sclerosis

MDPI

Case Report

Anti-CD20-Triggered Crohn's-like Disease with Severe Perianal Involvement in a Patient with Multiple Sclerosis: Case Report, Review of the Literature, and Potential Therapeutic Approach

Adrià Quesada-Simó [1], Francisco Giner [2,3], Lucas Barea-Moya [4], Alejandro Garrido-Marin [5], Alejandro Mínguez [5], Pilar Nos [5] and Sara Gil-Perotín [4,*]

1 Department of Neurology, University Hospital Dr. Peset, 46017 Valencia, Spain; quesada_adr@gva.es
2 Department of Pathology, University of Valencia, 46010 Valencia, Spain; francescginer@hotmail.com
3 Department of Pathology, University and Polytechnic Hospital La Fe, 46026 Valencia, Spain
4 Multiple Sclerosis Unit, Department of Neurology, University and Polytechnic Hospital La Fe, 46026 Valencia, Spain; barea.moya@gmail.com
5 Intestinal Bowel Diseases Unit, Gastroenterology Unit, University and Polytechnic Hospital La Fe, 46026 Valencia, Spain; alexgarridomarin@gmail.com (A.G.-M.); minguez_ale@gva.es (A.M.); nos_pil@gva.es (P.N.)
* Correspondence: sara.garcia@uv.es; Tel.: +34-961244000

Abstract: This case report describes a 38-year-old female patient with a 3-year history of multiple sclerosis who developed rituximab-induced pancolitis, possibly representing a new onset of inflammatory bowel disease. The patient presented with bloody diarrhea, epigastric pain, fever, and general malaise. Laboratory testing revealed elevated acute inflammation markers, and endoscopy showed deep ulcerations and severe perianal disease. The patient was treated effectively with corticosteroids. Monthly doses of ustekinumab have been administered during follow-up due to perianal disease that has remitted. Rituximab was discontinued and ozanimod was initiated with clinical and analytical stability to date.

Keywords: IBD; anti-CD20; rituximab; ulcerative colitis; multiple sclerosis

Citation: Quesada-Simó, A.; Giner, F.; Barea-Moya, L.; Garrido-Marin, A.; Mínguez, A.; Nos, P.; Gil-Perotín, S. Anti-CD20-Triggered Crohn's-like Disease with Severe Perianal Involvement in a Patient with Multiple Sclerosis: Case Report, Review of the Literature, and Potential Therapeutic Approach. *Sclerosis* **2024**, *2*, 7–12. https://doi.org/10.3390/sclerosis2010002

Academic Editor: Bradley Turner

Received: 4 October 2023
Revised: 4 January 2024
Accepted: 8 January 2024
Published: 16 January 2024

1. Introduction

Multiple sclerosis (MS) is an autoimmune disorder characterized by demyelination within the central nervous system (CNS). It encompasses both inflammatory and neurodegenerative elements and ranks as the most prevalent non-traumatic disabling neurological condition observed among young adults [1]. After the FDA granted approval for the first disease-modifying therapy in 1993, interferon beta-1b, several other treatment options emerged for the management of MS. Within the array of therapeutic options, we encounter anti-CD20 antibodies, high efficacy therapies, which include rituximab, ocrelizumab, and ofatumumab. While rituximab (RTX) lacks FDA approval for MS treatment, it remains widely used off-label in clinical practice. Ocrelizumab (OCR) received FDA approval in 2017 for the treatment of both active relapsing MS and primary progressive MS. Ofatumumab (OFA) secured FDA approval in 2020 for active relapsing MS and is distinctive for its subcutaneous administration. One of the toxicities associated with anti-CD20 therapies is gastrointestinal toxicity, encompassing conditions resembling inflammatory bowel disease (IBD). These syndromes manifest as enterocolitis with symptoms like diarrhea and abdominal pain, with a predilection for impacting the proximal colon and distal ileum [2].

This paper details a case that exemplifies the gastrointestinal side effects associated with the use of anti-CD20 therapy in a patient with MS.

2. Case Report

A 38-year-old female patient with a 3-year history of MS presented to our facility in July 2022 with a 1-month history of intermittent bloody diarrhea, epigastric pain, fever, joint pain, and general malaise. In the patient's medical history, dyslipidemia has been managed through dietary treatment, and she had experienced migraines, with no additional vascular risk factors such as hypertension or diabetes mellitus. There were no documented medical allergies, and she had not had any prior gastrointestinal conditions or hemorrhoids. She had no other pertinent medical history or familial history of IBD.

She was initially treated with RTX due to severe left optic neuritis and risk factors for very active disease from May 2019 (two doses of 1 g. days 1 and 15) to February 2022 (a single dose of 1 g after B cell repopulation). This medication effectively controlled inflammation and the clinical symptoms of MS. She had received antibiotics as part of treatment for a dental infection, and she had also developed oral and genital ulcerations just one week before the onset of her gastrointestinal symptoms.

On physical examination, there were mild epigastric pain, genital ulcerations, and several irregular indurations in the anal canal. Laboratory testing revealed elevated acute inflammation markers, including a C-Reactive Protein (CRP) level of up to 190.7 mg/L and a white blood cell count of 19×10^9/L, and calprotectin levels of 12.672 µg/g. Initial investigations also showed anemia, with a hemoglobin level of 10.8 g/dL, and a low albumin level of 3.2 g/dL. Stool testing for pathogens, including bacteria, viruses, and parasites, was negative. Viral serologies (IgMs) for herpes simplex virus (HSV), adenovirus, hepatitis B and C, and cytomegalovirus (CMV) were also negative.

A colonoscopy showed a terminal ileum without lesions. Deep ulcerations and moderate inflammation from the ascendent colon to proximal sigma with a patchy distribution were observed associated with a fistula orifice in the rectum (Figure 1A–D). Biopsy results from the colon demonstrated active chronic inflammation with cryptitis and crypt abscess formation, but no granulomas were observed. Further investigations, including a pelvic MRI, revealed several abscesses and fistulae in the anal canal (Figure 1E,F).

Based on the patient's symptoms and the findings of the colonoscopy and biopsies, it was determined that the patient had de novo Crohn's-like IBD. The patient was started on intravenous (IV) hydrocortisone, 100 mg every 6 h for 11 days, as well as IV antibiotics (initially with ciprofloxacin/metronidazole and at discharge with cefuroxime). Fever and diarrhea resolved within 48 h of starting IV hydrocortisone, and her CRP level improved to 58.9 mg/L after 1 week of treatment. The patient was discharged on a tapering dose of oral prednisolone. Since it had been reported that RTX could induce IBD, no further doses were administered. Although clinical and analytical follow-up were initially satisfactory, CRP and calprotectin levels increased after corticosteroid tapering to 5 mg and perianal disease persisted 3 months after hospital discharge. The decision to initiate subcutaneous (SC) ustekinumab (dose: 520 mg) was made and the patient is receiving monthly doses to date. As ustekinumab has not proven to be effective in controlling MS [3], and there was a risk of relapse of the disease, the referral neurologist decided to initiate anti-S1P therapy with ozanimod. The patient has remained stable in terms of her conditions. Two months after the initiation of ustekinumab, a follow-up colonoscopy revealed an almost complete resolution of ulcerative and fistulous disease with the only presence of small fibrin ulcerations (3–5 mm) surrounded by normal mucosa in the cecum, linear fibrin ulcerations in the sigmoid colon affecting less than 10% of the mucosal surface, and normal rectal mucosa.

Upon retrospectively reviewing the patient's records, it was found that her CRP had been mildly elevated (<20 g/L) since 2017, and the patient had reported occasional episodes of watery diarrhea. This led us to consider whether she had already been suffering from IBD before receiving RTX treatment or whether there was a favorable background for colonic inflammation that caused RTX to act as a trigger.

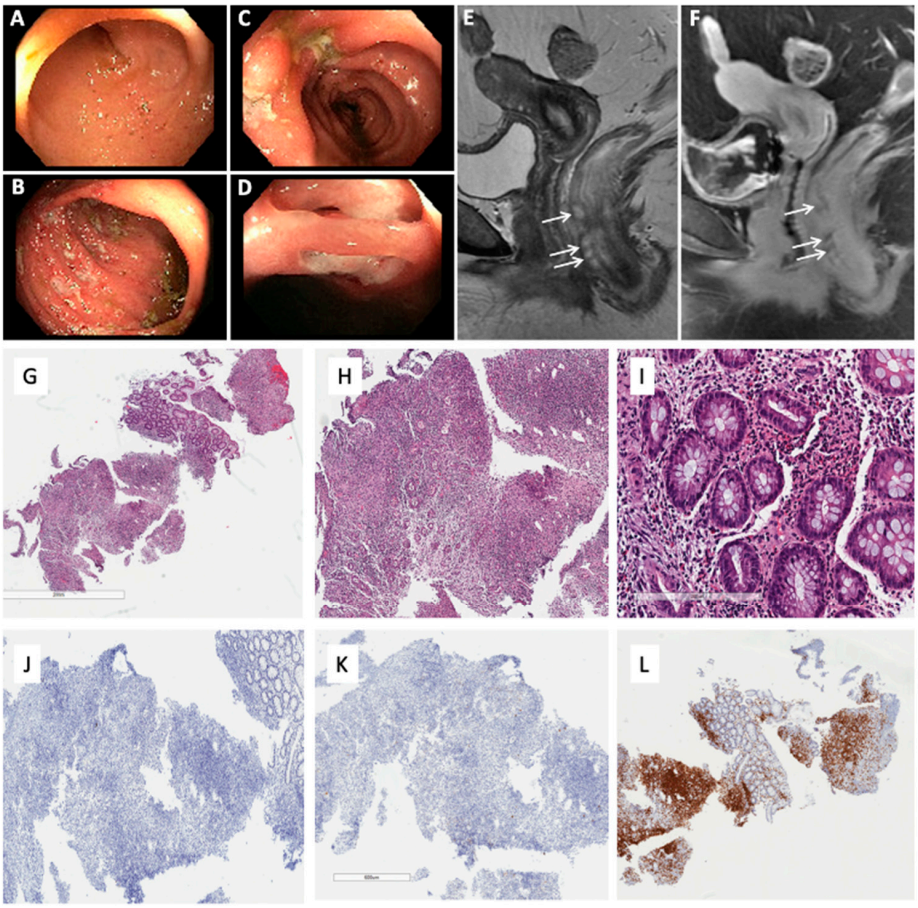

Figure 1. Description of the phenotype of IBD following treatment with anti-CD20 therapy infusion. (**A**–**D**): Colonoscopy. (**A**) Terminal ileum exhibited a preserved villous pattern and no macroscopic lesions. (**B**) The cecum, the appendiceal orifice, and the proximal ascending colon displayed multiple deep and superficial ulcers surrounded by inflamed mucous tissue. These ulcers covered approximately 30% of the mucous tissue. The pattern of haustration was maintained, though there was a slight constriction of the lumen at the level of the descending colon and sigma, likely because of edematous haustra. From the middle ascending colon to the proximal sigma, patchy distributions of both superficial and deep sac-like ulcers were found on areas of normal mucous tissue with a preserved vascular pattern. (**C**) The sigma exhibited a linear ulcer spanning several haustra, for which biopsies were taken due to their differing morphologies compared to the rest of the colon. (**D**) The rectum exhibited no lesions except for the 2–3 cm adjacent to the pectinate line, which displayed deep ulcers, mucous bridges, and possibly a fistulous orifice. Hypertrophic anal papillae were also present. (**E**,**F**): Pelvic MRI. (**E**,**F**) Three abscesses (white arrows) were observed in the anterior part of the anal canal. One abscess was located 6 cm from the anal canal, had walls that enhanced with contrast, and did not have a fistulous tract. The other two abscesses, which were connected to each other, were located 3.5 cm from the anal canal and were connected by two sphincteric fistulous tracts (1.9 cm in length) that ended as cul-de-sacs at approximately 2 cm from the anal margin. (**G**–**L**): Pathology: A colonic ulcer with regions of preserved mucosa is shown in H&E staining at a magnification of 1.7×. (**B**) Regions of epithelial ulceration with granulation tissue are seen in H&E staining at a magnification of 4.4×. (**C**) There is an abundance of eosinophils in the lamina propria and evidence of cryptitis, as seen in H&E staining at 20× magnification. (**D**) The granulation tissue lacks B lymphocytes, as indicated by the absence of cells reactive to anti-CD20 antibodies at a magnification of 3.3×. (**E**) Similarly, there is a lack of plasma cells, as indicated by the absence of immune expression of both CD20 and CD138 at magnifications of 3.3× and 3.5×, respectively. (**F**) The inflammatory infiltrate of T lymphocytes is intense and visible using anti-CD3 immunostaining at a magnification of 2×. IBD: inflammatory bowel disease; MRI: magnetic resonance imaging.

3. Discussion

MS and IBD have been found to be associated with each other, with higher prevalences of each condition in individuals with the other [4,5]. This association may be due to environmental factors or shared genetics, and both conditions involve complex relationships between immune cells, particularly T and B cells. In MS, B cells have been found to play a crucial role in the development of the disease, while in IBD, innate lymphoid cells are more relevant [6]. There are also similarities in the altered intestinal permeability and elevated IL-17 levels observed in both conditions [7]. However, the efficacy of treatment differs between the two conditions, with some treatments used for one condition worsening the other, suggesting that the immunopathogenic mechanisms are not superimposable.

It has been observed that regulatory B-cell depletion can lead to colitis in mice and has been found in the intestinal tissue and peripheral blood of individuals with ulcerative colitis [8]. This same mechanism may explain why anti-CD20 agents, such as rituximab, are not effective in treating IBD. Several studies have shown that patients treated with RTX are at higher risk of developing de novo inflammatory colitis [9] and there have been reports of cases with OCR but not with OFA [10]. Likewise, most patients experienced a resolution of symptoms within a few months of discontinuing the drug [9]. However, severe cases described that anti-CD20-induced colitis that initially responded to IV corticosteroids relapsed, resulting in a colectomy [11]. It is therefore suggested that anti-CD20-induced colitis with symptoms similar to IBD may be resolved by treatment with corticosteroids and discontinuation of the drug.

In a retrospective study conducted by Mallepally and colleagues, they examined cancer patients who had received RTX and subsequently underwent colonoscopy. Within this cohort, 4% of patients displayed symptoms of RTX-induced colitis, marked by diarrhea and, in some instances, bloody stools, along with abdominal pain. Several individuals also exhibited mucosal ulcerations upon endoscopic evaluation, accompanied by histological signs of active inflammation. The majority of patients experienced an improvement in their condition with symptomatic treatment. However, it is noteworthy that one patient necessitated surgical intervention due to a colonic perforation [2]. Instances of perianal Crohn's disease have been reported following RTX treatment, although it is a rare finding [12].

A population-based retrospective cohort study encompassing all individuals treated with RTX in Iceland from 2001 to 2018 revealed a sixfold elevated risk of developing IBD when contrasted with the general population. This study posits the possibility of CD20+ lymphocytes playing a regulatory role in the gastrointestinal system, which may be counteracted by their suppression through RTX treatment [13]. Pathologically, following treatment with RTX, there is a depletion of CD20+ B cells within the intestinal mucosa. This reduction is reversible upon discontinuation of the drug and this recovery may contribute to the resolution of colitis [14].

Healthcare professionals in this case were concerned about choosing the most effective biologic agent for treating IBD in a patient with MS. Tumor necrosis factor-alpha inhibitors (anti-TNF), which are the most effective therapies for IBD, are contraindicated in individuals with MS as they can trigger new episodes of inflammation or relapses [15]. Vedolizumab, a gut-specific anti-integrin inhibitor, may increase the risk of developing progressive multifocal leukoencephalopathy, just like natalizumab treatment does in MS-treated patients [16]. A phase II, multicenter, randomized, double-blind, placebo-controlled study evaluated the efficacy, safety, and pharmacokinetics of repeated SC injections of ustekinumab, an IL-12/IL-23 antagonist, in adult patients with RMS. This trial reported no statistically significant difference in the primary endpoint. Due to the lack of demonstrated efficacy in all dosage groups, this trial was discontinued after week 37 [3]. Despite this, ustekinumab has not been linked to increased risks of infection, malignancy, or neurological adverse effects [17] and could be considered a potential escalation therapy, especially when perianal disease is present. There have been no randomized clinical trials assessing the efficacy of ustekinumab in perianal disease as the primary endpoint. However, several retrospective observational studies and case reports have contributed valuable insights [18].

In a retrospective cohort study focused on patients with perianal fistulizing Crohn's disease, following the initiation of ustekinumab, 40% of patients achieved clinical remission of fistulas, and approximately 45% demonstrated radiological fistula healing based on post-treatment MRI [19]. A systematic review and meta-analysis reported a 41% rate of fistula response and a 17% rate of fistula remission after ustekinumab treatment, with a notable increase in the proportion of fistula response observed after a year of treatment [20]. Additionally, in a comprehensive review, ustekinumab is suggested as a second-line biologic therapy for patients with perianal disease who have not responded to or have failed anti-TNF treatments [21]. Given the potential exacerbation of MS by anti-TNF therapies, the selection of ustekinumab for our patient appeared reasonable.

Finally, the family of anti-S1P therapies may have a beneficial role in both conditions, as emerging research has demonstrated the involvement of S1P, a bioactive lipid mediator, in intestinal inflammation, specifically through the modulation of T cell activation, vascular endothelial integrity, and lymphocyte migration [22]. S1P1 modulation appears to selectively block the egress of effector T cells [CCR7+] from secondary lymphoid tissue to the gastrointestinal mucosa without impacting the surveillance activities of effector memory T cells [CCR7] in the mucosa [23]. Thus, these therapies show great potential for the treatment of both IBD and MS.

4. Conclusions

This case study sheds light on the relationship between MS and IBD, highlighting the potential of anti-CD20 monoclonal antibodies to trigger IBD-like phenotypes. Healthcare providers should consider this possibility and conduct careful endoscopic exams if a patient on anti-CD20 treatment consults for persistent intestinal symptoms. Our discussion underscores the complexity of immune system involvement in both conditions and the challenge of managing overlapping diseases. Treatment choices must weigh the risks and benefits, especially in patients with MS, as some IBD treatments can worsen their neurological condition. Ustekinumab shows promise in managing IBD-associated perianal disease but has proven ineffective in healing MS-related inflammation. Looking ahead, anti-S1P therapies hold potential for addressing both conditions by modulating common immune pathogenic responses. Further research is needed to assess their effectiveness and safety in combination, offering hope for improved treatment strategies in these patients.

Author Contributions: Conceptualization, S.G.-P., P.N. and A.Q.-S.; methodology and data curation, A.Q.-S., L.B.-M. and F.G.; writing—original draft preparation, A.Q.-S. and S.G.-P.; writing—review and editing, A.Q.-S., F.G., L.B.-M., A.G.-M., A.M., P.N. and S.G.-P.; funding acquisition, S.G.-P. and P.N. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding. S.G.-P.'s Juan Rodés contract is funded by the Health Research Institute Carlos III (ISCIII), Ministry of Health, Madrid, Spain with reference number JR20/00033. S.G.-P. is also a member of the CIBER network (CB06/05/1131). LBM (Lucas Barea Moya) contract is funded by the Health Research Institute La Fe (Valencia, Spain).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: As a case report, the patient gave her informed consent for publication.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy reason.

Conflicts of Interest: S.G.-P. has received speaker honoraria from Sanofi, Roche, Merck, Bristol Myers Squibb (BMS), and Biogen and has been advisor for BMS and Merck. The other authors have no conflicts of interest to disclose.

References

1. Wallin, M.T.; Culpepper, W.J.; Campbell, J.D.; Nelson, L.M.; Langer-Gould, A.; Marrie, R.A.; Cutter, G.R.; Kaye, W.E.; Wagner, L.; Tremlett, H.; et al. The prevalence of MS in the United States: A population-based estimate using health claims data. *Neurology* **2019**, *92*, e1029–e1040. [CrossRef] [PubMed]

2. Mallepally, N.; Abu-Sbeih, H.; Ahmed, O.; Chen, E.; Shafi, M.A.; Neelapu, S.S.; Wang, Y. Clinical Features of Rituximab-associated Gastrointestinal Toxicities. *Am. J. Clin. Oncol.* **2019**, *42*, 539–545. [CrossRef]
3. Segal, B.; Constantinescu, C.; Raychaudhuri, A.; Kim, L.; Fidelus-Gort, R.; Kasper, L.H. Repeated subcutaneous injections of IL12/23 p40 neutralising antibody, ustekinumab, in patients with relapsing-remitting multiple sclerosis: A phase II, double-blind, placebo-controlled, randomised, dose-ranging study. *Lancet Neurol.* **2008**, *7*, 796–804. [CrossRef] [PubMed]
4. Kosmidou, M.; Katsanos, A.H.; Katsanos, K.H.; Kyritsis, A.P.; Tsivgoulis, G.; Christodoulou, D.; Giannopoulos, S. Multiple sclerosis and inflammatory bowel diseases: A systematic review and meta-analysis. *J. Neurol.* **2017**, *264*, 254–259. [CrossRef] [PubMed]
5. Wang, X.; Wan, J.; Wang, M.; Zhang, Y.; Wu, K.; Yang, F. Multiple sclerosis and inflammatory bowel disease: A systematic review and meta-analysis. *Ann. Clin. Transl. Neurol.* **2022**, *9*, 132–140. [CrossRef]
6. Bar-Or, A.; Li, R. Cellular immunology of relapsing multiple sclerosis: Interactions, checks, and balances. *Lancet Neurol.* **2021**, *20*, 470–483. [CrossRef]
7. Shahmohammadi, S.; Sahraian, M.A.; Shahmohammadi, A.; Doosti, R.; Zare-Mirzaie, A.; Naser Moghadasi, A. A presentation of ulcerative colitis after rituximab therapy in a patient with multiple sclerosis and literature review. *Mult. Scler. Relat. Disord.* **2018**, *22*, 22–26. [CrossRef]
8. Wang, X.; Zhu, Y.; Zhang, M.; Wang, H.; Jiang, Y.; Gao, P. Ulcerative Colitis Is Characterized by a Decrease in Regulatory B Cells. *J. Crohns Colitis.* **2016**, *10*, 1212–1223. [CrossRef]
9. Eckmann, J.D.; Chedid, V.; Quinn, K.P.; Bonthu, N.; Nehra, V.; Raffals, L.E. De Novo Colitis Associated with Rituximab in 21 Patients at a Tertiary Center. *Clin. Gastroenterol. Hepatol.* **2020**, *18*, 252–253. [CrossRef]
10. Tolaymat, S.; Sharma, K.; Kagzi, Y.; Sriwastava, S. Anti-CD20 monoclonal antibody (mAb) therapy and colitis: A case series and review. *Mult. Scler. Relat. Disord.* **2023**, *75*, 104763. [CrossRef]
11. Sunjaya, D.B.; Taborda, C.; Obeng, R.; Dhere, T. First Case of Refractory Colitis Caused by Ocrelizumab. *Inflamm. Bowel Dis.* **2020**, *26*, e49. [CrossRef] [PubMed]
12. Fraser, D.; Boyle, S.; Amft, N. Perianal Crohn Disease after Treatment with Rituximab for Active Granulomatosis with Polyangiitis. *J. Rheumatol.* **2016**, *43*, 2199–2200. [CrossRef]
13. Kristjánsson, V.B.; Lund, S.H.; Gröndal, G.; Sveinsdóttir, S.V.; Agnarsson, H.R.; Jónasson, J.G.; Björnsson, E.S. Increased risk of inflammatory bowel disease among patients treated with rituximab in Iceland from 2001 to 2018. *Scand. J. Gastroenterol.* **2021**, *56*, 46–52. [CrossRef]
14. Zhou, W.; Huang, Y.; Lai, J.; Lu, J.; Feely, M.; Liu, X. Anti-Inflammatory Biologics and Anti-Tumoral Immune Therapies-Associated Colitis: A Focused Review of Literature. *Gastroenterol. Res.* **2018**, *11*, 174–188. [CrossRef]
15. Mohan, N.; Edwards, E.T.; Cupps, T.R.; Oliverio, P.J.; Sandberg, G.; Crayton, H.; Richert, J.R.; Siegel, J.N. Demyelination occurring during anti-tumor necrosis factor therapy for inflammatory arthritides. *Arthritis Rheum.* **2001**, *44*, 2862–2869. [CrossRef]
16. Clerico, M.; Artusi, C.; Liberto, A.; Rolla, S.; Bardina, V.; Barbero, P.; Mercanti, S.; Durelli, L. Natalizumab in Multiple Sclerosis: Long-Term Management. *Int. J. Mol. Sci.* **2017**, *18*, 940. [CrossRef] [PubMed]
17. Sandborn, W.J.; Gasink, C.; Gao, L.-L.; Blank, M.A.; Johanns, J.; Guzzo, C.; Sands, B.E.; Hanauer, S.B.; Targan, S.; Rutgeerts, P.; et al. Ustekinumab Induction and Maintenance Therapy in Refractory Crohn's Disease. *N. Engl. J. Med.* **2012**, *367*, 1519–1528. [CrossRef] [PubMed]
18. Godoy Brewer, G.M.; Salem, G.; Afzal, M.A.; Limketkai, B.N.; Haq, Z.; Tajamal, M.; Melia, J.; Lazarev, M.; Selaru, F.M.; Parian, A.M. Ustekinumab is effective for perianal fistulising Crohn's disease: A real-world experience and systematic review with meta-analysis. *BMJ Open Gastroenterol.* **2021**, *8*, e000702. [CrossRef]
19. Yao, J.; Zhang, H.; Su, T.; Peng, X.; Zhao, J.; Liu, T.; Wang, W.; Hu, P.; Zhi, M.; Zhang, M. Ustekinumab Promotes Radiological Fistula Healing in Perianal Fistulizing Crohn's Disease: A Retrospective Real-World Analysis. *J. Clin. Med.* **2023**, *12*, 939. [CrossRef]
20. Attauabi, M.; Burisch, J.; Seidelin, J.B. Efficacy of ustekinumab for active perianal fistulizing Crohn's disease: A systematic review and meta-analysis of the current literature. *Scand. J. Gastroenterol.* **2021**, *56*, 53–58. [CrossRef]
21. Wetwittayakhlang, P.; Al Khoury, A.; Hahn, G.D.; Lakatos, P.L. The Optimal Management of Fistulizing Crohn's Disease: Evidence beyond Randomized Clinical Trials. *J. Clin. Med.* **2022**, *11*, 3045. [CrossRef] [PubMed]
22. Verstockt, B.; Vetrano, S.; Salas, A.; Nayeri, S.; Duijvestein, M.; vande Casteele, N.; Danese, S.; D'Haens, G.; Eckmann, L.; Faubion, W.A.; et al. Sphingosine 1-phosphate modulation and immune cell trafficking in inflammatory bowel disease. *Nat. Rev. Gastroenterol. Hepatol.* **2022**, *19*, 351–366. [CrossRef] [PubMed]
23. Scott, F.L.; Clemons, B.; Brooks, J.; Brahmachary, E.; Powell, R.; Dedman, H.; Desale, H.G.; Timony, G.A.; Martinborough, E.; Rosen, H.; et al. Ozanimod (RPC1063) is a potent sphingosine-1-phosphate receptor-1 ($S1P_1$) and receptor-5 ($S1P_5$) agonist with autoimmune disease-modifying activity. *Br. J. Pharmacol.* **2016**, *173*, 1778–1792. [CrossRef] [PubMed]