

World Journal of *Gastroenterology*

World J Gastroenterol 2022 December 21; 28(47): 6619-6790



OPINION REVIEW

- 6619 How to avoid overtreatment of benign colorectal lesions: Rationale for an evidence-based management
Bustamante-Balén M

REVIEW

- 6632 Mucosal imaging in colon polyps: New advances and what the future may hold
Young EJ, Rajandran A, Philpott HL, Sathananthan D, Hoile SF, Singh R
- 6662 Acute liver injury in COVID-19 patients hospitalized in the intensive care unit: Narrative review
Polyzogopoulou E, Amoiridou P, Abraham TP, Ventoulis I
- 6689 Alterations of the gut microbiota in coronavirus disease 2019 and its therapeutic potential
Xiang H, Liu QP

MINIREVIEWS

- 6702 Microbiota in the stomach and application of probiotics to gastroduodenal diseases
Koga Y
- 6716 Liver injury in COVID-19: A minireview
Hu WS, Jiang FY, Shu W, Zhao R, Cao JM, Wang DP
- 6732 Obstructive and secretory complications of diverting ileostomy
Tsujinaka S, Suzuki H, Miura T, Sato Y, Shibata C
- 6743 Role of the combination of biologics and/or small molecules in the treatment of patients with inflammatory bowel disease
Balderramo D

ORIGINAL ARTICLE**Basic Study**

- 6752 Interleukin-34 deficiency aggravates development of colitis and colitis-associated cancer in mice
Liu ZX, Chen WJ, Wang Y, Chen BQ, Liu YC, Cheng TC, Luo LL, Chen L, Ju LL, Liu Y, Li M, Feng N, Shao JG, Bian ZL
- 6769 Dickkopf-related protein 1/cytoskeleton-associated protein 4 signaling activation by *Helicobacter pylori*-induced activator protein-1 promotes gastric tumorigenesis via the PI3K/AKT/mTOR pathway
Luo M, Chen YJ, Xie Y, Wang QR, Xiang YN, Long NY, Yang WX, Zhao Y, Zhou JJ

LETTER TO THE EDITOR

6788 The potential role of the three-dimensional-bioprinting model in screening and developing drugs

Deng CL, Wu B

ABOUT COVER

Editorial Board of *World Journal of Gastroenterology*, Guy D Eslick, DrPH, PhD, FACE, Professor, NHMRC Centre for Research Excellence in Digestive Health, The Hunter Medical Research Institute (HMRI), The University of Newcastle, Newcastle 2300, NSW, Australia. guy.eslick@newcastle.edu.au

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (WJG, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The WJG is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports, Index Medicus, MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 impact factor (IF) for WJG as 5.374; IF without journal self cites: 5.187; 5-year IF: 5.715; Journal Citation Indicator: 0.84; Ranking: 31 among 93 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2021 is 8.1 and Scopus CiteScore rank 2021: Gastroenterology is 18/149.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yi-Xuan Cai; Production Department Director: Xiang Li; Editorial Office Director: Jia-Ru Fan.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

December 21, 2022

COPYRIGHT

© 2023 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Role of the combination of biologics and/or small molecules in the treatment of patients with inflammatory bowel disease

Domingo Balderramo

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Gravina AG, Italy; M'Koma AE, United States; Parra RS, Brazil

Received: September 22, 2022

Peer-review started: September 22, 2022

First decision: October 18, 2022

Revised: October 26, 2022

Accepted: November 27, 2022

Article in press: November 27, 2022

Published online: December 21, 2022



Domingo Balderramo, Department of Gastroenterology, Hospital Privado Universitario de Córdoba, Instituto Universitario de Ciencias Biomédicas de Córdoba, Córdoba 5016, Argentina

Corresponding author: Domingo Balderramo, MD, PhD, Professor, Department of Gastroenterology, Hospital Privado Universitario de Córdoba, Instituto Universitario de Ciencias Biomédicas de Córdoba, Naciones Unidas 346, Córdoba 5016, Argentina.
dbalderramo@hospitalprivadosa.com.ar

Abstract

Inflammatory bowel disease (IBD) is a group of chronic diseases that includes ulcerative colitis, Crohn's disease, and indeterminate colitis. Patients with IBD require prolonged treatment and high utilization of healthcare resources for proper management. The treatment of patients with IBD is focused on achieving therapeutic goals including clinical, biochemical, and endoscopic variables that result in improvement of the quality of life and prevention of disability. Advanced IBD treatment includes tumor necrosis factor inhibitors, integrin antagonist, antagonist of the p40 subunit of interleukin 12/23, and small molecule drugs. However, despite the multiple treatments available, about 40% of patients are refractory to therapy and present with persistent symptoms that have a great impact on their quality of life, with hospitalization and surgery being necessary in many cases. Dual therapy, a strategy sometimes applicable to refractory IBD patients, includes the combination of two biologics or a biologic in combination with a small molecule drug. There are two distinct scenarios in IBD patients in which this approach can be used: (1) Refractory active luminal disease without extraintestinal manifestations; and (2) patients with IBD in remission, but with active extraintestinal manifestations or immune-mediated inflammatory diseases. This review provides a summary of the results (clinical response and remission) of different combinations of advanced drugs in patients with IBD, both in adults and in the pediatric population. In addition, the safety profile of different combinations of dual therapy is analyzed. The use of newer combinations, including recently approved treatments, the application of new biomarkers and artificial intelligence, and clinical trials to establish effectiveness during long-term follow-up, are needed to establish new strategies for the use of advanced treatments in patients with refractory IBD.

Key Words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Dual-therapy biologic therapy; Small molecule drugs; Clinical remission

Core Tip: Patients with inflammatory bowel disease (IBD) require prolonged treatment and high utilization of healthcare resources. About 40% of patients are refractory to different treatments with an increase need for hospitalization and surgery. Dual therapy, a strategy applicable to refractory IBD patients, includes the combination of two biologics or a biologic in combination with a small molecule drug. There are two distinct scenarios in IBD therapy in which this approach can be used: (1) Refractory active luminal disease without extraintestinal manifestations; and (2) patients with IBD in remission, but with active extraintestinal manifestations or immune-mediated inflammatory diseases.

Citation: Balderramo D. Role of the combination of biologics and/or small molecules in the treatment of patients with inflammatory bowel disease. *World J Gastroenterol* 2022; 28(47): 6743-6751

URL: <https://www.wjgnet.com/1007-9327/full/v28/i47/6743.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v28.i47.6743>

INTRODUCTION

Inflammatory bowel disease (IBD) is a group of chronic diseases that includes ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis. Patients with IBD require prolonged treatment and high utilization of healthcare resources for its proper management[1]. Medical treatment includes the use of so-called conventional drugs (mesalazine, immunosuppressants such as azathioprine or methotrexate and corticosteroids) and biologics [anti-tumor necrosis factor (anti-TNF), anti-integrins, and anti-interleukins (IL)], with small molecules (Janus kinase inhibitors and sphingosine 1-phosphate receptor modulators) having recently been added to the possible advanced treatments[2-5].

After the onset of therapy, the treatment of patients with IBD is focused on achieving therapeutic goals, which include improvement or normalization of clinical, biochemical, endoscopic variables, and also the quality of life and disability[6]. Despite the multiple treatments available, about 40% of patients are refractory to several treatments with different mechanisms of action, and these patients present with persistent symptoms that often have a great impact on their quality of life, due to the need for hospitalization and the requirement of surgery, which has to be carried out several times in some cases[7].

Extraintestinal manifestations (EIM) are present in about one-third of patients after diagnosis[8]. These mainly involve osteoarticular and dermatological manifestations. Some EIM are independent of IBD activity and require independent therapeutic management. In addition, some patients have multiple comorbidities throughout the course of the disease associated with prolonged corticosteroid treatment (diabetes, osteoporosis, adrenal insufficiency, and others), which is frequently used in these patients with a suboptimal response to advanced treatments[9].

Different studies have described a therapeutic window of opportunity, which implies the early use of advanced treatment in patients with IBD, especially in patients with early CD (< 2 years)[10]. These interventions are associated with a decrease in the progression of intestinal damage and complications such as stenosis and fistulas, and consequently reducing the need for hospitalization and surgery[10]. Finally, patients with long-standing IBD with persistent inflammatory activity represent a group at higher risk for the development of colorectal cancer, which develops by a different sequence to that of non-IBD colorectal cancer[11]. It has also been described that a better control of inflammatory activity may have an impact the development of this complication during long-term evolution[12,13].

DEFINITION AND INDICATIONS OF DUAL THERAPY

The development of new molecules and the implementation of new strategies are necessary to achieve better control of IBD activity in patients who are refractory to currently available treatments[14]. However, there are multiple pathways of inflammatory activity activated in patients with IBD, and for this reason, treatment with monotherapies may not be sufficient for the management of all patients[15]. Related to this, there are many scenarios in medicine in which dual therapy is used in both the induction and maintenance of treatment. This strategy involves the combination of two or more treatments with the aim of achieving optimal control of pathologies with different therapeutic targets. Indeed, this modality has seen great development in oncological or hematological treatments[14]. Similarly, in patients with rheumatologic pathologies, this approach is used in some patient subgroups [16]. This approach is also applicable to patients with refractory IBD to advanced treatments (dual therapy) by using two biologics simultaneously or a biologic in combination with a small molecule[16, 17]. In patients with IBD, there are two distinct scenarios in which it can be used: (1) Patients with

refractory IBD without EIM; and (2) patients with IBD in remission, but with active EIM or immune-mediated inflammatory diseases (IMID)[18].

EVIDENCE RELATED TO DUAL THERAPY

The first clinical trial that assessed a combination of biologics was developed in 2007[19,20]. Later, in 2010, the SONIC trial demonstrated that the association of infliximab and azathioprine is more effective compared with either infliximab or azathioprine monotherapy in CD patients, since which time multiple publications have described the results of different combinations of advanced drugs in patients with UC and CD, both in adults and in the pediatric population[21-35] (Figure 1). These combinations have varied according to the availability and practical experience of the drugs that were approved after the anti-TNFs. Table 1 shows the data from publications related to drug combination in patients with IBD. A major limitation of the dual therapy data is that they are mostly retrospective[19]. For this reason, the definitions of response evaluation (clinical, endoscopic and biochemical) are abbreviated and with the exception of few series are only described for short periods[33]. In addition, the definition of complications and the requirement for hospitalization and surgery can be subject to biases related to the follow-up time and the clinical condition prior to the start of the combined treatment[16]. Also, the differential evaluation of this strategy in patients with UC *vs* CD is not reported in many publications, which makes assessment difficult in some cases. Finally, some series include data on patients who received more than one combination, and it is possible that the effectiveness and adverse events could be different depending on the sequencing order of these combinations.

Effectiveness

The partial or complete response in patients with indication for dual therapy for refractory IBD has been evaluated using different meta-analyses[16,19,36]. In these studies, the patients included were mainly those with CD (70%), and in the great majority, the indication for dual therapy was for refractory endoluminal activity[16]. Overall, the observed clinical response varied between 60% and 84% in most of the publications[16,19]. However, clinical remission, which is a difficult clinical situation to achieve considering that these are multi-refractory patients, ranged between 47% and 80% of the patients who received combined therapy[16,18]. The therapeutic response of the different combinations has not been reported to reveal significant variation with respect to the main indication (refractory luminal activity *vs* active EIM or IMID)[16]. Persistence in the treatment of dual therapy varies according to the follow-up period. It has been published that globally 45% of patients may discontinue the dual scheme during its evolution, with loss of response being the main cause (64%) and intolerance together with adverse effects representing a smaller percentage (12%)[33]. It is noteworthy that in a recent study, 21% of patients were able to discontinue one of the drugs in the combination without impacting the subsequent evolution[33]. It is important to mention that many series have included a recycling strategy. This involves the use in the combination of a drug, which the patient did not respond to[14]. Several publications have mentioned such a situation, and have observed that the response in these patients was similar to that observed in those who had not been previously exposed to that drug[18]. This strategy requires further evolution, especially in areas with limited resources for access to new advanced treatments.

Safety

The combination of two biologics or a biologic plus a small molecule has been associated with a higher rate of complications in other indications[17,18]. This has been observed in studies of patients with rheumatologic diseases who received combination therapy[14]. However, in these series, a significant percentage of patients received different treatments with medications that present a higher rate of adverse events, such as the use of rituximab, abatacept, and tocilizumab[18]. On the other hand, in patients with IBD, most of the proposed combinations include drugs with a high relevant safety profile such as vedolizumab or ustekinumab, which are used in both the pediatric and adult populations[25, 29]. In a recent meta-analysis, the presence of adverse events varied from 6%-24% according to the combinations[16]. However, the presence of severe adverse events with indication for hospitalization or surgery was only present in 0%-12% of patients[16]. Within these severe adverse events, 75% were due to both intestinal and soft tissue infections[16]. In a recently published European series, a higher number of infections requiring hospitalization was observed in patients who received anti-TNF, corticosteroids, and immunomodulators, and who had a concomitant diagnosis of IMID/EIM (most frequently ankylosing spondylitis)[33]. Nevertheless, in this series, these complications developed only in patients with CD. Importantly, no case of reactivation of herpes zoster has been reported in any publication. Although one case of herpetic meningoencephalitis was diagnosed in a 43-year-old patient with CD who had received a combination including certolizumab, vedolizumab, and methotrexate, this was resolved after treatment[33]. Finally, one incident case of benign skin neoplasia (clear cell acanthoma) and one case of recurrence of basal cell skin cancer were reported[33,35]. No other cancers or treatment-related deaths have been reported.

Table 1 Publications including 2 or more adult or pediatric inflammatory bowel disease patients with use of combination therapy

Ref.	Study type (type of patients)	Disease (number of patients)	Combinations	Efficacy	Adverse events
Sands <i>et al</i> [20], 2007	Randomized controlled trial (adults)	CD (52)	NAT + IFX	Remission 37%	Headache, CD exacerbation, nausea, nasopharyngitis
Buer <i>et al</i> [22], 2018	Prospective cohort (adults)	CD (4), UC (6)	9 IFX + VDZ, 1 ADA + UST	Remission 100 %	3 upper airway infections
Mao <i>et al</i> [23], 2018	Case series (adults)	CD (4)	1 TNFi + UST/VDZ, 1 VDZ + UST, 2 VDZ + GOL	Remission 3/4	1 hand, foot and mouth disease, 1 influenza, 1 <i>Clostridioides difficile</i>
Kwapisz <i>et al</i> [24], 2020	Retrospective cohort (adults)	CD (14), UC (1)	8 VDZ + TNFi, 5 VDZ + UST, 2 UST + TNFi	Improvement 11/15	<i>Salmonella</i> , <i>Clostridioides difficile</i> , 4 infections, arthralgia
Olbjørn <i>et al</i> [25], 2020	Retrospective cohort (pediatrics)	CD (9), UC (4)	8 IFX + VDZ, 5 IFX + UST	Remission 9/13	Elevated transaminases, eczema, skin infection
Fumery <i>et al</i> [26], 2020	Case series (adults)	CD (5), UC (2)	5 TNFi + UST, 2 TNF + VDZ	Remission 6/7	No
Glassner <i>et al</i> [27], 2020	Retrospective cohort (adults)	CD (30), UC (18), IBD-U (1)	7 VDZ + TNFi, 25 VDZ + UST, 9 TOF + TNFi, 8 TOF + VDZ, 3 TOF + UST	Remission 50%	3 bacterial enteric infections (<i>E. coli</i>), 3 <i>Clostridioides difficile</i> , 1 peristomal cellulitis, 2 abdominal wall abscesses
Privitera <i>et al</i> [28], 2020	Retrospective cohort (adults)	CD (11), UC (5)	3 VDZ + UST, 9 VDZ + TNFi/other, 3 VDZ + UST	Clinical response 43%	1 cutaneous reaction, 1 drug-induced liver injury, 1 perianal abscess
Yang <i>et al</i> [29], 2020	Retrospective cohort (adults)	CD (22)	8 VDZ + UST, 13 VDZ + TNFi, 3 UST + TNFi	Remission 41%	1 drug induced lupus, 1 pneumonia, 1 <i>Clostridioides difficile</i> , 1 acinetobacter bacteremia
Alayo <i>et al</i> [30], 2021	Retrospective cohort (adults)	CD (10), UC (25)	24 VDZ + TOF, 5 TOF + UST	Remission 70% at 26 wk	1 <i>Clostridioides difficile</i> , 1 candida esophagitis, 1 abnormal lipid profile
Dolinger <i>et al</i> [31], 2021	Retrospective cohort (pediatrics)	CD (7), UC (8), IBD-U (1)	9 VDZ + TOF, 4 VDZ + UST, 3 UST + TOF	Remission 12/16	1 septic arthritis, 1 deep vein thrombosis
Llano <i>et al</i> [32], 2021	Retrospective cohort (adults)	CD (3), UC (10), IBD-U (1)	3 UST + VDZ, 2 VDZ + TNFi, 9 VDZ + TOF	Clinical or biochemical remission 50%	2 <i>Clostridioides difficile</i> , 2 pneumonia, 3 abnormal lipid profile
Goessens <i>et al</i> [33], 2021	Retrospective cohort (adults)	CD (58), UC (40)	41 VDZ + TNFi, 21 VDZ + UST, 11 UST + TNFi, 1 TOF + TNFi, 13 TOF + VDZ, 17 other	Clinical response 44%	10 serious or opportunistic infections
Howard <i>et al</i> [34], 2022	Case series (pediatrics)	CD (3)	3 VDZ + UST	Clinical remission 100%	Not reported
Lee <i>et al</i> [35], 2022	Retrospective cohort (adults)	CD (19)	7 TOF + VDZ, 11 TOF + UST, 1 TOF + TNFi	Remission 60%	1 basal cell carcinoma

ADA: Adalimumab; CD: Crohn's disease; GOL: Golimumab; IBD-U: Inflammatory bowel disease-unclassified; IFX: Infliximab; NAT: Natalizumab; TNFi: Tumor necrosis factor inhibitor; TOF: Tofacitinib; UC: Ulcerative colitis; UST: Ustekinumab; VDZ: Vedolizumab.

Data in pediatric population

Different case series in pediatric patients have reported results with various combinations in both CD and UC[37]. In one study, 75% of patients with luminal activity achieved a clinical remission free of corticosteroids at 6 mo, with the median time to achieve this goal being 88 d[31]. Interestingly, another potential indication that has been described in pediatric patients is the use of dual therapy (vedolizumab and tofacitinib) in patients with acute severe UC[31]. Nevertheless, more data are needed to explore this indication in an urgent and severe situation in patients with IBD. Different adverse events have been described in pediatric patients, but in general there are less frequent than in adult patients[25]. In a series of 16 pediatric patients, 1 (6%) patient presented septic arthritis and subsequent deep vein thrombosis[31].

NEW HORIZONS

It is necessary to establish new strategies for the use of advanced treatments in patients with refractory IBD, which must take into account health costs in order to be sustainable[14]. The sequencing of

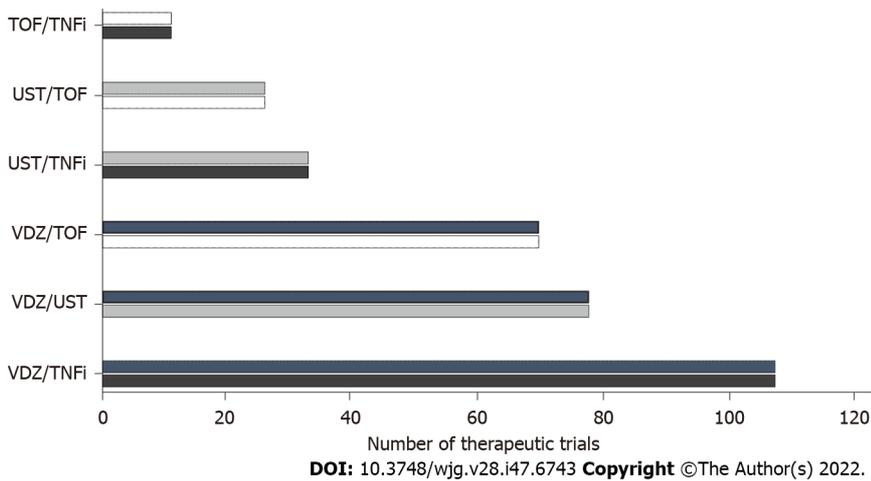


Figure 1 Number of therapeutic trials described in studies including 2 or more inflammatory bowel disease patients. TNFi: Tumor necrosis factor inhibitor; TOF: Tofacitinib; UST: Ustekinumab; VDZ: Vedolizumab.

biologics or small molecules in patients in remission is a strategy that probably results in a better cost balance. Related to this, some series described patients who achieved remission with two biologics, with the subsequent suspension of one of these (usually anti-TNF) not leading to the presence of disease reactivation during follow-up[22]. In addition, other studies have shown that patients in remission on infliximab were able to maintain their clinical status after initiation of vedolizumab and discontinuation of anti-TNF[38]. The implementation of these strategies requires further research, and in particular, clinical trials are needed to establish their effectiveness during long-term follow-up.

The use of artificial intelligence and the implementation of new biomarkers in the future will possibly be able to differentiate the patients who will benefit from certain combination schemes. Artificial intelligence may also enable remote monitoring to provide new data as well as algorithms to ensure better decision making in refractory patients[39]. In addition, biomarkers might improve patient stratification. Recent data have shown that HLA-DQA1*05 is non-uniformly distributed in patients with or without anti-TNF failure[40]. Likewise, IL-23 receptor expansion is a mechanism of anti-TNF resistance and is reflected as a secondary loss of response[41]. According to this, the use of ustekinumab may allow to regained response in patients with prior anti-TNF.

It is possible that in the near future new combinations with different effectiveness and safety profile will be described, with the use of ozanimod, upadacitinib, risankizumab, guselkumab, and mirikizumab, among others, expanding the current options[18]. In this regard, it is important to note that future clinical trials will be developed to compare current therapy with the combination of two biologic treatments (golimumab and guselkumab) or the combination of two biologics (vedolizumab and adalimumab) and an immunomodulator (methotrexate)[42-44]. Moreover, the design of the new pivotal studies has been modified. Recently, a phase 2 study in patients with CD compared different doses of guselkumab with placebo but also included a ustekinumab arm as this provides better comparative information[45].

Another point to consider is that some good results have been reported after the change of formulation (from intravenous to subcutaneous) of the same drug such is the case of as infliximab or vedolizumab[46,47]. This could be important in future combinations, since it would facilitate logistics and reduce associated costs. In addition to the combination of biological drugs or small molecules, the future role of other approaches should be determined, such as the use of probiotics and gut flora regulators as well as the role of microbiota transplantation[48,49].

Finally, the development of more real-life evidence will be of great importance. Currently most of the data comes from Europe and North America[16]. In this sense, it would be very useful to develop international registries involving several countries currently experiencing a clear increase in the incidence of IBD, such as Latin America and Asia, and which have greater difficulty in accessing advanced treatments[50-52]. In this regard, the costs associated with dual therapy are the main limitation to access, which restrict the provision of a personalized treatment in patients with indication for this strategy[53]. Moreover, it is of great relevance to inform the health insurance of these patients about the objectives and advantages of the dual therapy strategy to obtain the appropriate approval in a timely manner for the indication.

CONCLUSION

The combination of biologics and/or small molecules is a strategy applicable to refractory IBD patients in two distinct scenarios: (1) Refractory active luminal disease without extraintestinal manifestations; and (2) patients with IBD in remission, but with active extraintestinal manifestations or immune-mediated inflammatory diseases. The observed clinical response using this strategy varied between 60% and 84% in most of the publications, and severe adverse events were observed in a few patients. However, most of the data on dual therapy are retrospective and with short-term follow-up. New clinical trials are needed to establish dual therapy effectiveness and safety during long-term follow-up. Finally, it is expected that new combinations using new drugs with different efficacy and safety profiles will be described in the coming years, expanding the current options.

ACKNOWLEDGEMENTS

The author thanks Dr. Paul Hobson, a native speaker, for the English edition of the manuscript.

FOOTNOTES

Author contributions: Balderramo D performed the writing and editing of the manuscript and prepared the figure and table.

Conflict-of-interest statement: Balderramo D reports receiving payment for speaker's fee from AbbVie, Takeda, and Janssen, and receiving consulting fees from AbbVie, Takeda, Janssen, and Amgen.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Argentina

ORCID number: Domingo Balderramo [0000-0001-9598-2577](https://orcid.org/0000-0001-9598-2577).

S-Editor: Zhang H

L-Editor: Filipodia

P-Editor: Zhang H

REFERENCES

- 1 **van der Have M**, Mangen MJ, van der Valk ME, Smeets HM, van Bodegraven A, Dijkstra G, Fidder HH, de Jong DJ, Pierik M, Ponsioen CY, van der Meulen-de Jong AE, van der Woude CJ, van de Meeberg PC, Romberg-Camps MJ, Clemens CH, Jansen JM, Mahmmud N, Bolwerk CJ, Vermeijden JR, Siersema PD, Leenders M, Oldenburg B; COIN Study Group; Dutch Initiative on Crohn and Colitis. Effect of aging on healthcare costs of inflammatory bowel disease: a glimpse into the future. *Inflamm Bowel Dis* 2014; **20**: 637-645 [PMID: [24518606](https://pubmed.ncbi.nlm.nih.gov/24518606/) DOI: [10.1097/01.MIB.0000442677.55051.03](https://doi.org/10.1097/01.MIB.0000442677.55051.03)]
- 2 **Feuerstein JD**, Isaacs KL, Schneider Y, Siddique SM, Falck-Ytter Y, Singh S; AGA Institute Clinical Guidelines Committee. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. *Gastroenterology* 2020; **158**: 1450-1461 [PMID: [31945371](https://pubmed.ncbi.nlm.nih.gov/31945371/) DOI: [10.1053/j.gastro.2020.01.006](https://doi.org/10.1053/j.gastro.2020.01.006)]
- 3 **Raine T**, Bonovas S, Burisch J, Kucharzik T, Adamina M, Annese V, Bachmann O, Bettenworth D, Chaparro M, Czuber-Dochan W, Eder P, Ellul P, Fidalgo C, Fiorino G, Gionchetti P, Gisbert JP, Gordon H, Hedin C, Holubar S, Iacucci M, Karmiris K, Katsanos K, Kopylov U, Lakatos PL, Lytras T, Lyutakov I, Noor N, Pellino G, Piovani D, Savarino E, Selvaggi F, Verstockt B, Spinelli A, Panis Y, Doherty G. ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment. *J Crohns Colitis* 2022; **16**: 2-17 [PMID: [34635919](https://pubmed.ncbi.nlm.nih.gov/34635919/) DOI: [10.1093/ecco-jcc/jjab178](https://doi.org/10.1093/ecco-jcc/jjab178)]
- 4 **Torres J**, Bonovas S, Doherty G, Kucharzik T, Gisbert JP, Raine T, Adamina M, Armuzzi A, Bachmann O, Bager P, Biancone L, Bokemeyer B, Bossuyt P, Burisch J, Collins P, El-Hussuna A, Ellul P, Frei-Lanter C, Furfaro F, Gingert C, Gionchetti P, Gomollon F, González-Lorenzo M, Gordon H, Hlavaty T, Juillerat P, Katsanos K, Kopylov U, Krustins E, Lytras T, Maaser C, Magro F, Marshall JK, Myrelid P, Pellino G, Rosa I, Sabino J, Savarino E, Spinelli A, Stassen L, Uzzan M, Vavricka S, Verstockt B, Warusavitarne J, Zmora O, Fiorino G. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. *J Crohns Colitis* 2020; **14**: 4-22 [PMID: [31711158](https://pubmed.ncbi.nlm.nih.gov/31711158/) DOI: [10.1093/ecco-jcc/jjz180](https://doi.org/10.1093/ecco-jcc/jjz180)]
- 5 **Feuerstein JD**, Ho EY, Shmidt E, Singh H, Falck-Ytter Y, Sultan S, Terdiman JP; American Gastroenterological Association Institute Clinical Guidelines Committee. AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. *Gastroenterology* 2021; **160**: 2496-2508 [PMID: [34635919](https://pubmed.ncbi.nlm.nih.gov/34635919/)]

- 34051983 DOI: [10.1053/j.gastro.2021.04.022](https://doi.org/10.1053/j.gastro.2021.04.022)]
- 6 **Turner D**, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, Bettenworth D, Sandborn WJ, Sands BE, Reinisch W, Schölmerich J, Bemelman W, Danese S, Mary JY, Rubin D, Colombel JF, Peyrin-Biroulet L, Dotan I, Abreu MT, Dignass A; International Organization for the Study of IBD. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. *Gastroenterology* 2021; **160**: 1570-1583 [PMID: [33359090](https://pubmed.ncbi.nlm.nih.gov/33359090/) DOI: [10.1053/j.gastro.2020.12.031](https://doi.org/10.1053/j.gastro.2020.12.031)]
 - 7 **Peyrin-Biroulet L**, Lémann M. Review article: remission rates achievable by current therapies for inflammatory bowel disease. *Aliment Pharmacol Ther* 2011; **33**: 870-879 [PMID: [21323689](https://pubmed.ncbi.nlm.nih.gov/21323689/) DOI: [10.1111/j.1365-2036.2011.04599.x](https://doi.org/10.1111/j.1365-2036.2011.04599.x)]
 - 8 **Balderramo D**, Trakal J, Herrera Najum P, Vivas M, Gonzalez R, Benavidez A, López Villa D, Daino D, Raiden K, Germán A, Corzo MA, Ponce de León J, Ferrer L, Germán C, Bálzola S, Idoeta A, Zárate F, Defagó MR; Grupo Córdoba de Cooperación para el Manejo y Estudio de la Enfermedad Inflamatoria Intestinal (CEMEI Group). High ulcerative colitis and Crohn's disease ratio in a population-based registry from Córdoba, Argentina. *Dig Liver Dis* 2021; **53**: 852-857 [PMID: [33531211](https://pubmed.ncbi.nlm.nih.gov/33531211/) DOI: [10.1016/j.dld.2021.01.006](https://doi.org/10.1016/j.dld.2021.01.006)]
 - 9 **McDonnell M**, Harris RJ, Borca F, Mills T, Downey L, Dharmasiri S, Patel M, Zare B, Stammers M, Smith TR, Felwick R, Cummings JRF, Phan HTT, Gwiggner M. High incidence of glucocorticoid-induced hyperglycaemia in inflammatory bowel disease: metabolic and clinical predictors identified by machine learning. *BMJ Open Gastroenterol* 2020; **7**: e000532 [PMID: [33187976](https://pubmed.ncbi.nlm.nih.gov/33187976/) DOI: [10.1136/bmjgast-2020-000532](https://doi.org/10.1136/bmjgast-2020-000532)]
 - 10 **Ungaro RC**, Aggarwal S, Topaloglu O, Lee WJ, Clark R, Colombel JF. Systematic review and meta-analysis: efficacy and safety of early biologic treatment in adult and paediatric patients with Crohn's disease. *Aliment Pharmacol Ther* 2020; **51**: 831-842 [PMID: [32202328](https://pubmed.ncbi.nlm.nih.gov/32202328/) DOI: [10.1111/apt.15685](https://doi.org/10.1111/apt.15685)]
 - 11 **Rajamäki K**, Taira A, Katainen R, Välimäki N, Kuosmanen A, Plaketti RM, Seppälä TT, Ahtiainen M, Wirta EV, Vartiainen E, Sulo P, Ravanti J, Lehtipuro S, Granberg KJ, Nykter M, Tanskanen T, Ristimäki A, Koskensalo S, Renkonen-Sinisalo L, Lepistö A, Böhm J, Taipale J, Mecklin JP, Aavikko M, Palin K, Aaltonen LA. Genetic and Epigenetic Characteristics of Inflammatory Bowel Disease-Associated Colorectal Cancer. *Gastroenterology* 2021; **161**: 592-607 [PMID: [33930428](https://pubmed.ncbi.nlm.nih.gov/33930428/) DOI: [10.1053/j.gastro.2021.04.042](https://doi.org/10.1053/j.gastro.2021.04.042)]
 - 12 **Bonovas S**, Fiorino G, Lytras T, Nikolopoulos G, Peyrin-Biroulet L, Danese S. Systematic review with meta-analysis: use of 5-aminosalicylates and risk of colorectal neoplasia in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2017; **45**: 1179-1192 [PMID: [28261835](https://pubmed.ncbi.nlm.nih.gov/28261835/) DOI: [10.1111/apt.14023](https://doi.org/10.1111/apt.14023)]
 - 13 **Wijnands AM**, de Jong ME, Lutgens MWMD, Hoentjen F, Elias SG, Oldenburg B; Dutch Initiative on Crohn and Colitis (ICC). Prognostic Factors for Advanced Colorectal Neoplasia in Inflammatory Bowel Disease: Systematic Review and Meta-analysis. *Gastroenterology* 2021; **160**: 1584-1598 [PMID: [33385426](https://pubmed.ncbi.nlm.nih.gov/33385426/) DOI: [10.1053/j.gastro.2020.12.036](https://doi.org/10.1053/j.gastro.2020.12.036)]
 - 14 **Privitera G**, Pugliese D, Lopetuso LR, Scaldaferrri F, Neri M, Guidi L, Gasbarrini A, Armuzzi A. Novel trends with biologics in inflammatory bowel disease: sequential and combined approaches. *Therap Adv Gastroenterol* 2021; **14**: 17562848211006669 [PMID: [33995579](https://pubmed.ncbi.nlm.nih.gov/33995579/) DOI: [10.1177/17562848211006669](https://doi.org/10.1177/17562848211006669)]
 - 15 **Graham DB**, Xavier RJ. Pathway paradigms revealed from the genetics of inflammatory bowel disease. *Nature* 2020; **578**: 527-539 [PMID: [32103191](https://pubmed.ncbi.nlm.nih.gov/32103191/) DOI: [10.1038/s41586-020-2025-2](https://doi.org/10.1038/s41586-020-2025-2)]
 - 16 **Alayo QA**, Fenster M, Altayar O, Glassner KL, Llano E, Clark-Snustad K, Patel A, Kwapisz L, Yarur AJ, Cohen BL, Ciorba MA, Thomas D, Lee SD, Loftus EV Jr, Fudman DI, Abraham BP, Colombel JF, Deepak P. Systematic Review With Meta-analysis: Safety and Effectiveness of Combining Biologics and Small Molecules in Inflammatory Bowel Disease. *Crohns Colitis* 2022; **4**: otac002 [PMID: [35310082](https://pubmed.ncbi.nlm.nih.gov/35310082/) DOI: [10.1093/crocol/otac002](https://doi.org/10.1093/crocol/otac002)]
 - 17 **Abreu MT**. Combining Biologic Agents in Inflammatory Bowel Disease. *Gastroenterol Hepatol (N Y)* 2019; **15**: 549-551 [PMID: [31802979](https://pubmed.ncbi.nlm.nih.gov/31802979/)]
 - 18 **Gold SL**, Steinlauf AF. Efficacy and Safety of Dual Biologic Therapy in Patients With Inflammatory Bowel Disease: A Review of the Literature. *Gastroenterol Hepatol (N Y)* 2021; **17**: 406-414 [PMID: [34602905](https://pubmed.ncbi.nlm.nih.gov/34602905/)]
 - 19 **Ahmed W**, Galati J, Kumar A, Christos PJ, Longman R, Lukin DJ, Scherl E, Battat R. Dual Biologic or Small Molecule Therapy for Treatment of Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2022; **20**: e361-e379 [PMID: [33798711](https://pubmed.ncbi.nlm.nih.gov/33798711/) DOI: [10.1016/j.cgh.2021.03.034](https://doi.org/10.1016/j.cgh.2021.03.034)]
 - 20 **Sands BE**, Kozarek R, Spainhour J, Barish CF, Becker S, Goldberg L, Katz S, Goldblum R, Harrigan R, Hilton D, Hanauer SB. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission while receiving infliximab. *Inflamm Bowel Dis* 2007; **13**: 2-11 [PMID: [17206633](https://pubmed.ncbi.nlm.nih.gov/17206633/) DOI: [10.1002/ibd.20014](https://doi.org/10.1002/ibd.20014)]
 - 21 **Colombel JF**, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; **362**: 1383-1395 [PMID: [20393175](https://pubmed.ncbi.nlm.nih.gov/20393175/) DOI: [10.1056/NEJMoa0904492](https://doi.org/10.1056/NEJMoa0904492)]
 - 22 **Buer LCT**, Høivik ML, Warren DJ, Medhus AW, Moum BA. Combining Anti-TNF- α and Vedolizumab in the Treatment of Inflammatory Bowel Disease: A Case Series. *Inflamm Bowel Dis* 2018; **24**: 997-1004 [PMID: [29668901](https://pubmed.ncbi.nlm.nih.gov/29668901/) DOI: [10.1093/ibd/izx110](https://doi.org/10.1093/ibd/izx110)]
 - 23 **Mao EJ**, Lewin S, Terdiman JP, Beck K. Safety of dual biological therapy in Crohn's disease: a case series of vedolizumab in combination with other biologics. *BMJ Open Gastroenterol* 2018; **5**: e000243 [PMID: [30538822](https://pubmed.ncbi.nlm.nih.gov/30538822/) DOI: [10.1136/bmjgast-2018-000243](https://doi.org/10.1136/bmjgast-2018-000243)]
 - 24 **Kwapisz L**, Raffals LE, Bruining DH, Pardi DS, Tremaine WJ, Kane SV, Papadakis KA, Coelho-Prabhu N, Kisiel JB, Heron V, Faubion WA, Loftus EV Jr. Combination Biologic Therapy in Inflammatory Bowel Disease: Experience From a Tertiary Care Center. *Clin Gastroenterol Hepatol* 2021; **19**: 616-617 [PMID: [32068149](https://pubmed.ncbi.nlm.nih.gov/32068149/) DOI: [10.1016/j.cgh.2020.02.017](https://doi.org/10.1016/j.cgh.2020.02.017)]
 - 25 **Olbjorn C**, Rove JB, Jahnsen J. Combination of Biological Agents in Moderate to Severe Pediatric Inflammatory Bowel Disease: A Case Series and Review of the Literature. *Paediatr Drugs* 2020; **22**: 409-416 [PMID: [32378002](https://pubmed.ncbi.nlm.nih.gov/32378002/) DOI: [10.1007/s40272-020-00396-1](https://doi.org/10.1007/s40272-020-00396-1)]
 - 26 **Fumery M**, Yzet C, Brazier F. Letter: combination of biologics in inflammatory bowel diseases. *Aliment Pharmacol Ther* 2020; **52**: 566-567 [PMID: [32656825](https://pubmed.ncbi.nlm.nih.gov/32656825/) DOI: [10.1111/apt.15891](https://doi.org/10.1111/apt.15891)]

- 27 **Glassner K**, Oglat A, Duran A, Koduru P, Perry C, Willhite A, Abraham BP. The use of combination biological or small molecule therapy in inflammatory bowel disease: A retrospective cohort study. *J Dig Dis* 2020; **21**: 264-271 [PMID: 32324969 DOI: 10.1111/1751-2980.12867]
- 28 **Privitera G**, Onali S, Pugliese D, Renna S, Savarino E, Viola A, Ribaldone DG, Buda A, Bezzio C, Fiorino G, Fantini MC, Scaldaferrì F, Guidi L, Danese S, Gasbarrini A, Orlando A, Armuzzi A. Dual Targeted Therapy: a possible option for the management of refractory Inflammatory Bowel Disease. *J Crohns Colitis* 2020 [PMID: 32674156 DOI: 10.1093/ecco-jcc/jjaa149]
- 29 **Yang E**, Panaccione N, Whitmire N, Dulai PS, Vande Castele N, Singh S, Boland BS, Collins A, Sandborn WJ, Panaccione R, Battat R. Efficacy and safety of simultaneous treatment with two biologic medications in refractory Crohn's disease. *Aliment Pharmacol Ther* 2020; **51**: 1031-1038 [PMID: 32329532 DOI: 10.1111/apt.15719]
- 30 **Alayo QA**, Khatiwada A, Patel A, Zulfiqar M, Gremida A, Gutierrez A, Rood RP, Ciorba MA, Christophi G, Deepak P. Effectiveness and Safety of Combining Tofacitinib With a Biologic in Patients With Refractory Inflammatory Bowel Diseases. *Inflamm Bowel Dis* 2021; **27**: 1698-1702 [PMID: 34037225 DOI: 10.1093/ibd/izab112]
- 31 **Dolinger MT**, Spencer EA, Lai J, Dunkin D, Dubinsky MC. Dual Biologic and Small Molecule Therapy for the Treatment of Refractory Pediatric Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2021; **27**: 1210-1214 [PMID: 33125058 DOI: 10.1093/ibd/izaa277]
- 32 **Llano EM**, Shrestha S, Burstein E, Boktor M, Fudman DI. Favorable outcomes combining vedolizumab with other biologics or tofacitinib for treatment of inflammatory bowel disease. *Crohns Colitis* 2021; **3**: otab030 [DOI: 10.1093/crocol/otab030]
- 33 **Goessens L**, Colomel JF, Outtier A, Ferrante M, Sabino J, Judge C, Saeidi R, Rabbitt L, Armuzzi A, Domenech E, Michalopoulos G, Cremer A, Garcia-Alonso FJ, Molnar T, Karmiris K, Gecse K, Van Oostrom J, Löwenberg M, Farkas K, Atreya R, Ribaldone DG, Selinger C, Hoentjen F, Bihin B, Sebastian S; European COMBIO study group, Rahier JF. Safety and efficacy of combining biologics or small molecules for inflammatory bowel disease or immune-mediated inflammatory diseases: A European retrospective observational study. *United European Gastroenterol J* 2021; **9**: 1136-1147 [PMID: 34694746 DOI: 10.1002/ueg2.12170]
- 34 **Howard G**, Weiner D, Bar-Or I, Levine A. Dual biologic therapy with Vedolizumab and Ustekinumab for refractory Crohn's disease in children. *Eur J Gastroenterol Hepatol* 2022; **34**: 372-374 [PMID: 34034281 DOI: 10.1097/MEG.0000000000002203]
- 35 **Lee SD**, Singla A, Harper J, Barahimi M, Jacobs J, Kamp KJ, Clark-Snustad KD. Safety and Efficacy of Tofacitinib in Combination With Biologic Therapy for Refractory Crohn's Disease. *Inflamm Bowel Dis* 2022; **28**: 309-313 [PMID: 34347103 DOI: 10.1093/ibd/izab176]
- 36 **Ribaldone DG**, Pellicano R, Vernero M, Caviglia GP, Saracco GM, Morino M, Astegiano M. Dual biological therapy with anti-TNF, vedolizumab or ustekinumab in inflammatory bowel disease: a systematic review with pool analysis. *Scand J Gastroenterol* 2019; **54**: 407-413 [PMID: 30945576 DOI: 10.1080/00365521.2019.1597159]
- 37 **Wlazlo M**, Kierkuś J. Dual Biologic Therapy for the Treatment of Pediatric Inflammatory Bowel Disease: A Review of the Literature. *J Clin Med* 2022; **11** [PMID: 35407612 DOI: 10.3390/jcm11072004]
- 38 **Wang Y**, Wang J, Pekow J, Dalal S, Cohen RD, Ollech J, Israel A, Shogan BD, Micic D, Cannon L, Umanskiy K, Hurst R, Hyman N, Rubin DT, Sakuraba A. Outcome of elective switching to vedolizumab in inflammatory bowel disease patients under tumor necrosis factor antagonist-maintained clinical remission. *J Gastroenterol Hepatol* 2019; **34**: 2090-2095 [PMID: 31169926 DOI: 10.1111/jgh.14751]
- 39 **Gubatan J**, Levitte S, Patel A, Balabanis T, Wei MT, Sinha SR. Artificial intelligence applications in inflammatory bowel disease: Emerging technologies and future directions. *World J Gastroenterol* 2021; **27**: 1920-1935 [PMID: 34007130 DOI: 10.3748/wjg.v27.i17.1920]
- 40 **Sazonovs A**, Kennedy NA, Moutsianas L, Heap GA, Rice DL, Reppell M, Bewshea CM, Chanchlani N, Walker GJ, Perry MH, McDonald TJ, Lees CW, Cummings JRF, Parkes M, Mansfield JC, Irving PM, Barrett JC, McGovern D, Goodhand JR, Anderson CA, Ahmad T; PANTS Consortium. HLA-DQA1*05 Carriage Associated With Development of Anti-Drug Antibodies to Infliximab and Adalimumab in Patients With Crohn's Disease. *Gastroenterology* 2020; **158**: 189-199 [PMID: 31600487 DOI: 10.1053/j.gastro.2019.09.041]
- 41 **Schmitt H**, Billmeier U, Dieterich W, Rath T, Sonnwald S, Reid S, Hirschmann S, Hildner K, Waldner MJ, Mudter J, Hartmann A, Grützmann R, Neufert C, Münster T, Neurath MF, Atreya R. Expansion of IL-23 receptor bearing TNFR2+ T cells is associated with molecular resistance to anti-TNF therapy in Crohn's disease. *Gut* 2019; **68**: 814-828 [PMID: 29848778 DOI: 10.1136/gutjnl-2017-315671]
- 42 Efficacy and Safety of Combination Induction Therapy With Guselkumab and Golimumab in Participants With Moderately to Severely Active Ulcerative Colitis: Results Through Week 12 of a Phase 2a Randomized, Double-Blind, Active-Controlled, Parallel-Group, Multicenter, Proof-of-Concept Study. *Gastroenterol Hepatol (N Y)* 2022; **18**: 9-10 [PMID: 35610992]
- 43 A Study of Combination Therapy with Guselkumab and Golimumab in Participants with Moderately to Severely Active Ulcerative Colitis. [accessed 2022 Sept 10]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: <http://clinicaltrials.gov/show/NCT05242484> ClinicalTrials.gov Identifier: NCT05242484
- 44 Triple Combination Therapy in High-Risk Crohn's Disease. [accessed 2022 Sept 10]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: <http://clinicaltrials.gov/show/NCT02764762> ClinicalTrials.gov Identifier: NCT02764762
- 45 **Sandborn WJ**, D'Haens GR, Reinisch W, Panés J, Chan D, Gonzalez S, Weisel K, Germinaro M, Frustaci ME, Yang Z, Adedokun OJ, Han C, Panaccione R, Hisamatsu T, Danese S, Rubin DT, Sands BE, Afzali A, Andrews JM, Feagan BG; GALAXI-1 Investigators. Guselkumab for the Treatment of Crohn's Disease: Induction Results From the Phase 2 GALAXI-1 Study. *Gastroenterology* 2022; **162**: 1650-1664.e8 [PMID: 35134323 DOI: 10.1053/j.gastro.2022.01.047]
- 46 **Buisson A**, Nachury M, Reymond M, Yzet C, Wils P, Payen K, Laugie M, Manlay L, Mathieu N, Pereira B, Fumery M. Effectiveness of Switching From Intravenous to Subcutaneous Infliximab in Patients With Inflammatory Bowel Diseases: the REMSWITCH Study. *Clin Gastroenterol Hepatol* 2022 [PMID: 35987302 DOI: 10.1016/j.cgh.2022.08.011]

- 47 **Sandborn WJ**, Baert F, Danese S, Krznarić Ž, Kobayashi T, Yao X, Chen J, Rosario M, Bhatia S, Kisfalvi K, D'Haens G, Vermeire S. Efficacy and Safety of Vedolizumab Subcutaneous Formulation in a Randomized Trial of Patients With Ulcerative Colitis. *Gastroenterology* 2020; **158**: 562-572.e12 [PMID: 31470005 DOI: 10.1053/j.gastro.2019.08.027]
- 48 **Parada Venegas D**, De la Fuente MK, Landskron G, González MJ, Quera R, Dijkstra G, Harmsen HJM, Faber KN, Hermoso MA. Short Chain Fatty Acids (SCFAs)-Mediated Gut Epithelial and Immune Regulation and Its Relevance for Inflammatory Bowel Diseases. *Front Immunol* 2019; **10**: 277 [PMID: 30915065 DOI: 10.3389/fimmu.2019.00277]
- 49 **Pu D**, Zhang Z, Feng B. Alterations and Potential Applications of Gut Microbiota in Biological Therapy for Inflammatory Bowel Diseases. *Front Pharmacol* 2022; **13**: 906419 [PMID: 35734396 DOI: 10.3389/fphar.2022.906419]
- 50 **Windsor JW**, Kaplan GG. Evolving Epidemiology of IBD. *Curr Gastroenterol Rep* 2019; **21**: 40 [PMID: 31338613 DOI: 10.1007/s11894-019-0705-6]
- 51 **Kaplan GG**. The global burden of IBD: from 2015 to 2025. *Nat Rev Gastroenterol Hepatol* 2015; **12**: 720-727 [PMID: 26323879 DOI: 10.1038/nrgastro.2015.150]
- 52 **Kotze PG**, Underwood FE, Damião AOMC, Ferraz JGP, Saad-Hossne R, Toro M, Iade B, Bosques-Padilla F, Teixeira FV, Juliao-Banos F, Simian D, Ghosh S, Panaccione R, Ng SC, Kaplan GG. Progression of Inflammatory Bowel Diseases Throughout Latin America and the Caribbean: A Systematic Review. *Clin Gastroenterol Hepatol* 2020; **18**: 304-312 [PMID: 31252191 DOI: 10.1016/j.cgh.2019.06.030]
- 53 **Santiago M**, Dias CC, Alves C, Ministro P, Gonçalves R, Carvalho D, Portela F, Correia L, Lago P, Magro F. The Magnitude of Crohn's Disease Direct Costs in Health Care Systems (from Different Perspectives): A Systematic Review. *Inflamm Bowel Dis* 2022; **28**: 1527-1536 [PMID: 35179190 DOI: 10.1093/ibd/izab334]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

