Side Effects of Biologics for IBD – Scientific Research

IBD Biologics Fact Sheet

https://www.crohnscolitisfoundation.org/sites/default/files/legacy/assets/pdfs/biologic-therapy.pdf

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1. Mantzaris GJ. When can we cure Crohn's?. Best Pract Res Clin Gastroenterol. 2014;28(3):519-529. doi:10.1016/j.bpg.2014.04.008.

   https://doi.org/10.1016/j.bpg.2014.04.008

   ABSTRACT: Crohn's disease is a life-long idiopathic inflammatory disease which affects the entire gastrointestinal tract and occasionally extra-intestinal organs. CD is thought to result from complex interactions between environmental factors, the gut microbes, and the genetic background and the immune system of the host. In the last decades research on these pathogenetic components, and especially on mucosal immunity, has led to the development of biologic agents and therapeutic strategies that have improved dramatically the treatment of CD but we are still far away from curing the disease. If there is a treatment for CD that will probably evolve through methodical steps towards integrating research on all the components involved in the pathogenesis of CD. This holistic and global approach may aid at unravelling the mysteries of CD and developing novel agents and therapeutic strategies which by targeting multiple pathogenetic pathways and at different stages of disease may lead hopefully to cure.

2. Cleynen, I., Vermeire, S. Paradoxical inflammation induced by anti-TNF agents in patients with IBD. Nat Rev Gastroenterol Hepatol 9, 496–503 (2012).

   https://doi.org/10.1038/nrgastro.2012.125

   ABSTRACT: Anti-TNF antibodies have acquired a prominent place in the management of IBD (including Crohn's disease and ulcerative colitis), rheumatologic conditions (such as rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis) and psoriasis. They have a good safety profile, especially when contraindications such as demyelinating disease, active infections and/or abscesses are ruled out, and when necessary precautions to prevent reactivation of tuberculosis are taken. However, with increasing use of these agents, paradoxical adverse events have been reported. Some of these features are shared with the underlying disease for which these drugs are given, making management of these conditions challenging. For example, anti-TNF therapy is used for the treatment of psoriasis, but psoriasiform lesions are sometimes observed in patients receiving therapy. Similarly, anti-TNF therapy is used for the treatment of rheumatologic diseases, but arthralgias and

arthritis are sometimes observed in patients receiving anti-TNF agents. We review the paradoxical inflammation induced by anti-TNF agents in patients with IBD, provide hypotheses for the occurrence of this paradoxical inflammation and give practical advice on how to manage these patients.

3. Van Assche G, Van Ranst M, Sciot R, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. N Engl J Med. 2005;353(4):362-368. doi:10.1056/NEJMoa051586

   https://www.nejm.org/doi/full/10.1056/NEJMoa051586

   ABSTRACT: The prior diagnosis of fatal astrocytoma in a 60-year-old man with Crohn's disease treated with natalizumab, a monoclonal antibody against α4 integrins, was reclassified as JC virus–related progressive multifocal leukoencephalopathy (PML). Analysis of frozen serum samples showed that JC virus DNA had appeared in the serum three months after the initiation of open-label natalizumab monotherapy and two months before the appearance of symptomatic PML. There was staining of the brain lesion for polyomavirus. This case report, along with two others, suggests that anti–α4-integrin therapy can result in JC virus–induced PML.

4. Li H, Shi FH, Huang SY, Zhang SG, Gu ZC, Wei JF. Clinical adverse effects of natalizumab: Protocol for a meta-analysis of randomized double-blind placebo-controlled clinical trails. Medicine (Baltimore). 2018;97(28):e11507. doi:10.1097/MD.0000000000011507

   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6076155/

   ABSTRACT: Background: Natalizumab (NAT), a humanized monoclonal antibody, which binds in both α4β1 integrins and α4β7 integrins, is approved for the treatment of multiple sclerosis (MS) and Crohn's disease (CD). An uncommon but serious adverse event from NAT treatment is known as progressive multifocal leukoencephalopathy (PML). However, clinical comprehensive safety evidence of NAT is limited.

   Methods: We will search Medline, Embase, Cochrane library, and ClinicalTrials.gov website from inception to May 9, 2018. Double-blind, randomized placebo-controlled trials reporting safety data of NAT will be eligible for inclusion. Outcome variables will include adverse events (AEs) varying degrees and AEs occurring in ≥ 5% patients with NAT or placebo. STATA software (version 12, Statacorp, College Station, TX) will be utilized to assess risk of bias and synthesize data. Outcomes will be reported by weight mean difference (WMD), risk ratios (RRs), and their 95% confidence intervals (95% CIs). I statistic will be used to evaluate heterogeneity among studies.

   Results: This systemic review and meta-analysis will evaluate serious AEs and AEs of NAT as compared to placebo.

Conclusion: Our study will provide a comprehensive picture of AEs of NAT.

5. Lichtenstein GR, Hanauer SB, Sandborn WJ. Risk of Biologic Therapy-Associated Progressive Multifocal Leukoencephalopathy: Use of the JC Virus Antibody Assay in the Treatment of Moderate-to-Severe Crohn's Disease. Gastroenterol Hepatol (N Y). 2012;8(11 Suppl 8):1-20.

   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4027896/

   ABSTRACT: For treatment of moderate-to-severe active Crohn's disease, clinicians generally rely on immunosuppressants (including azathioprine and 6-mercaptopurine), corticosteroids, and antibodies against tumor necrosis factor α. However, a significant proportion of patients do not respond to these therapies, lose response over time, or are intolerant to these therapies. In such cases, one of the only remaining pharmacologic treatment options is natalizumab, an α4 integrin-targeted antibody. Unfortunately, 3 cases of progressive multifocal leukoencephalopathy (PML) were reported in natalizumab-treated patients in 2005, shortly after natalizumab's approval by the US Food and Drug Administration (FDA). Natalizumab was subsequently withdrawn from the market but was then reintroduced in 2006 under close supervision by the FDA. Careful review of postmarketing data revealed 3 major risk factors for the development of natalizumab-associated PML, the most significant of which is prior exposure to the JC virus (JCV). To help identify patients who may be at higher risk for developing natalizumab-associated PML, a JCV antibody assay was developed that can detect anti-JCV antibodies in patients' blood. Clinicians can now consider a patient's anti-JCV antibody status together with the other major risk factors for natalizumab-associated PML—duration of natalizumab therapy and prior immunosuppressant use—to more accurately gauge the risks and benefits of natalizumab therapy in a particular patient.

6. Borman ZA, Côté-Daigneault J, Colombel JF. The risk for opportunistic infections in inflammatory bowel disease with biologics: an update. Expert Rev Gastroenterol Hepatol. 2018;12(11):1101-1108. doi:10.1080/17474124.2018.1530983

   https://doi.org/10.1080/17474124.2018.1530983

   ABSTRACT: Crohn's disease and Ulcerative Colitis are forms of inflammatory bowel disease (IBD), chronic diseases treated with medical and surgical therapy. Patients with IBD are treated with potent immunomodulatory agents, leading to immunosuppression, and the potential for opportunistic infections. In 2014, the ECCO guidelines were released to guide the prevention, diagnosis and treatment of a variety of these opportunistic infections. Since 2014, there have been a number of new agents released as well as a significant expansion in our knowledge of the safety profile of IBD medications. In this article, we review the literature after 2014 regarding opportunistic infections and updates on safety data. Areas covered: We review updates in immunomodulatory therapies for IBD and opportunistic infections since the 2014 ECCO guidelines were published. Expert commentary: The prevention, diagnosis, and treatment of opportunistic infections continue to evolve, as new

drugs are approved, and the use of a combination of biologic agents are considered for therapy in clinical trials. What causes some patients to fail to respond to vaccination, or for others to develop severe infections, remains unclear. Improved risk stratification for opportunistic infections in IBD patients and updated ECCO 2014 guidelines would be of significant benefit.

7. Chan HC, Ng SC. Emerging biologics in inflammatory bowel disease. J Gastroenterol. 2017;52(2):141-150. doi:10.1007/s00535-016-1283-0

   https://doi.org/10.1007/s00535-016-1283-0

   ABSTRACT: Early biologic therapy is recommended in patients with inflammatory bowel disease and poor prognostic factors and in those refractory to conventional medications. Anti-tumor necrosis factor (anti-TNF) agents are the most commonly used biologic agents. However, some patients may not have an initial response to anti-TNF therapy, and one-third will develop loss of response over time. Anti-TNF drugs can also be associated with side effects. In addition, the use of biologics is currently limited by their cost, especially in developing countries. A number of new therapeutic targets, including novel small molecules, and cellular therapy are available or under investigation. These novel molecules include oral Janus kinase (JAK) inhibitor (tofacitinib), interleukin inhibitor (ustekinumab), oral SMAD7 antisense oligonucleotide (mongersen), and anti-integrin inhibitors (vedolizumab). Here, we review the mechanisms of action, the efficacy, and the safety data of these novel agents. Biological products that are highly similar to reference biologic products whose patents have expired-also known as "biosimilars"-can be produced at lower cost with similar efficacy, and are also available for the treatment of IBD. We review the efficacy data for such agents as well.

8. Hindryckx P, Novak G, Bonovas S, Peyrin-Biroulet L, Danese S. Infection Risk With Biologic Therapy in Patients With Inflammatory Bowel Disease. Clin Pharmacol Ther. 2017;102(4):633-641. doi:10.1002/cpt.791

   https://doi.org/10.1002/cpt.791

   ABSTRACT: The development of biologic drugs revolutionized the management of inflammatory bowel diseases: Crohn's disease and ulcerative colitis. However, while their efficacy has been well established, it remains uncertain to what extent biologic treatments may be associated with important safety risks, such as serious infections, opportunistic infections, or tuberculosis reactivation. Herein, we review and discuss the current evidence on the infection risk associated with biologic therapy in patients with inflammatory bowel disease (IBD).

9. Quezada SM, McLean LP, Cross RK. Adverse events in IBD therapy: the 2018 update. Expert Rev Gastroenterol Hepatol. 2018;12(12):1183-1191. doi:10.1080/17474124.2018.1545574

https://doi.org/10.1080/17474124.2018.1545574

ABSTRACT: Crohn's disease and ulcerative colitis affect an increasing number of patients, and utilization of immune suppressant and biologic therapies is also increasing. These agents are linked to adverse events ranging from mild nuisance symptoms to potentially life-threatening complications including infections and malignancies. Areas covered: This review provides an updated discussion on adverse events associated with immunomodulator, anti-TNF-α, anti-integrin, and anti-IL 12/IL-23 antibody therapies. In addition, we review the risk profile of the currently widely available infliximab biosimilar medication. Expert commentary: Providers should engage in risk-benefit discussion with information specific to each medication discussed, and consider individualized risk factors when selecting therapeutic agents. Drug monitoring and shared decision-making results in more personalized medical management of inflammatory bowel disease.

10. McConachie SM, Wilhelm SM, Bhargava A, Kale-Pradhan PB. Biologic-Induced Infections in Inflammatory Bowel Disease: The TNF-α Antagonists. Ann Pharmacother. 2018;52(6):571-579. doi:10.1177/1060028018754896

https://doi.org/10.1177/1060028018754896

ABSTRACT: Objective: To review the mechanism and association of infectious risk among the tumor-necrosis factor α (TNF-α) antagonists used in inflammatory bowel disease.

Data sources: A PubMed literature search was performed using the following search terms: infliximab, adalimumab, certolizumab, golimumab, inflammatory bowel disease, crohn's, ulcerative colitis, adverse effects, adverse events, safety, and infection.

Study selection and data extraction: Meta-analyses and cohort studies with outcomes pertaining to quantitative infectious risk were reviewed. Case reports and case series describing association between TNF-α inhibitors and infection were also reviewed.

Data synthesis: A total of 7 recent meta-analyses of randomized trials demonstrate inconclusive association of infection with TNF-α antagonists. Registry data suggest that medications carry an independent risk of opportunistic infections. Risk factors for infection include older age, malnutrition, diabetes, and possibly combination therapy. Reported infections vary widely but include intracellular and granulomatous bacteria, viruses, and fungi.

Conclusion: TNF-α antagonists are associated with an increased risk of opportunistic infection, although this risk has not been demonstrated conclusively in randomized controlled trials. Knowledge of concomitant risk factors, mechanism of infectious risk, and available treatment options can improve patient care in the clinical setting.

11. Ledder O, Turner D. Antibiotics in IBD: Still a Role in the Biological Era?. Inflamm Bowel Dis. 2018;24(8):1676-1688. doi:10.1093/ibd/izy067

https://doi.org/10.1093/ibd/izy067

ABSTRACT: Despite compelling evidence pointing to a critical role of gut microflora in inflammatory bowel disease (IBD) pathogenesis, the role of antibiotics in clinical practice remains limited, largely due to heterogeneous trials with often conflicting evidence. In this review, we revisit previous randomized controlled trials and high-quality uncontrolled studies in an effort to better elucidate the role of antibiotics in contemporary treatment algorithms. The most established role of antibiotics is in perianal Crohn's disease (CD), utilizing ciprofloxacin with or without metronidazole often as an adjunct to biological therapy. Evidence also points to a likely modest role of various antibiotic classes in mild to moderate luminal CD, including ciprofloxacin, metronidazole, azithromycin, and rifaximin. The benefit of metronidazole in preventing postoperative recurrence in CD is well reported; however, the long-term benefit of this intervention remains uncertain. The use of antibiotics in ulcerative colitis (UC) is even more controversial, but studies using broad-spectrum oral antibiotic cocktails have reported a possible role in acute severe colitis and chronic persistent UC. Similarly, the role of oral vancomycin and gentamicin in very early-onset IBD has interesting preliminary results. Adverse events of antibiotics, the resulting alterations in the microbiome with its associated unknown long-term sequela, and the emergence of antibiotic-resistant strains must be carefully balanced. Therefore, although antibiotics may be underused in the treatment of IBD, their integration into clinical practice must be approached judiciously and individually.

12. Shivaji UN, Sharratt CL, Thomas T, et al. Review article: managing the adverse events caused by anti-TNF therapy in inflammatory bowel disease. Aliment Pharmacol Ther. 2019;49(6):664-680. doi:10.1111/apt.15097

https://doi.org/10.1111/apt.15097

ABSTRACT: Background: Biological therapy is currently widely used to treat IBD. Infliximab, adalimumab and golimumab are currently licensed anti-TNF therapies. Biosimilar anti-TNF monoclonal antibodies are increasingly used. Anti-TNF therapies are widely used and their adverse effects are well characterised, and may cause significant morbidity and mortality in a small proportion of exposed patients. Gastroenterologists need to understand the mechanisms for these effects, recognise these swiftly and manage such events appropriately.

Aim: To cover the range of potential adverse reactions as a result of biologic therapy and specifically management of these events.

Methods: A Medline and Pubmed search was undertaken. Search terms included were "anti-TNF," "infliximab" or "adalimumab" or "golimumab" combined with the keywords

"ulcerative colitis" or "Crohn's disease" or "inflammatory bowel disease" and then narrowed to articles containing the keywords "complications," "side effects" or "adverse events" or "safety profile." International guidelines were also reviewed where relevant.

Results: Adverse events discussed in this review include infusion reactions, blood disorders and infections (including bacterial, viral, fungal and opportunistic infections) as well as autoimmune, dermatological disorders, cardiac and neurological conditions. Malignancies including solid organ, haematological and those linked to viral disease are discussed.

Conclusions: Anti-TNF therapy has wide-ranging effects on the immune system resulting in a spectrum of potential adverse events in a small proportion of patients. Research advances are improving the understanding, recognition and management of these adverse events.

13. Sousa P, Allez M. Complications of biologics in inflammatory bowel disease. Curr Opin Gastroenterol. 2015;31(4):296-302. doi:10.1097/MOG.0000000000000191

    https://doi.org/10.1097/mog.0000000000000191

    ABSTRACT: Purpose of review: The treatment of inflammatory bowel disease (IBD) in the modern area has improved with more biological agents available. Although the efficacy of these drugs has been demonstrated, concerns about their safety profile have been raised, and new data have emerged in the past year.

    Recent findings: New data regarding the safety profile of anti-TNF were published over the last year, with a better identification of patients at risk of infection, and specific recommendations for the prevention of infections. There is a mild increase in malignancy in patients receiving anti-TNF, mainly lymphoma and skin cancer, which seems mainly attributable to combination with thiopurines. Specific recommendations for management of pregnancy were published.

    Summary: Biological treatments are effective and safe in the treatment of IBD, provided that the recommendations for their use and monitoring are followed.

14. Tran-Minh ML, Sousa P, Maillet M, Allez M, Gornet JM. Hepatic complications induced by immunosuppressants and biologics in inflammatory bowel disease. World J Hepatol. 2017;9(13):613-626. doi:10.4254/wjh.v9.i13.613

    http://www.ncbi.nlm.nih.gov/pmc/articles/pmc5424291/

    ABSTRACT: The incidence of inflammatory bowel diseases (IBD) is rising worldwide. The therapeutic options for IBD are expanding, and the number of drugs with new targets will rapidly increase in coming years. A rapid step-up approach with close monitoring of intestinal inflammation is extensively used. The fear of side effects represents one the most limiting factor of their use. Despite a widespread use for years, drug induced liver injury

(DILI) management remains a challenging situation with Azathioprine and Methotrexate. DILI seems less frequent with anti-tumor necrosis factor agents and new biologic therapies. The aim of this review is to report incidence, physiopathology and practical guidelines in case of DILI occurrence with the armamentarium of old and new drugs in the field of IBD.

15. Fousekis FS, Theopistos VI, Katsanos KH, Tsianos EV, Christodoulou DK. Hepatobiliary Manifestations and Complications in Inflammatory Bowel Disease: A Review. Gastroenterology Res. 2018;11(2):83-94. doi:10.14740/gr990w

    http://www.ncbi.nlm.nih.gov/pmc/articles/pmc5916631/

    ABSTRACT: Liver and biliary track diseases are common extraintestinal manifestations of inflammatory bowel disease (IBD), reported both in Crohn's disease and ulcerative colitis, and may occur at any time during the natural course of the disease. Their etiology is mainly related to pathophysiological changes induced by IBD, and secondary, due to drugs used in IBD. Fatty liver is considered as the most frequent hepatobiliary manifestation in IBD, while primary sclerosing cholangitis (PSC) is the most correlated hepatobiliary disorder and is more prevalent in patients with ulcerative colitis. PSC can cause serious complications from the liver, biliary tree, and gallbladder and can lead to liver failure. Less frequently, IBD-associated hepatobiliary manifestations include cholelithiasis, granulomatous hepatitis, portal vein thrombosis, IgG4-related cholangiopathy, pyogenic liver abscess, hepatic amyloidosis and primary biliary cirrhosis. Most of the drugs used for IBD treatment may cause liver toxicity. Methotrexate and thiopurines carry the higher risk for hepatotoxicity, and in many cases, dose adjustment may normalize the liver biochemical tests. Reactivation of hepatitis B and C virus during immunosuppressive use, especially during use of biological agents, is a major concern, and adequate screening, vaccination and prophylactic treatment is warranted.

16. Chao YS, Visintini S. Biologics Dose Escalation for the Treatment of Inflammatory Bowel Disease: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2018.

    http://www.ncbi.nlm.nih.gov/books/nbk537799/

    ABSTRACT: Up to one-third of inflammatory bowel disease(IBD) patients can experience that biologics become less effective and fail to maintain disease remission. In these cases, dose intensification or more frequent dosing have been considered and tried. However, the safety profile of intensified dosing and the effects on paradoxical reactions remain a subject of research. There is a need to review the effectiveness and risks of the biologics that are infused more frequently or at higher doses. To answer this question, we aim to review the literature and compare the clinical utilities and cost-effectiveness of higher or more frequent than standard dosing of biologics with standard dosing for the treatment of IBD.

17. Kruis W, Nguyen PG, Morgenstern J. Promises and Dangers of Combination Therapy. Dig Dis. 2017;35(1-2):56-60. doi:10.1159/000449084

https://doi.org/10.1159/000449084

ABSTRACT: The efficiency of the existing methods of treating inflammatory bowel disease (IBD) is limited. There are 2 ways to address this problem - either create new treatment modalities or optimize current therapies. Optimisation may be accomplished by using combinations of established therapeutic strategies. With regard to topically acting compounds such as 5-aminosalicylic acid, combining oral and rectal preparations is a commonly used method. Another commonly used combination is anti-tumor necrosis factor (TNF)-α antibody modalities together with immunosuppressants (thiopurines, methotrexate). Several aspects favour those combinations such as increased effectivity, prevention of immunogenicity and perhaps less adverse events. Currently, discussion on directly additive therapeutic effects is in progress, which have been demonstrated in some clinical trials. As on date, the combination of infliximab with azathioprine is most likely the most effective treatment of Crohn's disease. On the other hand, a combination therapy with both compounds affecting the immune system has, of course, risks. For sure, the frequency with which serious infectious complications are arising is increasing. Furthermore, the number of patients experiencing malignancies such as hepato-splenic lymphoma or melanoma is strongly suspected to be on the rise. In summary, combinations of current treatments for IBD are widely established. Various strategies have been studied and significant improvements of therapeutic effects have been demonstrated. Unfortunately, some of those proven combinations increase therapeutic risks, for example, increase the frequency of serious infections and also of some malignancies. Therefore, great caution has to be exercised when applying combination therapies.

18. Summary of article:
https://gastroenterology.acponline.org/archives/2019/03/22/2.htm

Singh S, Facciorusso A, Dulai PS, Jairath V, Sandborn WJ. Comparative Risk of Serious Infections With Biologic and/or Immunosuppressive Therapy in Patients With Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis. Clin Gastroenterol Hepatol. 2020;18(1):69-81.e3. doi:10.1016/j.cgh.2019.02.044

https://doi.org/10.1016/j.cgh.2019.02.044

ABSTRACT: Background & aims: We performed a systematic review and meta-analysis to evaluate the comparative risk of serious infections with tumor necrosis factor (TNF) antagonists, non-TNF targeted biologics, tofacitinib, and immunosuppressive agents in patients with inflammatory bowel diseases (IBDs).

Methods: In a systematic search of publications, through March 18, 2018, we identified 15 observational studies (>500 person-years) of patients with IBD treated with TNF

antagonists, non-TNF targeted biologics, tofacitinib, and/or immunosuppressive agents (thiopurines, methotrexate) that reported risk of serious infections. Only studies with active comparators were included, to allow appropriate comparative synthesis. We performed random-effects meta-analysis and estimated relative risk (RR) and 95% CIs.

Results: Compared with anti-TNF monotherapy, risk of serious infection increased with the combination of anti-TNF and an immunosuppressive agent (in 6 cohorts: RR, 1.19; 95% CI, 1.03-1.37), with anti-TNF and a corticosteroid (in 4 cohorts: RR, 1.64; 95% CI, 1.33-2.03), or with all 3 drugs (in 2 cohorts: RR, 1.35; 95% CI, 1.04-1.77); there was minimal heterogeneity among studies. In contrast, monotherapy with an immunosuppressive agent was associated with a lower risk of serious infections than monotherapy with a TNF antagonist (7 cohorts: RR, 0.61; 95% CI 0.44-0.84) or a TNF antagonist with an immunosuppressive agent (2 cohorts: RR, 0.56; 95% CI, 0.39-0.81). Infliximab-based therapy was associated with a lower risk of serious infections compared with adalimumab-based therapy in patients with ulcerative colitis (4 cohorts: RR, 0.57; 95% CI, 0.33-0.97), but not Crohn's disease (4 cohorts: RR, 0.91; 95% CI, 0.49-1.70). Few data were available on the comparative safety of biologic agents that do not inhibit TNF and tofacitinib.

Conclusions: Combination therapies for IBD that include TNF antagonists, especially with corticosteroids, are associated with a higher risk of serious infection, whereas monotherapy with an immunosuppressive agent is associated with a lower risk, compared with monotherapy with a TNF antagonist. Studies are needed to evaluate the comparative safety of non-TNF targeted biologics and small molecules for treatment of IBD.

19. Summary of article: https://www.healio.com/gastroenterology/inflammatory-bowel-disease/news/online/%7B5f395ab8-521e-4788-9b70-a6cb716bc033%7D/biologic-persistence-rates-suggest-patient-dissatisfaction-in-ibd-therapy

    Chao Chen, PhD, Abraham G Hartzema, PhD, Hong Xiao, PhD, Yu-Jung Wei, PhD, Naueen Chaudhry, MD, Ofor Ewelukwa, MD, Sarah C Glover, DO, Ellen M Zimmermann, MD, Real-world Pattern of Biologic Use in Patients With Inflammatory Bowel Disease: Treatment Persistence, Switching, and Importance of Concurrent Immunosuppressive Therapy, Inflammatory Bowel Diseases, Volume 25, Issue 8, August 2019, Pages 1417–1427.

    https://doi.org/10.1093/ibd/izz001

    ABSTRACT: Background and aims
    Medication persistence, defined as the time from drug initiation to discontinuation of therapy, has been suggested as a proxy for real-world therapeutic benefit and safety. This study seeks to compare the persistence of biologic drugs among patients with inflammatory bowel disease (IBD).
    Methods
    Patients with newly diagnosed IBD were included in a retrospective study using Truven MarketScan database. Treatment persistence and switching was compared among biologic

medications including infliximab, adalimumab, certolizumab, golimumab, and vedolizumab. Predictors for discontinuation and switching were evaluated using time-dependent proportional hazard regression.
Results
In total, 5612 patients with Crohn's disease (CD) and 3533 patients with ulcerative colitis (UC) were included in this analysis. Less than half of the patients continued using their initial biologic treatment after 1 year (48.48% in CD cohort; 44.78% in UC cohort). In the first year, adalimumab had the highest persistence and lowest switching rates for both CD (median survival time: 1.04 years) and UC (median survival time: 0.84 years). In subsequent years, infliximab users were more likely to persist in the use of biologic. Combination therapy with immunomodulators significantly decreased the risk of discontinuation, especially when immunomodulator therapy was started more than 30 days before the biologic (hazard ratio [HR], 0.22; CI, 0.16, 0.32). The major predictors for noncompliance included infection and hospitalization.
Conclusion
Overall, the persistence profiles of biologics suggest a high rate of dissatisfaction or adverse disease outcomes resulting in discontinuation and switching to a different agent. Early initiation of immunomodulators will substantially increase the persistence of biologic treatment.

20. Roblin X, Phelip JM. Risks of Combining Immunosuppressive and Biological Treatments in Inflammatory Bowel Disease. Arch Intern Med. 2008;168(6):667. doi:10.1001/archinte.168.6.667

https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/414097?utm_source=TrendMD&utm_medium=cpc&utm_campaign=_JAMA_Internal_Medicine_TrendMD_1

ABSTRACT: Sorrentino et al1 report the results of infliximab with low-dose methotrexate for the prevention of postsurgical recurrence of ileocolonic Crohn disease (CD). The authors elected to coadminister methotrexate because it is known to reduce the long-term immunogenicity of infliximab.2 This is true only with episodic treatment with infliximab. Despite the observation that therapy with concomitant immunosuppressive agents reduces the development of antibodies against biological treatments, the authors have not significantly altered the response to infliximab3 in the treatment of CD when the agents are administered as an induction course followed by scheduled maintenance treatment. Recently, Maser et al4 demonstrated that the rate of clinical remission was higher for patients with a detectable trough serum concentration of infliximab compared with patients in whom serum infliximab was undetectable, including those without antibodies (82% vs 6%; P < .001). In this study, concurrent immunomodulators did not alter outcomes.4 A preliminary report from Van Assche et al5 suggested that the immunosuppressive therapy could be discontinued after 6 months with no effect on the loss of response to infliximab over 2 years. So the concept of combination immunosuppressive therapy needs to be

discussed in light of the expanding reports of potential increases in severe infections and neoplasms.6