Leah Lourenco ’26

Introduction

Intense abdominal pain, crippling fatigue, and incessant visits to the bathroom plague a growing subset of patients daily. This is a reality for an estimated 2.8 million people in the US and 10 million worldwide, with no cure in sight (CDC, 2024; World IBD Day, n.d.). These individuals live with Inflammatory Bowel Disease (IBD), an umbrella term composed primarily of Crohn’s Disease (CD) and Ulcerative Colitis (UC) **(Fig. 1)** (Crohn’s & Colitis Foundation of America, 2014).

IBD is an autoimmune condition in which the patient’s immune system mistakenly attacks healthy cells throughout the gastrointestinal system (CDC, 2024). In healthy individuals, the intestinal epithelium is the primary barrier between the food passing through the system and the rest of the human body. This barrier, sealed by intercellular connections, protects the body from infiltration of any harmful microorganisms. In patients with IBD, this epithelium is incomplete due to intercellular junction disconnections resulting from innate dysfunction or severe inflammation (McDowell, 2024). This compromised epithelial barrier increases patients’ risk of infection from food-borne microbes.

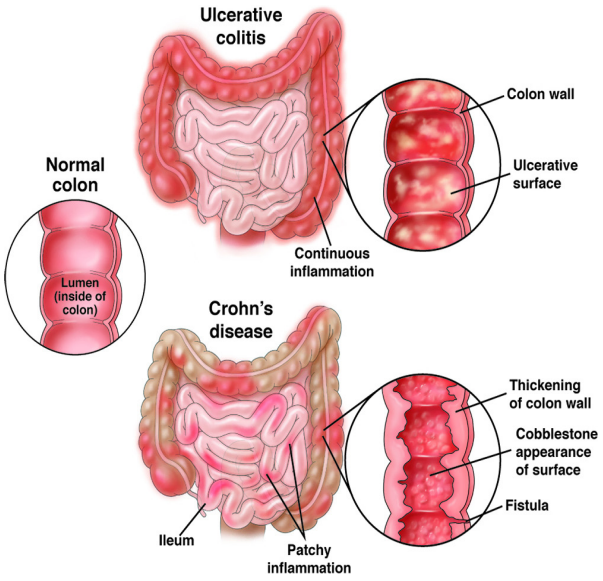

Figure 1. Comparison of CD vs. healthy vs. UC colons (American Gastroenterological Association, 2021).

Patients using conventional IBD treatments may experience a broad range of medication efficacy, leaving many unsatisfied

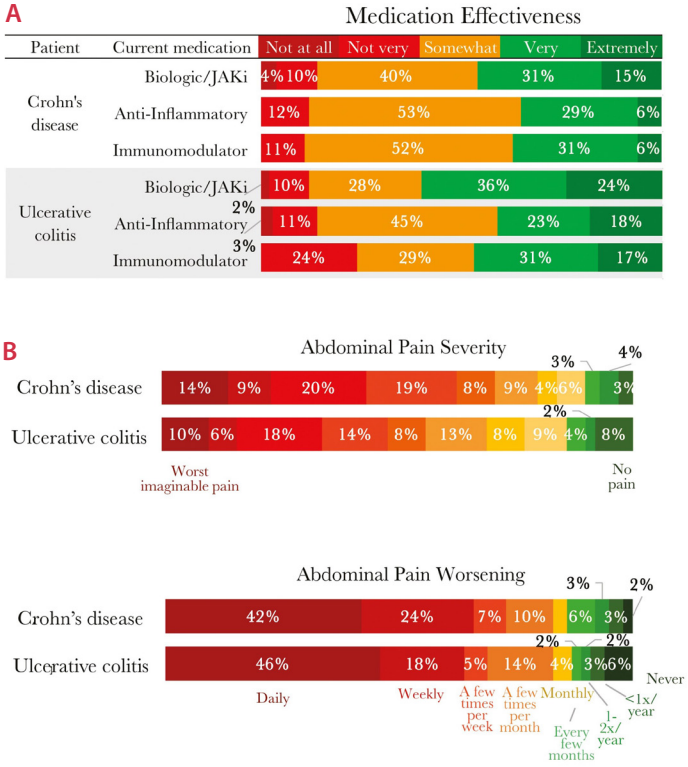

Figure 2. A. Patient-observed medication efficacy (sample size: CD, N = 189; UC, N = 87). B. Patient-rated severity of abdominal pain (Charabaty et al., 2022).

with their treatment (**Fig. 2A**). Furthermore, patients with both CD and UC continue to experience both severe or worsening abdominal pain daily (**Fig. 2B**). There is a need for novel and improved solutions for these patient populations. To develop novel solutions, it is critical to understand the CD and UC therapies developed and administered in the past.

Therapy of the Past

IBD was first reported by Matthew Baillie in 1793; ever since, researchers have made great strides in understanding the disease's function and best treatment practices. In the early 1900s, practitioners could only treat IBD patients by prescribing bed rest and performing colon irrigations, a procedure that involves flushing the bowel with fluid (Actis et al., 2019). This procedure can often cause symptoms to worsen and even damage the intestinal lining (Mayo Clinic, n.d.).

Between the 1950s and the early 1990s, a variety of drugs were used to treat and manage UC and CD. This included corticosteroids, aminosalicylic acids, and thiopurines (Actis et al., 2019). Thiopurines are immunosuppressants used to prevent T cells from causing inflammation in the body (Neurath, 2010). Although these therapeutics could improve IBD symptoms, their lack of specificity resulted in a weakened immune system throughout the body, putting patients at risk of opportunistic infections.

In 1998, more modern treatments entered the gastroenterology clinic space **(Fig. 3)**. Infliximab, commonly known as Remicade, was the first modern therapy approved for CD, achieving FDA approval in 1998 (Actis et al., 2019). Infliximab functions by binding to and inhibiting the inflammatory tumor necrosis factor (TNF) produced by several types of immune cells (Fatima et al., 2024). However, infliximab contains rodent-derived components, which led to adverse immune responses in patients. To resolve this challenge researchers developed adalimumab, also known as Humira—a fully human monoclonal antibody that functions similarly to infliximab—which was approved for IBD treatment in 2007 (Drugs, n.d.; Venaa & Cassano, 2007).

A different class of monoclonal antibodies known as IL-12 and IL-23 inhibitors acts to prevent immune response in IBD by selectively inhibiting the immune system (Actis et al., 2019). The most common drug of this class is ustekinumab—also known as Stelara—and it was approved for IBD in 2016 (Drugs, n.d.). These therapies act throughout the body and do not focus solely on the gut. Therefore, side effects from ustekinumab can manifest anywhere. Vedolizumab, another monoclonal antibody, was a breakthrough therapy in 2014 that addressed this issue, serving as the first localized treatment for IBD (Drugs, n.d.; Actis et al., 2019). Given that each of these therapies is biological in nature, it is common for patients undergoing such treatments to experience negative immune responses. When this happens, patients must be taken off of the medications, necessitating alternative therapeutic options.

Due to the patient-specific nature of IBD, scientists have experienced difficulty in developing an all-encompassing therapy. Many patients are still using non-selective immunosuppressive therapies that are over a decade old and often result in numerous adverse side effects. As a result, there is a great need for a new era of innovation in the IBD space.

Current Therapeutic Landscape

Three main pathways are currently being explored in IBD treatment: drug delivery strategies, cell-based therapies, and precision medicine.

Novel approaches to drug delivery strategy in IBD are dominated by nanotechnology. Nanotechnology is advantageous due to its highly localized nature, which reduces systemic immunologic reactions in patients. It promises to be particularly useful in IBD applications because, as inflammation becomes more severe, the colon becomes more permeable. This allows nanoparticles to permeate exclusively in the locations where inflammation is present. Furthermore, when the colonic epithelium is damaged, positively charged

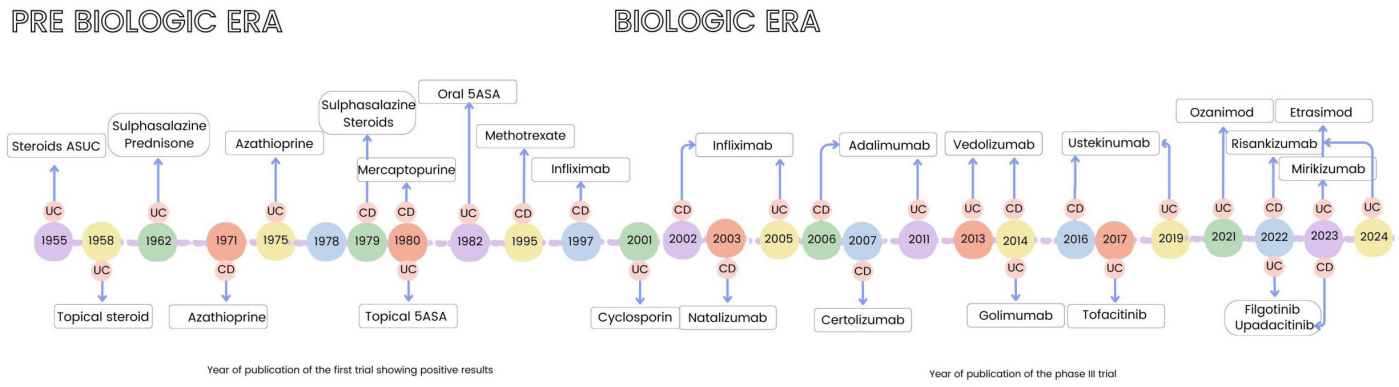

Figure 3. Approval timeline of IBD drugs since 1955 (IBD-EII, n.d).

proteins accumulate around the inflammation. By negatively charging the surfaces of the nanoparticles, researchers can further direct their localization to sites of inflammation (Yasmin et al., 2022). Researchers have also identified a variety of other ways to control nanoparticles such as inflammatory surface marking and redox sensitivity.

Another drug delivery strategy is the use of prodrugs, in which drug release is controlled through exposure to specific activating enzymes (Yasmin et al., 2022). For example, cyclosporine, a prevalent immunosuppressant, has been successfully studied as a prodrug candidate in vitro. Researchers developed a material complex that stores cyclosporine and only allows the cyclosporine to be released when the complex comes in contact with the phospholipase A2 (PLA2) enzyme, which is concentrated in the inflamed intestine (Markovic et al., 2022). This approach provides a localized method of delivering cyclosporine, an established treatment for IBD.

Cell-based therapy primarily focuses on healing the soft intestinal lining and preventing inflammation. These aims have been approached using both immune and human stem cell therapies. T regulatory cells (Tregs) and tolerogenic dendritic cells (Tol-DCs) are both involved in maintaining immune homeostasis (Hossein-Khannazer et al., 2021), with Tregs inhibiting immune responses by secreting anti-inflammatory cytokines (Leung et al., 2010). Additionally, by controlling Tol-DC maturity and antigen expression, researchers can engineer them to prevent adverse immune responses (Hossein-Khannazer et al., 2021).

Two main stem cell types have been explored for IBD treatment: hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) (Hossein-Khannazer et al., 2021). HSCs are characterized by their ability to differentiate into blood and immune cells. Scientists are able to utilize this characteristic to heal tissues damaged by IBD. However, this approach is significantly limited by the immune response caused by HSC administration. MSCs, conversely, can differentiate into any cell type other than embryonic cells. They are capable of both targeted tissue regeneration and immune regulation. The most common stem cell therapy for IBD is MSC transplantation to supplement tissue healing and immune control (Tian, 2023). MSCs have low immunogenicity, so the body does not engage in an immune response against them. However, MSC therapies are currently limited because MSCs are also capable of developing pro-inflammatory phenotypes due to their high differentiation potential.

Finally, precision medicine is perhaps the most promising yet difficult-to-execute therapeutic direction being researched today. IBD affects each patient differently, with varying triggers, symptoms, and even treatment efficacies. The aim of precision medicine is to specifically calibrate the therapeutic approach to each patient. By looking at a patient's genes, microbiome, molecular pathways, and other markers, researchers hope to provide a personalized therapeutic approach (Annese &

Annese, 2023). One of the many potential applications of precision medicine in IBD is in predicting an individual's response to a certain therapy. In one case study, researchers sprayed anti-TNF markers on the intestinal surface during endoscopy to quantify cells expressing TNF. Only patients with high TNF initially responded well to anti-TNF drugs (Annese & Annese, 2023). Using strategies such as these, researchers may be able to predict patient response to treatment and thereby avoid long periods of ineffective therapy.

Dr. Ashwin Ananthakrishnan, M.P.H., M.B.B.S., M.D, an expert in IBD research and practicing gastroenterologist at Massachusetts General Hospital provided insight on the current outlook of IBD treatment. Dr. Ananthakrishnan studies the environmental factors that contribute to IBD in the general population and develops predictive models for IBD development and response to treatment. Additionally, Dr. Ananthakrishnan's group is seeking to "identify if biomarkers in the tissue, blood, or stool can identify which treatment is most likely to work for a given patient and thus help make treatment selection less of a random choice." Successful identification of these biomarkers would allow practitioners to make more informed decisions about their patients' treatment plans.

Dr. Ananthakrishnan stated that "while no treatment has promised 100% effectiveness, during the past 10 years, we have seen the approval of over ten different medications including four different medication classes." He further emphasized the need for a more holistic understanding of the treatment timeline, patient monitoring, and incorporation of more non-invasive techniques. Also promising is the "role of the microbiome in IBD and how it can be beneficially modified" to improve IBD treatment. Dr. Ananthakrishnan also commented on the impact of COVID-19 on emerging IBD therapies and referenced the "substantial decline in in-person clinical contact." This decreased patient involvement in clinical trials and in-person assessments as well as blood, tissue, or stool collection over the last several years. Clinical trial enrollments have increased once more, but researchers are still facing a reduction in involvement due to trial complexity, treatment availability, administrative burden, and trial requirements.

"While no treatment has promised 100% effectiveness, during the past 10 years, we have seen the approval of over ten different medications including four different medication classes."

Conclusion

The modern history of IBD research is short, and progress from corticosteroids to monoclonal antibodies to small molecules has been quick. Now, patients are looking towards new solutions and improvements to existing treatments. Current therapies are accompanied by a host of side effects that often result in immunocompromisation for patients. It is time for a breakthrough in IBD therapy research. While cell-based therapies and personalized medicine are exciting innovations, they are challenging both to research and also to implement practically. Potentially the most promising practical research areas are in improving and optimizing pre-existing treatments.

For treatment to have come this far since the 1950s is an impressive feat. Moving forward, patients, researchers, and clinicians have a hand in the future of IBD treatment. With improved patient involvement in clinical trials and researcher–practitioner collaboration, it seems certain that research and technology will only continue to provide better options for the 10 million people around the world who face their IBD diagnosis daily.

References

About IBD (Inflammatory Bowel Diseases) organisations | World IBD Day. (n.d.). World IBD Day, 19th May. Retrieved November 2, 2024, from https://worldibdday.org/about-us.

Actis, G. C., Pellicano, R., Fagoonee, S., & Ribaldone, D. G. (2019). History of Inflammatory Bowel Diseases. Journal of Clinical Medicine, 8(11), 1970. https://doi.org/10.3390/jcm8111970.

CDC. (2024, July 19). What Causes IBD. Inflammatory Bowel Disease (IBD). https://www.cdc.gov/inflammatory-bowel-disease/causes/index.html.

CDC. (2024, July 22). IBD Facts and Stats. Inflammatory Bowel Disease (IBD). https://www.cdc.gov/inflammatory-bowel-disease/php/facts-stats/index.html.

Charabaty, A., Schneider, B., Zambrano, J. A., & Keefer, L. (2022). Living With Inflammatory Bowel Disease: Online Surveys Evaluating Patient Perspectives on Treatment Satisfaction and Health-Related Quality of Life. Crohn's & colitis 360, 4(3), otac035. https://doi.org/10.1093/crocol/otac035.

Crohn's & Colitis Foundation of America (2014). "Updated IBD Factbook." https://www.crohnscolitisfoundation.org/sites/default/files/2019-02/Updated%20IBD%20Factbook.pdf.

Desreumaux, P., & Ghosh, S. (2006). Review article: Mode of action and delivery of 5-aminosalicylic acid – new evidence. Alimentary Pharmacology & Therapeutics, 24(s1), 2–9. https://doi.org/10.1111/j.1365-2036.2006.03069.x.

Entyvio (vedolizumab) FDA Approval History—Drugs.com. (n.d.). Retrieved November 2, 2024, from https://www.drugs.com/history/entyvio.html.

Fatima, R., Bittar, K., & Aziz, M. (2024). Infliximab. In StatPearls. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK500021/.

Guo, Y., Lee, H., & Jeong, H. (2020). Chapter Three—Gut microbiota in reductive drug metabolism. In J. Sun (Ed.), Progress in Molecular Biology and Translational Science (Vol. 171, pp. 61–93). Academic Press. https://doi.org/10.1016/bs.pmbts.2020.04.002.

Hossein-Khannazer, N., Torabi, S., Hosseinzadeh, R., Shahrokh, S., Aghdaei, H. A., Memarnejadian, A., Kadri, N., & Vosough, M. (2021a). Novel cell-based therapies in inflammatory bowel diseases: The established concept, promising results. Human Cell, 34(5), 1289. https://doi.org/10.1007/s13577-021-00560-w.

Humira (adalimumab) FDA Approval History. (n.d.). Drugs.Com. Retrieved November 2, 2024, from https://www.drugs.com/history/humira.html.

IBD cheat sheet | IBD-EII. (n.d.). Retrieved November 18, 2024, from https://ibd-eii.com/ibdcheatsheet/.

Inflammatory bowel disease (IBD)—Diagnosis and treatment—Mayo Clinic. (n.d.). Retrieved November 2, 2024, from https://www.mayoclinic.org/diseases-conditions/inflammatory-bowel-disease/diagnosis-treatment/drc-20353320.

JAK inhibitors for inflammatory bowel disease: Recent advances | Frontline Gastroenterology. (n.d.). Retrieved November 2, 2024, from https://fg.bmj.com/content/15/1/59.

Leung, S., Liu, X., Fang, L., Chen, X., Guo, T., & Zhang, J. (2010). The cytokine milieu in the interplay of pathogenic Th1/Th17 cells and regulatory T cells in autoimmune disease. Cellular & Molecular Immunology, 7(3), 182–189. https://doi.org/10.1038/cmi.2010.22.

Markovic, M., Abramov-Harpaz, K., Regev, C., Ben-Shabat, S., Aponick, A., Zimmermann, E. M., Miller, Y., & Dahan, A. (2022). Prodrug-Based Targeting Approach for Inflammatory Bowel Diseases Therapy: Mechanistic Study of Phospholipid-Linker-Cyclosporine PLA2-Mediated Activation. International Journal of Molecular Sciences, 23(5), 2673. https://doi.org/10.3390/ijms23052673.

McDowell, C., Farooq, U., & Haseeb, M. (2024). Inflammatory Bowel Disease. In StatPearls. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK470312/.

Neurath, M. (2010). Thiopurines in IBD: What Is Their Mechanism of Action? Gastroenterology & Hepatology, 6(7), 435.

Seif, F., Khoshmirsafa, M., Aazami, H., Mohsenzadegan, M., Sedighi, G., & Bahar, M. (2017). The role of JAK-STAT signaling pathway and its regulators in the fate of T helper cells. Cell Communication and Signaling, 15(1), 23. https://doi.org/10.1186/s12964-017-0177-y.

Stelara (ustekinumab) FDA Approval History—Drugs.com. (n.d.). Retrieved November 2, 2024, from https://www.drugs.com/history/stelara.html.

American Gastroenterological Association (2021, July 6). Inflammatory bowel disease (IBD). AGA GI Patient Center. https://patient.gastro.org/inflammatory-bowel-disease-ibd/.

Tian, C.-M., Zhang, Y., Yang, M.-F., Xu, H.-M., Zhu, M.-Z., Yao, J., Wang, L.-S., Liang, Y.-J., & Li, D.-F. (2023). Stem Cell Therapy in Inflammatory Bowel Disease: A Review of Achievements and Challenges. Journal of Inflammation Research, 16, 2089. https://doi.org/10.2147/JIR.S400447.

Vena, G. A., & Cassano, N. (2007). Drug focus: Adalimumab in the treatment of moderate to severe psoriasis. Biologics : Targets & Therapy, 1(2), 93.

Watkinson, G. (1986). Sulphasalazine: A Review of 40 Years' Experience. Drugs, 32(1), 1–11. https://doi.org/10.2165/00003495-198600321-00003.

What you should know about colon cleansing. (n.d.). Mayo Clinic. Retrieved November 5, 2024, from https://www.mayoclinic.org/healthy-lifestyle/consumer-health/expert-answers/colon-cleansing/faq-20058435

Yasmin, F., Najeeb, H., Shaikh, S., Hasanain, M., Naeem, U., Moeed, A., Koritala, T., Hasan, S., & Surani, S. (2022). Novel drug delivery systems for inflammatory bowel disease. World Journal of Gastroenterology, 28(18), 1922. https://doi.org/10.3748/wjg.v28.i18.1922.