Updates in the Medical Management of Crohn's Disease

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Abstract:

Since the publication of our last article, *Current and Emerging Strategies in the Management of Crohn's Disease*, several major advances have occurred in the field of IBD care. Perhaps the most visible are the additions of vedolizumab and ustekinumab to the spectrum of medical therapies. Other key trends, such as a more aggressive approach to treatment, termed "top-down therapy", drug monitoring, the use of noninvasive disease markers, reduction in mesalamine usage, and the rise of synthetic drugs termed "biosimilars" merit discussion as well. Additionally, numerous new therapeutic targets are under study. In this review, we aim to highlight updates and contemporary trends in the medical treatment of Crohn's Disease (CD) for the gastroenterologist and the primary care physician.

Keywords: Crohn's Disease, IBD, Biologics, Top-Down, Biosimilars

I. General Approach to Treatment

Crohn's disease encompasses several distinct and overlapping phenotypes and may occur throughout the GI tract, from mouth to anus.[1] The initial injury to the intestinal mucosa is characterized by a predominantly inflammatory infiltrate that progresses to fibrosis over time.[2] Historically, convention has been to use the "mildest" therapies early (salicylates, non-systemic corticosteroids like budesonide) before escalating to the next tier (immunomodulators, systemic steroids), reserving biological therapies for patients who fail to respond or lose their initial response. This approach is termed "step

up" and has fallen out of favor for several reasons, namely that it does not prevent the complications of fibrosis and is slower to induce disease remission.[3] The alternative strategy, termed "top down" refers to the early and aggressive use of systemic medications, including biologics with or without immunomodulators or corticosteroids, to curtail mucosal damage and attempt to alter the natural history of disease.[4] Although patients with mucosal damage often have severe symptoms of abdominal pain and diarrhea, it has been shown that clinical symptoms do not directly correlate with mucosal injury, making endoscopic remission the intended goal of therapy.[5] Anti-TNF biologicals have been shown to induce mucosal healing, maintain steroid-free remission and reduce the need for surgery.[6] We have described these concepts in a previous publication and will herein provide an update of key trends in the current era of IBD care.[7]

Anti-TNF agents have been on the market for twenty years: Infliximab was approved in 1998, adalimumab in 2007, and certolizumab in 2008. These drugs were met with initial concerns regarding infections, infusion reactions, side effects, implications in pregnancy, and increased risk of malignancy such as non-melanomatous skin cancer and lymphoma. Long-term data is available for each of these agents in their respective drug registries and many of the initial fears about serious infections and cancers have since been allayed.[8] Data from the TREAT registry, a long-term cohort of patients with Crohn's disease on infliximab do not show a statistically significant overall risk of malignancy compared to no therapy.[9] Similar conclusions have been drawn in the pediatric population.[10] In fact, newer data show that thiopurines (azathioprine, 6-MP) appear to confer a greater risk of skin cancer and other malignancies compared to biologics in addition to their known risks of bone marrow suppression, hepatotoxicity and pancreatitis.[11] Additionally, long-term exposure to steroids confers a greater risk of side effects and long-term complications such as diabetes and osteoporosis, in addition to inferior maintenance of disease control.[12] As such, we favor early and aggressive therapy with biologicals for the treatment of Crohn's disease in patients with moderate to severe disease, gross endoscopic signs of inflammation, or high-risk disease phenotypes (fistulizing, stricturing, and perianal disease).

*Definitions – In clinical trials, an aggregate scoring system composed of symptoms and laboratory values is commonly used to measure response and remission. This scale is known as the Crohn's Disease Activity Index (CDAI) and is laborious to calculate. The CDAI score ranges from 0-450. Generally, remission is defined as a score <150, mild to moderate disease falls between 150-220, and moderate to severe disease is considered to be 220-450. A response is most commonly defined as a fall of 100 points from the baseline score, but some trials consider a fall of 70 points significant. Understanding the difference between response (a drop from the initial score) and remission (a score below 150) is critical to interpretation of studies. Additionally, *induction* refers to the first dose or several doses of medication (Example: dose at weeks 0, 2, and 6 for infliximab) whereas *maintenance* therapy refers to recurrent dosing at regular intervals after induction, which may range from every 2 to 8 weeks depending on the medication.

II. Use of Salicylates

Aminosalicylates (5-ASA) are a family of medications with various formulations that deliver the active

ingredient, mesalamine, to target sites. This class was one of the first available therapies for IBD. Mesalamine acts as an anti-inflammatory at the intestinal epithelium and remains a cornerstone of induction and maintenance therapy in Ulcerative Colitis (UC). In the past, salicylates including sulfasalazine have been used in CD, but more recent literature argues against their routine use. Because a hallmark of CD is transmural (full thickness) inflammation, topical therapies have proven inadequate. Ford et al. performed a systematic review and meta analysis to examine the role of salicylates in active or quiescent CD.[13] Twenty-three placebo-controlled trials were identified that compared the use of salicylates to placebo. Results varied between trials, but overall, 5-ASAs were only slightly superior to placebo for inducing remission (RR 0.89 95% CI = 0.80-0.99). In over 1200 patients, 5-ASAs were not superior to placebo for prevention of disease relapse (RR 0.97, 95% CI = 0.90-1.05). These agents are still used by some practitioners for mild disease, although there is limited evidence in the literature to support the practice. Certain CD patients with left sided disease (confined to the colon, distal to the splenic flexure) may benefit from 5-ASAs, particularly sulfasalazine, although the side effect profile of sulfa drugs can limit therapy. Certain mesalamine formulations, particularly those with pH dependent release in the small bowel (Pentasa, Shire) may improve symptoms but have not been proven to induce mucosal healing as monotherapy.[14]

III. Vedolizumab

Approved in 2014 for adults with adults with moderate to severely active CD, vedolizumab (Entyvio), represents a novel therapeutic pathway for Crohn's treatment. Vedolizumab is a gut-specific monoclonal antibody (mAb) that inhibits leukocyte migration by blocking alpha-4 beta-7 integrin expressed on gut-homing lymphocytes.[15] This prevents chemotaxis and decreases the mucosal immune response, particularly in the large bowel. Its predecessor, natalizumab, also approved for CD, inhibits both alpha-4 beta-1 and alpha-4 beta-7 integrins. Alpha-4 beta-1 integrins are found in the CNS, and natalizumab has been implicated in JC virus reactivation causing progessive multifocal leukoencephalopathy (PML), a lethal disorder.[16] To date, no cases of PML have been identified with vedolizumab treatment.

Vedolizumab is given as a 300mg IV infusion at weeks zero, two, and six then every 8 weeks thereafter. The GEMINI trials led to vedolizumab's entrance to the market.[17,18] Three hundred sixty-eight patients with moderate to severe CD and a failure of other treatments were randomized to receive vedolizumab or placebo. Fifteen percent were in clinical remission at 6 weeks compared to 7% for placebo (p=0.02). In a second open-label cohort, 747 patients received vedolizumab at weeks 0 and 2. In this group, 34% had a clinical response and 18% were in remission week 6. Then, the 307 patients from both trials who exhibited a response were included in a 52-week maintenance study. After 1 year of therapy, 36% and 39% were in clinical remission when dosed at every 4 or every 8 weeks, respectively compared to 21% for placebo, showing that dosing every 8 weeks was sufficient. Some seasoned gastroenterologists use vedolizumab every 4 weeks in select situations, but this is based on individual experience. In another separate trial dubbed GEMINI III, vedolizumab was tested in 315 patients with 1 or more anti-TNF failures at weeks 6 and 10. Stricter criteria (fall of 100 points in CDAI) was applied to qualify as a response to therapy. In this

very sick population, after 6 weeks of therapy, no difference was seen between vedolizumab and placebo (15% vs 12%, p=0.43). However, at week 10, the treatment group showed a significantly higher proportion patients in remission than placebo (27% vs 12%, p=.001).

These data argue that it takes time, up to 14 weeks to gain full pharmacologic effect. If no response is seen by week 14, vedolizumab should be discontinued. Additionally, the relatively low response and remission rates (compared to infliximab, for example) may be explained by several factors. Firstly, the patients in these trials had a long duration of disease (9 years) history of surgeries (41%) or fistulizing disease (37%); in other words, they were long into their disease course and the fibrotic (rather than acute inflammatory) stage of disease. Additionally, we have learned from other studies that exposure to sequential immunosuppressive agents lowers the response rate to subsequent therapy. For biologicals, your first chance for response is often your best, and early therapy may prevent long-term complications. Additionally, subgroup analyses in CD studies and more favorable outcomes in UC studies have led to the idea that vedolizumab demonstrates better efficacy in the colon than the small bowel, positioning it as a better choice for UC patients.

The key advantage of this drug is its safety profile.[19] Across the 6 trials of vedolizumab for UC and CD, risk of serious infection was *higher in placebo* compared to treatment (83 infections per 100 person years [PY] vs. 64/100 PY). The occurrence rate of malignancy while on therapy is low (18 total cancers across 2830 patients). Neither have there been signals for bone marrow suppression or hepatotoxicity. In summary, vedolizumab is an option for CD patients who have failed conventional or anti TNF therapy, and is best positioned for use in populations at higher risk for malignancy or infections (the very young and very old) or those with isolated colonic disease. A modicum of patience is required as effect tends to peak between 10-14 weeks.

IV. Ustekinumab

Ustekinumab is a monoclonal antibody that has been used in the treatment of psoriasis and psoriatic arthritis since 2009. The FDA approved ustekinumab in 2016 for the treatment of moderate to severe Crohn's disease. It targets the shared p40 subunit of interleukin-12 and interleukin-23, thus representing a novel therapeutic mechanism. Inhibiting this subunit prevents T-cell maturation and differentiation, along with some natural killer cell and antigen presenting cell populations.[20] Ustekinumab is administered in a unique manner: the first dose is a rough weight-based infusion, followed by a standard maintenance dose of 90mg subcutaneously every 8 weeks. In this way, it offers the convenience of SC dosing after the initial infusion, a factor many patients appreciate.

The UNITI trials evaluated safety and efficacy for this medication in CD patients. UNITI-1 examined induction in patients with moderate to severe disease who had failed therapy with one or more TNF-alpha inhibitors.[21] A total of 741 patients were randomized to one of three treatment arms: IV Placebo, IV ustekinumab 130mg, or weight based ustekinumab 6mg/kg (260mg for ≤ 55kg, 390mg for 56-85kg, 520mg for > 85kg). At week 6, 34% of patients receiving 130mg of ustekinumab and 34% of the patients receiving weight based dosing showed a clinical response compared to 22% for placebo (p = 0.003 for both groups). Twenty-one percent of

patients on weight-based ustekinumab were in remission at 8 weeks compared to 7% for placebo ($p<0.001$) after a single infusion.

UNITI-2 examined efficacy and safety of IV ustekinumab induction in patients who had failed either corticosteroids or immunomodulators, but were naïve or had not failed TNF inhibitors – essentially a group with less drug and disease exposure. In this trial, 628 patients were randomized to one of three treatment arms: ustekinumab 130mg, weight based ustekinumab, or placebo.[22] After 6 weeks, 52% of patients who received 130mg of ustekinumab and 56% of patients on weight based ustekinumab showed a clinical response compared to 29% for placebo ($p<0.001$ for both groups). Remission rates at 8 weeks were 31% and 40% for standard vs weight based dosing ($p=0.009$ and <0.001, respectively compared to 20% of patients in the control group. Finally, ustekinumab shows very promising maintenance data. Clinical responders from UNITY I and II were randomized to receive SC ustekinumab every 8 or 12 weeks compared to placebo. At one year, 53.1% of patients on 8-week dosing and 48.8% of patients on 12-week dosing were in remission compared to 35.9% of those receiving placebo ($p<0.01$).

Similar to vedolizumab, ustekinumab enjoys a very favorable safety profile. As with all biologic agents, concern for reactivation of latent tuberculosis or hepatitis prompts testing for exposure to these infections prior to starting therapy. However, after 8 weeks of therapy with ustekinumab, the incidence of adverse events, serious adverse events, as well as infections were no different from placebo. There were no deaths, major cardiac events, or cases of tuberculosis.

In summary, ustekinumab is a very promising therapy for CD patients. As CD is a T-cell mediated disease, modifying T-cell maturation is a plausible approach to treatment. Response and remission rates are very promising for patients with longstanding disease and recent diagnoses alike. Package labeling indications are for those that have failed immunomodulators, corticosteroids, or biologics, but some experts predict that this agent could be positioned as first line therapy in the future, given its overall efficacy, safety profile and convenience of administration.

V. Noninvasive Disease Monitoring

In recent years, testing for the presence of proteins called calprotectin and lactoferrin in the stool has become accepted as a noninvasive measure of disease activity. Calprotectin is a protein present in the cytosol of gut neutrophils and macrophages in the intestinal epithelium.[23] Similarly, lactoferrin is a iron-containing bactericidal enzyme contained in secretory granules of PMNs and mucous membranes.[24] The concentration of both enzymes is increased in the setting of acute inflammation and is a reliable indicator of disease activity.[25] Both markers are highly sensitive and specific, with studies demonstrating the use of calprotectin to differentiate inflammatory bowel disease from other disease states with similar symptomatology, including irritable bowel syndrome (IBS). Fecal calprotectin levels correlate closely with endoscopic disease activity and can even predict flares.[26] The choice of which biomarker to use varies regionally based on local laboratory availability and institutional practice. Following the concentration of fecal calprotectin over time is often done to monitor disease activity and assess response to therapy, and since the cost of the test is relatively low compared to colonoscopy, it can be used as a substitute to reduce the frequency of endoscopic procedures.

VI. Drug Monitoring

Biologic therapy is more often being tailored to the individual by periodic assessment of drug concentration, otherwise known as therapeutic monitoring. Multiple factors including the patient's volume of distribution, serum protein levels, extent and severity of endoscopic disease (allowing for leakage of protein via the gut), and high baseline CRP all influence the concentration of mAb in serum.[27] Studies demonstrate that drug concentration must meet a certain threshold for therapeutic efficacy, although the exact level may differ from patient to patient.[28] In general, concentrations of infliximab above 3.5 ug/mL are associated with a greater chance of remission and lower risk of relapse while some experts advocate a target of 5 ug/mL[29,30]. The utility of therapeutic drug monitoring for vedolizumab and ustekinumab remains to be seen as their pharmacokinetic profile is not weight based and there is little evidence supporting dose escalation.

It has long been recognized that exposure to monoclonal antibodies can lead to formation of anti-drug antibodies (ADA) in a small fraction of patients. This type of immunogenicity most commonly occurs with interrupted or episodic dosing, and once antibodies against the drug are present in sufficient quantity, they neutralize the drug rendering therapy less effective or ineffective entirely.[31] The presence of ADA also increases the risk of infusion reactions and can lower the drug concentration. ADA formation is of particular concern with TNF inhibitors, with the highest rates (6-61%) seen in infliximab.[32] Conversely, in the GEMINI trials, antibody formation against Vedolizumab was 4%.[17] If a patient has interruptions in therapy or loses response during treatment, it becomes appropriate to check for anti-drug antibodies. If anti-drug antibodies are detected at high levels without a measurable drug trough, a change in medication is indicated. Additionally, the use of immunomodulators (azathioprine, methotrexate) has been shown both to reduce the incidence antibody formation and increase drug trough levels.[33]

VII. Biosimilars

Recently, products that mirror the pharmacologic effects of monoclonal antibodies have reached the market. Termed "biosimilars", these compounds are copies of the reference product, in this case, monoclonal antibodies; although biosimilars have become available for other biological products including proteins (GCSF, erythropoietin), insulin, gene therapy, and vaccines.[34] Biosimilars must be "highly similar" and without "clinically meaningful differences in safety, purity, or potency of the product.[35] Practitioners have voiced concerns regarding the efficacy, safety, and interchangeability of these products.

Manufacturers of biosimilars must provide analytic (pharmacodynamics, pharmacokinetics) along with nonclinical and clinical data to the FDA. After rigorous analysis and proof of similarity, these complex molecules may be approved for use and substituted for the reference product, although laws regarding substitution vary from state to state. Based on the principle of extrapolation, the FDA has not required that biosimilars be tested for each approved indication. In other words, after demonstrating clinical noninferiority and similar safety in one population, biosimilars may be used and exchanged for indications that have not been formally studied. In the case of infliximab, its analogue compound, CT-P13 was compared to reference IFX in 606 patients in a double blinded multinational RCT for active *rheumatoid arthritis* (RA).[36] In the study, comparable rates of disease

response, adverse events, and antibody formation were seen for the two drugs. Similar head to head results were seen in 250 patients with active Ankylosing Spondylitis along with identical risk of tuberculosis and infusion reactions.[37] CT-P13 was approved for Crohn's disease the basis of these two studies.

Current clinical experience with biosimilars in IBD then, comes from observational cohorts. Most show comparable treatment effects along with rates of ADA formation and drug levels[38-40]. A meta-analysis of 11 nonrandomized studies showed favorable initial response and remission rates to CT-P13 for both CD and UC.[41] Patients who switched from infliximab to the biosimilar also maintained their response and rates of adverse events were similar. The Norswitch trial randomized nearly 500 patients 1:1 to receive continued infliximab or biosimilar and found that drug switching across multiple indications to the biosimilar product was not inferior.[42] Randomized data in IBD however, is limited.

Cost saving is the key purported advantage of biosimilars. Models project reduction in drug cost of about 10-30%, along with hundreds of millions in savings in the process of drug approval[43]. The potential multinational impact across multiple indications is massive. At this writing, there are 3 biosimilar versions of infliximab (Inflectra, Renflexis, Ifixi). As biological patents expire and more biosimilars reach the market, we may expect individual drug costs to further decrease and thus predict increased usage of biosimilars in the treatment of IBD as payers look for methods of cost reduction. Long-term treatment registries to monitor safety and efficacy are needed to examine the impact of biosimilars on IBD care.

VIII. Conclusions

Many significant shifts and developments have occurred in the treatment of Crohn's disease over the last 5-10 years. As we progress toward an age of individualized IBD therapy, gastroenterologists attempt to match the intensity of therapy with disease severity and where possible choose medications that target areas affected by inflammation. We have learned from numerous trials that patients with less exposure to immunosuppressive medications and shorter durations of disease have a greater chance of responding to early treatment with biologics. Data shows that the benefits of salicylates are few for most patients with CD. Step up therapy is increasingly recognized to delay or reduce the complications of this menacing disease and may lead to better outcomes and lower costs. Vedolizumab and Ustekinumab are novel therapeutic agents with excellent safety profiles and are they flanked by numerous medications under study in phase II and III trials. Therapeutic drug monitoring and noninvasive disease markers are increasingly used to tailor medical therapy. Finally, twenty years after the first biologic became available; we now have biosimilars reaching the market. Time will tell if this class truly offers identical efficacy. The future is bright for patients and clinicians alike in the fight against IBD.

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References:

1. Sleisenger MH, Feldman M, Friedman LS, Brandt LJ. Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management. Philadelphia: Saunders/Elsevier, 2010.
2. Pineton de Chambrun G, Peyrin-Biroulet L, et al. Clinical implications of mucosal healing for the management of IBD. *Nat Rev Gastroenterol Hepatol* . 2010 Jan 1;7(1):15-29.
3. D'Haens G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet*, 2008. 371(9613): 660-667.
4. Hanauer SB. Crohn's disease: step up or top down therapy. *Best Pract Res Clin Gastroenterol*. 2003 Feb 1;17(1): 131-7.
5. Baert F, Moortgat L, Van Assche G, et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. *Gastroenterology*. 2010 Feb 1;138(2):463-8.
6. Schnitzler F, Fidder H, Ferrante M, et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. *Inflamm bowel dis*. 2009 Sep 1;15(9):1295-301.
7. Randall CW, Vizuete JA, Wendorf G, et al. Current and emerging strategies in the management of Crohn's disease. *Best Pract Res Clin Gastroenterol.* 2012; (26) 601-610.
8. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. *Am J Gastroenterol*. 2012 Sep 1;107(9):1409-22.
9. Lichtenstein GR, Feagan BG, Cohen RD, et al. Drug therapies and the risk of malignancy in Crohn's disease: results from the TREAT™ Registry. *Am J Gastroenterol*. 2014 Feb 1;109(2):212-23.
10. Hyams JS, Lerer T, Griffiths A, et al. Long-term outcome of maintenance infliximab therapy in children with Crohn's disease. *Inflamm bowel dis*. 2008 Dec 23;15(6):816-22.
11. Abbas AM, Almukhtar RM, Loftus EV, et al. Risk of melanoma and non-melanoma skin cancer in ulcerative colitis patients treated with thiopurines: a nationwide retrospective cohort. *Am J Gastroenterol*. 2014 Nov 1;109(11):1781-93.
12. Selinger CP, Parkes GC, Bassi A, et al. A multi-centre audit of excess steroid use in 1176 patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2017 Nov 1;46(10):964-73.
13. Ford AC, et al. Efficacy of 5-aminosalicylates in Crohn's disease: systematic review and meta-analysis. *Am J Gastroenterol*. 2011. 106(4): p. 617-29.
14. Hanauer SB, Strömberg U. Oral Pentasa in the treatment of active Crohn's disease: a meta-analysis of double-blind, placebo-controlled trials. *Clin Gastroenterol Hepatol*. 2004 May 31;2(5):379-88.
15. Soler D, Chapman T, Yang LL, et al. The binding specificity and selective antagonism of vedolizumab, an anti-α4β7 integrin therapeutic antibody in development for inflammatory bowel diseases. *J Pharmacol Exp Ther*. 2009 Sep 1;330(3):864-75.
16. Bloomgren G, Richman S, Hotermans C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med*. 2012; 366:1870-1880.
17. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2013 Aug 22; 369(8):711-21.
18. Sands BE, Feagan BG, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology*. 2014 Sep 30;147(3):618-27.
19. Colombel J, Sands BE, Rutgeerts P, *et al*. The safety of vedolizumab for ulcerative colitis and Crohn's disease *Gut*. Published Online First: 18 February 2016. doi: 10.1136/gutjnl-2015-311079
20. Feagan, Brian G., William J. Sandborn, Christopher Gasink, Douglas Jacobstein, Yinghua Lang, et al. "Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease." *N Engl J Med*. 2016 (375) 1946-960.
21. Sandborn W, Gasink C, Gao L, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med* 2012. (367)1519-1528.
22. Simon E., Ghosh S.,Lacucci M., Moran G. (2016). Ustekinumab for the treatment of Crohn's disease: can it find its niche? *Therap Adv Gastroenterol*. 2016 Jan; 9(1): 26–36.
23. Røseth AG, Fagerhol MK, Aadland E, et al. Assessment of the neutrophil dominating protein calprotectin in feces: a methodologic study. *Scand J Gastroenterol*. 1992 Jan 1;27(9):793-8.
24. Langhorst J, Elsenbruch S, Koelzer J, et al. Noninvasive markers in the assessment of

intestinal inflammation in inflammatory bowel diseases: performance of fecal lactoferrin, calprotectin, and PMN-elastase, CRP, and clinical indices. *Am J Gastroenterol*. 2008 Jan 1;103(1):162-9.
25. Vieira A, Fang CB, Rolim EG, et al. Inflammatory bowel disease activity assessed by fecal calprotectin and lactoferrin: correlation with laboratory parameters, clinical, endoscopic and histological indexes. *BMC res notes*. 2009 Oct 29;2(1):221.
26. D'haens G, Ferrante M, Vermeire S, et al. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. *Inflamm bowel dis*. 2012 Dec 1;18(12):2218-24.
27. Afif W, Loftus Jr EV, Faubion WA, Kane SV, Bruining DH, Hanson KA, Sandborn WJ. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. *Am J Gastroenterol*. 2010 May;105(5):1133
28. Maser EA, Villela R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. *Clin Gastroenterol Hepatol*. 2006 Oct 1;4(10):1248-54.
29. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'haens G, Diamond RH, Broussard DL, Tang KL. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Eng J Med*. 2010 Apr 15;362(15):1383-95.
30. Ordás I, Feagan BG, Sandborn WJ. Therapeutic drug monitoring of tumor necrosis factor antagonists in inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2012 Oct 1;10(10):1079-87.
31. Strik AS, Bots SJ, D'haens G, et al. Optimization of anti-TNF therapy in patients with inflammatory bowel disease. *Expert Rev Clin Pharmacol*. 2016 Mar 3;9(3):429-39.
32. Vincent FB, Morand EF, Murphy K, et al. Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective. *Ann rheum dis*. Nov 2012.
33. Vermeire S, Noman M, Van Assche G, et al. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. *Gut*. 2007 Sep 1;56(9):1226-31.
34. Weise M, Bielsky MC, De Smet K, et al. Biosimilars: what clinicians should know. *Blood*. 2012 Dec 20;120(26):5111-7.
35. FDA guidance on Biosimilar Products. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM581282.pdf Accessed 20 Feb, 2018.
36. Yoo DH, Hrycaj P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann rheum dis*. 2013 May 17:annrheumdis-2012.
37. Park W, Hrycaj P, Jeka S, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. *Ann rheum dis*. 2013 May 17:annrheumdis-2012.
38. Ruiz-Agüello MB, Maguregui A, Martínez A, et al. P387 Infliximab therapeutic drug monitoring test validated for measuring CT-P13 and SB2 biosimilars. *J Crohns Colitis*. 2018 Jan 16;12(supplement_1):S299
39. Kim YH, Ye BD, Pesegova M, et al. Phase III randomized, double-blind, controlled trial to compare biosimilar infliximab (CT-P13) with innovator infliximab (INX) in patients with active Crohn's disease: early efficacy and safety results. *Gastroenterology*. 2017 Apr 1;152(5):S65.
40. Ben-Horin S, Yavzori M, Benhar I, et al. Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima. *Gut*. 2015 Apr 18:gutjnl-2015.
41. Komaki Y, Yamada A, Komaki F, et al. Systematic review with meta-analysis: the efficacy and safety of CT-P13, a biosimilar of anti-tumour necrosis factor-α agent (infliximab), in inflammatory bowel diseases. *Aliment Pharmacol Ther*. 2017 Apr 1;45(8):1043-57.
42. Jørgensen, Kristin K., et al. "Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial." *The Lancet* 389.10086 (2017): 2304-2316.
43. Jha A, Upton A, Dunlop WC, et al. The budget impact of biosimilar infliximab (Remsima®) for the treatment of autoimmune diseases in five European countries. *Advances in therapy*. 2015 Aug 1;32(8):742-56.

