonal antibody targeting the IL-23 p19 subunit (60).

Efficacy: Extended induction treatment with open-label intravenous risankizumab was effective in increasing clinical response and remission rates at week 26. Of the 108 patients who completed the 12-week double-blind induction trial, six patients were in deep remission and entered the 12-week washout phase. 102 patients were not in deep remission, 101 of whom received 12 weeks of 600 mg risankizumab (33 from the original placebo group, 34 from the 200 mg risankizumab group, and 34 from the 600 mg risankizumab group); the other patient declined to continue the study. At week 26, 54 (53%) of 101 patients treated with 600 mg rizankizumab were in clinical remission. Among patients included in the open-label extension trial, clinical remission rates at week 26 versus week 12 were: 18 (55%) versus six (18%) of 33 patients in the original placebo group; 20 (59%) versus seven (21%) of 34 patients in the original 200 mg risankizumab group; and 16 (47%) versus nine (26%) of 34 patients in the original 600 mg risankizumab group (61).

Side Effects: arthralgia, headache, abdominal pain, nasopharyngitis, nausea, and pyrexia.

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https://www.gastrojournal.org/article/S0016-5085(17)34357-3/fulltext

Class of Drug: anti interleukin 23A antibody

Generic name: Upadacitinib

Brand Name:

Mechanism of Action: Janus kinase inhibitor that is selective for the JAK1 subtype of this enzyme over the JAK2 (74-fold), JAK3 (58-fold) and TYK2 subtypes (62).

Efficacy: Of the 220 enrolled active CD patients, 180 (82%) completed 16 weeks of induction. Mean age was40.7±12.9 yrs, CDAI 302.7±63.4 and disease duration 13.2±10.0 yrs. Ninety six percent had failed, or were intolerant to TNF antagonists. Significantly more patients on 6 mg Upadacitinib vs placebo achieved clinical remission. A significant dose-response relationship was observed with Upadacitinib vs placebo for endoscopic remission. Compared with placebo, more patients achieved clinical response with 6 and 24 mg of Upadacitinib, and endoscopic response with Upadacitinib doses ≥6 mg BID at Week 16. This dose-ranging study demonstrated endoscopic improvement andclinical benefit of ABT-494 as induction therapy in patients with moderate-to-severe refractory CD (63).

Side Effects: nausea, headache, and chest infections (62).

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5969213/

Class of Drug: Biologic Antibody

Generic name: SHP647

Brand Name:

Mechanism of Action: SHP647 is an antihuman monoclonal antibody targeting mucosal addressin cell adhesion molecule-1 (MAdCAM-1). As an extracellular protein, SHP-647 is important in the adhesion and movement of leukocytes into the GI tract. Blocking this pathway may allow for targeted reduction of inflammation in the GI tract while not impairing leukocyte migration to other organs (64).

Efficacy: In a trial enrolling 265 CD patients who had failed or could not tolerate anti-TNF therapy or immunosuppressants received placebo or SHP647 injections of 22.5 mg, 75 mg, or 225 mg of SHP-647 every four weeks. The primary endpoint, a 70-point decrease in CDAI score, was seen in 58.6% of placebo patients and in 62%, 64.7%, and 57.5% of patients receiving 22.5 mg, 75 mg, and 225 mg of SHP-647, respectively. CDAI remission at week 12 was seen in 23% of placebo patients compared with 26.8%, 28.5%, and 29.6% of patients receiving 22.5 mg, 75 mg, and 225 mg of SHP-647 (66). Given the negative clinical findings of the OPERA study, the positioning of SHP-647 in the treatment of CD may be difficult (67).

Side Effects: flares of UC, headache, and nervous system disorders.

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https://link.springer.com/article/10.1007%2Fs10620-019-05492-y

Class of Drug: JAK inhibitor

Generic name: Tofacitinib

Brand Name: Xeljanz

Mechanism of Action: Tofactinib is an inhibitor of the enzyme janus kinase 1 (JAK1) and janus kinase 3 (JAK 3) and interferes with the JAK-STAT signaling pathway (69).

Efficacy: In a small study**,** 58 patients (53 UC, 4 Crohn's, 1 pouchitis) completed at least 8 weeks of treatment with tofacitinib. 93% of the patients previously failed treatment with anti-TNF. At 8 weeks of treatment, 21 patients (36%) achieved a clinical response, and 19 (33%) achieved clinical remission. Steroid-free remission at 8 weeks was achieved in 15 patients (26%). Of the 48 patients followed for 26 weeks, 21% had clinical, steroid-free remission. Of the 26 patients followed for 12 months, 27% were in clinical, steroid-free remission. Overall Ii this cohort of patients with moderate-to-severe, anti-TNF resistant IBD, tofacitinib induced clinical response in 69% of the patients. 27% were in clinical, steroid-free remission by 1 year of treatment (68).

Side Effects: headache, diarrhea, skin rash.

Antibiotics

Class of Drug: Antibiotic

Generic name: Rifaximin

Brand Name: Xifaxan

Mechanism of Action: Two mechanisms of action have been observed for rifaximin. The first is that it inhibits RNA synthesis in bacteria. It does this by binding to the beta-subunit of bacterial RNA polymerase. This binding prevents transcription from occurring, so the bacterial cell is incapable of producing essential proteins. The second mechanism of action that has been observed is that rifaximin activates pregnane X receptors (PXR). Once PXR is activated, it inhibits the transcription factor NF-kappa B, which is involved in promoting inflammation (37).

Efficacy: A study comprised of 402 patients examined the efficacy of rifaximin in treating active Crohn's disease. They found that patients that received an 800 mg dosage twice a day for 12 weeks had a

remission rate of 62%. Those that received the placebo had a remission rate of 43% (30). Another study with 168 patients with Crohn's disease found that the 83 patients that received rifaximin treatment (800 mg, twice a day) had a remission rate of 100% after 12 weeks, compared to the placebo group's remission rate of 84% (31).

Side Effects: Nausea, vomiting, constipation, bloating, gas, stomach pain, headache, dizziness, tiredness, and swelling in extremities.

Class of Drug: Antibiotic (quinolone)

Generic name: Ciprofloxacin

Brand Name: Cipro, Cipro XR, Cipro I.V.

Mechanism of Action: Ciprofloxacin targets both gram-positive and gram-negative bacteria. Once it has entered a bacterial cell, it targets and inhibits two enzymes: topoisomerase II and topoisomerase IV. Both enzymes are required for maintaining the stability of the DNA during its replication. Topoisomerase II relieves stress on the DNA while it is being unwound by inducing negative supercoiling ahead of helicase (35).

Efficacy: A trial containing 47 patients with Crohn's disease showed that patients receiving 500 mg twice a day of ciprofloxacin reported a significant change in their CDAI, compared to the placebo group (2). In another Crohn's disease trial, 28 patients received 1 gram/day of ciprofloxacin for 6 months. 76% of the patients went into remission (11). Another Crohn's disease trial with 18 patients receiving 1 gram/day of ciprofloxacin for 6 weeks found that 56% of patients also went into remission (12).

Side Effects: Diarrhea, headache, dizziness, drowsiness, stomach upset, abdominal pain, nausea, blurred vision, nervousness, and skin rash.

Class of Drug: Antibiotic

Generic name: Ornidazole

Brand Name: Avrazor

Mechanism of Action: Ornidazole specifically targets anaerobic bacteria. The nitro group on the molecule becomes reduced by proteins within the anaerobic microbe. This causes the nitro group to become reactive and damage the DNA within the cell, destabilizing the double helix and preventing it from replicating its DNA (36).

Efficacy: A randomized, double-blind trial examined the efficacy of ornidazole in reducing recurrence rates of Crohn's disease in postoperative patients. In the study, 80 patients were randomized and received either ornidazole (1 g/day) or a placebo. After a year, the recurrence rate in the placebo group was 37.5% (15/40 patients) as compared to the 7.9% (3/38 patients) in the ornidazole group (32).

Side Effects: Drowsiness, dizziness, headache, and tremors.

Class of Drug: Antibiotic

Generic name: Metronidazole

Brand Name: Flagyl, Flagyl IV, Flagyl 375

Mechanism of Action: Metronidazole selectively targets anaerobic bacteria. In its unionized state, it can cross the cellular membrane and then become reduced and activated. Once in the bacterial cell, it binds to DNA and disrupts the helical structure. This inhibits the synthesis of the DNA and leads to the death of the bacterial cell (34).

Efficacy: In a double-blind study that examined the efficacy of metronidazole in treating patients with Crohn's disease, it was seen that patients receiving the drug showed a significant improvement in CDAI when compared to those receiving the placebo. Out of the 33 patients that received a 10 mg/kg dosage, 36% entered remission. The remission rate for the 30 patients that received 20 mg/kg of metronidazole was 27%. The 36 patients in the placebo group had a remission rate of 25% (33).

Side Effects: Nausea, abdominal cramps, stomach upset, vomiting, diarrhea, constipation, headache, dizziness, weight loss, and dry mouth.

Probiotics

Class of Drug: Probiotic

Generic name: Bifidobacterium, lactobacillus, and streptococcus

Brand Name: VSL#3

Mechanism of Action: Probiotics have several mechanisms for their beneficial effects. Probiotics can contain species that reduce intestinal pH and they can contain species that protect against invasion by pathogenic organisms. *S. boulardii* can secrete proteins that inhibit the production of proinflammatory cytokines by interfering with NF-kB. *Lactobacillus paracasei* decreases the plasma content proinflammatory cytokines in patients with ulcerative colitis (53).

Efficacy: In a multicenter, randomized, double-blind trial with 147 patients with ulcerative colitis, it was seen that VSL#3 had higher rates of clinical responses and remission than a placebo did. After 12 weeks, patients given VSL#3 had a remission rate of 42.9%, compared to the placebo group's remission rate of 15.7% (54).

Side Effects: Stomach bloating and discomfort.

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