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Review

Evaluating Efficacy of Vedolizumab, Ustekinumab, and Golimumab in the Management of Inflammatory Bowel Disease and the Combined Role of Nutritional Therapy with Biologics: A Review

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Abstract: Inflammatory bowel disease (IBD), which encompasses both ulcerative colitis (UC) and Crohn's disease (CD), is a major health burden worldwide. There are increasing concerns surrounding the impacts of this disease due to significant rises in the prevalence rates of IBD across the world. In consideration of the complexities of managing IBD along with this marked rise in prevalence and incidence, developing new forms of treatment for this condition has become a major priority. In recent years, a potential new form of treatment for IBD has emerged in the form of biologic therapies. While there is a high level of optimism due to the development of these therapies, there is also a clear need to evaluate their effectiveness, and their overall safety profiles. For this review, we have evaluated three specific biologics used for the treatment IBD. More precisely, the focus of this review is to analyze and critically appraise the literature for vedolizumab, ustekinumab, and golimumab, and determine their roles in the management of UC and CD, respectively. After doing so, we have also briefly synthesized important new findings regarding the role of dietary and nutritional approaches. In doing so, we have aimed to contextualize the findings regarding biologics, and, in order to evaluate potential new treatment approaches for the future to augment biologic therapies, we have discussed the potential for combined approaches that incorporate the usage of both biologics and nutritional interventions for patients.

Keywords: monoclonal antibodies; biologics; biologic therapy; inflammatory bowel disease; ulcerative colitis; Crohn's disease

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1. Introduction

Inflammatory bowel disease (IBD) is a major gastrointestinal condition that is a cause of concern globally. IBD is a condition that encompasses Crohn's disease (CD) and ulcerative colitis (UC). Alarmingly, there is concern that UC and CD are increasing in prevalence across the world. These chronic, relapsing conditions affect millions worldwide, leading to severe gastrointestinal symptoms, reduced quality of life, and substantial healthcare costs. Recent data indicate a global rise in IBD cases, with prevalence rates increasing by over 47% from 1990 to 2019, highlighting the persistent and growing impact of these diseases [1]. Furthermore, it is predicted that IBD will continue to be a cause of disability-adjusted life-years (DALYs) and mortality into the future [1].

Based on the overall complexities of IBD, there are a wide range of treatment approaches. However, they have been shown to frequently have limited efficacy in the past. More precisely, they have been shown to have limited roles in maintaining remission for disease and have largely been unsuccessful in preventing the complications of the condition [2]. Based on the limited successes of therapies that have been utilized in the past,

there is a clear and pressing need for newer forms of management. However, biologic therapies have emerged in recent years as a promising newer form of management of inflammatory conditions such as IBD. Biologic therapies, which are monoclonal antibodies (such as anti-tumor-necrosis factors), work by targeting specific aspects of one's immune response. By focusing on the immune response specifically, they may offer potential for effective and tailored interventions, and hence significantly alter the disease course for many patients [2].

While the development of biologic therapies for conditions such as IBD has been highly encouraging, there is a clear need to thoroughly analyze and investigate the effects of biologics rigorously and quantitatively. This will be important if we are to determine whether this form of management can truly be successful in managing CD and UC; it will also be important for determining safety profiles, the risks of adverse events, and the consequences of such adverse events. This also entails evaluating the long-term outcomes of these drugs and their cost-effectiveness. In doing so, clinical recommendations for healthcare providers can be developed and adapted so that they are tailored for patients to optimize their overall outcomes and care in IBD. Therefore, the purpose of this review is to evaluate and critically synthesize findings for clinical trials, focusing on three specific biologic therapies for IBD: vedolizumab, g limumab, and ustekinumab. Thereafter, we will also discuss the increasing evidence for dietary and nutritional interventions for IBD, and the emerging need to evaluate combined approaches that implement the utilization of biologic therapies along with dietary/nutritional management. These forms of management may have a valuable role in synergizing with biologic therapies, and hence in improving the outcomes for IBD patients overall.

2. Review

2.1. Golimumab

Golimumab is a fully human anti-tumor-necrosis factor-α (TNF-α) antibody that is administered subcutaneously (SC) [3]. Previously, it had only been used in rheumatologic cases such as rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis, in which TNF plays an important role in the pathogenesis; now, it is one of many biologic agents considered for first-line induction and maintenance therapy of moderate-to-severe ulcerative colitis (UC) [3,4]. The Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment, Subcutaneous (PURSUIT-SC) and Intravenous (PURSUIT-IV), as well as its subsequent study PURSUIT, Maintenance, were landmark trials in establishing the use of golimumab in patients with UC [3,5].

PURSUIT-SC was a 6-week multicenter, randomized, double-blind, placebo-controlled, integrated phase 2–3 trial that sought to assess the safety and efficacy of the use of golimumab as induction therapy for moderate-to-severe UC [3]. It included TNF-α antagonist-naïve patients who had an established diagnosis of UC regardless of duration, with moderate-to-severe disease activity, as defined by a Mayo score of 6–12, coupled with an endoscopic sub-score $\geq$ 2 [3]. These patients continued to have stable doses of their UC medications, such as oral 5-aminosalicylates, oral steroids, azathioprine (AZA), and 6-mercaptopurine, throughout the study [3]. Those classified as treatment failure included unauthorized changes in concomitant medications for UC or those who had a colectomy or ostomy [3]. These may have underestimated the efficacy of the results, as these patients would have been categorized automatically as failure. Studying this particular population may have been very enlightening as it is practical, with many patients having different changes in their regimens from time to time. The impact of previous or concurrent medications is thus yet to be fully understood. Phase 2 sought to evaluate the dose–response relationship in order to determine the specific induction regimens [3]. A total of 169 patients were randomized to receive either the placebo or one of the golimumab regimens (100/50 mg, 200/100 mg, or 400/200 mg) at both weeks 0 and 2 [3]. Patients were randomized using an adaptive randomization technique with the investigative site as a

stratification [3]. While the phase 2 data analysis was ongoing, 122 more patients were enrolled and included in the overall safety and pharmacokinetic analyses [3].

At week 6, more patients assigned to 400/200 mg achieved clinical response or remission, mucosal healing, and better health-related quality of life compared to those taking the placebo [3]. Noticeably, those at the higher concentration quartiles had greater improvement in Mayo scores, clinical response, and remission at week 6 [3]. Median serum golimumab concentrations were proportional at all levels throughout the study, with a peak at week 2, and safety across the three golimumab groups was consistent [3].

Phase 3 then evaluated the safety and efficacy of the aforementioned regimens [3]. The 200/100 mg and 400/200 mg regimens were used in this phase. A total of 774 patients were randomized (1:1:1) to take either a placebo, 200/100 mg of golimumab, or 400/200 mg of golimumab at weeks 0 and 2 [3]. Patients were randomized using a permuted block randomization technique with the investigative site as a stratification [3]. The primary end point was clinical response at week 6, defined by decrease in baseline in the Mayo score $\geq$30% and $\geq$3 points, accompanied by either a rectal bleeding sub-score of 0 or 1 or a decrease in the rectal bleeding sub-score $\geq$1 [3]. The secondary end points included clinical remission, mucosal healing, and quality of life (using the Inflammatory Bowel Disease Questionnaire [6]) change from baseline, all measured at week 6 [3].

At week 6, there were more in the golimumab 200/100 mg (51.0%) and 400/200 mg (54.9%) groups who achieved clinical response compared to placebo ($p < 0.0001$) [3]. As early as the second week, median decreases in partial Mayo score and mean decreases in C-reactive protein (CRP) for both 200/100 mg and 400/200 mg groups were seen [3]. Both regimens were also shown to have greater effects on clinical remission, mucosal healing, and quality of life. At this juncture, serum golimumab concentrations were also seen to be dose-proportional throughout the study, consistent with Phase 2 findings [3]. Clinical efficacy was seen to be similar between the 200/100 mg and 400/200 mg groups [3]. Adverse events noted were headache, nasopharyngitis, serious infections (0.5% vs. 1.8%), and UC exacerbation (1.1% vs. 2.4%) which were similar among golimumab- and placebo-treated patients [3]. There were four golimumab-treated and three placebo-treated patients who did not proceed with the study due to an adverse event [3].

PURSUIT-IV was another six-week multicenter, randomized, double-blind, placebo-controlled study that evaluated induction therapy administered intravenously (IV) [5]. Eligibility criteria were the same as those of PURSUIT-SC [3,5]. Phase 2 also included a dose-finding part to select the final IV golimumab induction regimens to be used for phase 3, which then evaluated the safety and efficacy of these regimens [5].

For phase 2, 176 patients were randomized (1:1:1:1) to placebo or one of three golimumab induction doses of 1, 2, or 4 mg/kg via adaptive randomization [5]. During analysis, 71 additional patients were enrolled and randomized via permuted block randomization [5]. The endpoints measured were similar to those used in PURSUIT-SC [3,5]. No dose–response relation was seen, but higher concentrations saw greater efficacy, leading to the use of 2 mg/kg and 4 mg/kg doses for phase 3 [5].

It is important to note that, for phase 3, enrollment was stopped during the interim analysis as the efficacy was seen to be lower than expected [5]. Data showed that clinical response rate, remission, and mucosal healing were not significantly different from those of the placebo [5]. Thus, an insufficient statistical power for primary endpoint analysis was noted due to a failure to achieve the desired statistical size [5]. In light of this, the investigators opted to include all the randomized patients from phase 2 and 3 to their efficacy analysis. This warrants reasonable critique as this may have led to overestimation of the efficacy of IV formulations in the treatment of moderate-to-severe UC.

In their analysis, a greater clinical response was seen in the 2 mg/kg and in the 4 mg/kg golimumab groups as compared to the placebo-treated group (44% and 41.6% vs. 30.1%), while clinical remission and mucosal healing were similar on all groups [5]. Health-related quality of life was seen to be higher at week 6 compared to placebo, with the 2 mg/kg group and 4 mg/kg group achieving mean changes of 23.0 ($p = 0.031$) and

24.4 (p = 0.016), respectively, as compared to the placebo (12.9) [5]. Serum golimumab concentrations were seen to be dose-proportional through week 6 and those in the highest quartiles were shown to have greater mean improvement in Mayo scores and clinical response compared to placebo and the lower quartiles [5]. The most observed adverse events in golimumab-treated patients were UC exacerbations, cough, and headache, while infections were higher among those taking golimumab compared to placebo [5]. Serious adverse events were generally low and comparable among the groups [5].

Golimumab was also then established as a maintenance therapy for moderate-to-severe UC via the 54-week PURSUIT-M trial [7]. The same patients who completed PURSUIT-SC or PURSUIT-IV were then recruited to participate in this study to receive SC golimumab maintenance therapy every four weeks for five weeks total [7]. PURSUIT-M was a phase 3, multicenter, placebo-controlled, double-blind, randomized study which had similar inclusion and exclusion criteria as the past two studies [7].

Patients were randomized (1:1:1) to receive SC placebo, golimumab 50 mg, or golimumab 100 mg every four weeks until week 52 via an adaptive randomization procedure [7]. Placebo-induction responders from the previous PURSUIT trials were not randomized and continued to receive placebo in this trial [7]. Thus, only those who showed clinical response in prior induction studies were included in the efficacy analyses [7]. The study was a randomized withdrawal trial, meaning that responders from a previous trial then proceed to be randomized to receive either the intervention or placebo in the next trial, while the non-responders are dropped [8]. Although logistically more advantageous, carry-over effects from the previous trial may persist throughout the next one [8]. Additionally, the strict restriction to golimumab-induction responders may also affect external validity of the results, and the treatment effect may be overestimated [8].

The primary end point was the maintenance of clinical response until week 54 in those who previously responded to golimumab induction [7]. This means that there should be no treatment failure at any point in the study for it to be determined to be responsive, which can present as a very strict measure of UC disease activity control and may risk disregarding many participants who may have fit the criteria [7,9]. Major secondary end points were clinical remission at both weeks 30 and 54, mucosal healing at both weeks 30 and 54, clinical remission at both weeks 30 and 54 in patients who had clinical remission at baseline, and corticosteroid-free remission at week 54 among those receiving concurrent steroids at baseline [7].

Notably, only 75.6% of randomized patients (351 out of 464) completed the study through week 54 [7]. Although there were more than 70% in each group who completed, these drop-out rates can signify incorrect estimations of the true effects of golimumab maintenance therapy [7,10].

In terms of efficacy, clinical response was significantly higher in the 100 mg (49.7%; $p < 0.001$) and 50 mg groups (47.0%; p = 0.0.10) than placebo (31.2%) [4]. The calculated number needed to treat (NNT) was 5 for the 100 mg group and 6 for the 50 mg group [7]. Clinical remission was also seen more often for the 100 mg group compared to placebo (p = 0.004), with an NNT of 8 for both weeks 30 and 54 [7]. Mucosal healing rate was also significantly greater for patients receiving 100 mg compared to placebo for both weeks 30 and 54 (p = 0.002) [7]. Reductions in the median partial Mayo scores, the longer time to the loss of clinical response, and the greater proportions of clinical remission were seen in golimumab-treated patients vs. placebo-treated patients [7]. Those who were in the higher concentration quartiles achieved clinical response compared to those in the lower quartiles [7]. Adverse events were similar across groups and included infections, UC exacerbations, and injection-site reactions, among many others [7]. There was a higher proportion of patients who experienced at least one serious adverse event in the 100 mg group compared with the other groups [7].

Of particular importance is that the majority (>80%) of the participants were Caucasian in all PURSUIT trials [3,5,7]. This may affect the applicability and generalizability to patients

of other ethnicities that may have different outcomes. Studies incorporating other groups are thus required to further understand the use of golimumab in these patient populations.

In conclusion, the current evidence has exhibited the utility of golimumab in both induction and maintenance therapies for patients with moderate-to-severe UC. However, caution is still recommended in interpreting the results due to issues in the study design, participant selection, and clinical applicability.

2.2. Vedolizumab

A newer biological drug, vedolizumab, has been approved for the treatment of moderate-to-severe UC cases, refractory to standard medications [11]. Vedolizumab is a humanized monoclonal antibody (HMA) with an inhibitory effect on $\alpha 4\beta 7$ integrin [12,13]. The GEMINI trials have been pivotal in demonstrating vedolizumab's effectiveness for both inducing and maintaining remission in IBD patients [14–16]. These high-quality, randomized, double-blind, placebo-controlled studies led to the approval of vedolizumab for treating adult patients with UC/CD that is moderate-to-severe and active and who have an inadequate response to standard therapies or TNFα antagonists.

The GEMINI 1 trial included more than 800 participants with UC that was classified as moderate-to-severe, defined as having a Mayo score between 6 and 12, along with an endoscopic sub-score that is 2 or higher [14]. The study included a double-blind cohort of 374 patients who were randomly assigned to receive either 300 mg IV vedolizumab or a placebo at weeks 0 and 2. Additionally, a second cohort of 521 patients received open-label vedolizumab to ensure an adequate number of responders for the maintenance phase [14]. The eligible study participants were those who had not responded to or had experienced unacceptable side effects from other forms of IBD management [14].

In the initial cohort, a greater percentage of patients receiving vedolizumab experienced clinical response, clinical remission, and healing of the mucosa after 6 weeks, in comparison to those who received placebo. At week 6, 47.1% of patients treated with vedolizumab achieved clinical response vs. 25.5% of patients in the placebo-treated group ($p < 0.001$) [14].

Patients from both cohorts who achieved a clinical response to vedolizumab at 6 weeks were randomized to receive vedolizumab 300 mg IV every 4 weeks or 8 weeks, or to receive placebo in the maintenance phase for up to 52 weeks. Remission rates at week 52 (main outcome during maintenance) were significantly higher in patients receiving vedolizumab compared to those receiving placebo. Specifically, 44.8% of patients in the 4-weekly vedolizumab-treated group and 41.8% in the 8-weekly group achieved remission, compared to only 15.9% in the placebo-treated group ($p < 0.001$) [14]. Additionally, a significantly higher number of patients in the vedolizumab-treated groups reported durable clinical remission, defined as remission at both week 6 and week 52, with 24.0% in the 4-weekly group and 20.5% in the 8-weekly group, versus 8.7% in the placebo-treated group ($p = 0.001$ and $p = 0.008$, respectively, compared to placebo). Vedolizumab treatment also resulted in higher rates of healing of mucosa ($p < 0.001$ for both vedolizumab-treated groups versus the placebo-treated group) and higher rates of steroid-free remission ($p < 0.001$ for each of the two groups with vedolizumab in comparison to the placebo-treated group) [14].

The GEMINI 2 and GEMINI 3 clinical trials evaluated vedolizumab's effectiveness in patients with moderately–severely active CD [15]. In the GEMINI 2 study, 368 patients were randomly assigned to receive either 300 mg of IV vedolizumab or placebo at weeks 0 and 2. Additionally, a separate cohort of 747 patients received open-label vedolizumab, similar to the approach used in the GEMINI 1 trial [15]. The eligibility criteria for this study included a Crohn's Disease Activity Index (CDAI) [17] score of 220-450, along with either a serum CRP level above 2.87 mg/L, colonoscopic documentation of at least 3 large ulcers or 10 aphthous ulcers, or fecal calprotectin levels exceeding 250 µg/g, confirmed by imaging methods such as CT or MRI enterography, small-bowel radiography, or capsule endoscopy showing Crohn's ulcers [15].

The GEMINI-2 trial had two co-primary end points: clinical remission and CDA-100 response evaluated at the 6-week mark [15]. Patients who received vedolizumab had significantly higher clinical remission rates at week 6 compared to the placebo-treated group (14.5% vs. 6.8%; $p = 0.02$), although the CDAI-100 response rates were similar between the two groups (31.4% vs. 25.7%; $p = 0.23$). In the phase of maintenance, patients who responded to vedolizumab were randomized to receive 300 mg IV at either 4-week or 8-week intervals until week 52 [15]. Clinical remission at week 52, the primary endpoint, was significantly higher in the vedolizumab-treated groups (36.4% and 39.0%) compared to the placebo-treated group (21.6%; $p = 0.004$ and $p < 0.001$) [15]. Additionally, vedolizumab-treated patients had significantly higher rates of steroid-sparing remission ($p = 0.04$ and $p < 0.02$, respectively), while rates of clinical remission that were durable did not show differences [15].

In the GEMINI 3 trial, patients were randomly assigned to receive either 300 mg of IV vedolizumab or placebo at weeks 0, 2, and 6 [16]. The study's primary endpoint, clinical response at week 6, was not met, with 15.2% of patients in the vedolizumab-treated group achieving this outcome compared to 12.1% in the placebo-treated group ($p = 0.4$). However, clinical remission rates at week 10 were significantly higher in the vedolizumab-treated group (26.6%) compared to the placebo-treated group (12.1%; $p = 0.001$) [16]. This indicates a delayed response in achieving clinical remission, with benefits becoming apparent at week 10 [16]. In clinical practice, a fourth induction dose at week 10 may be considered for patients with CD who show insufficient response to the initial three doses of vedolizumab [16].

The phase 3, open-label GEMINI LTS (long-term safety) study (initiated May 2009) enrolled patients with UC or CD from four prior clinical trials and vedolizumab-naïve patients. The primary endpoint was the long-term safety for vedolizumab; efficacy and patient-reported outcomes were the exploratory endpoints. In this study, just over 2000 patients were administered 300 mg of IV vedolizumab every four weeks. The median cumulative exposure was 42.4 months (range: 0.03–112.2) for UC and 31.5 months (range: 0.03–100.3) CD [16]. Over an eight-year period, adverse events (AEs) were reported in 93% of UC patients and 96% of CD patients, with disease exacerbations being the most common (36% for UC and 35% for CD). Serious AEs were observed in 31% of UC patients and 41% of CD patients. Discontinuation of vedolizumab due to AEs occurred in 15% of UC patients and 17% of CD patients. There were no new patterns of infections, malignancies, infusion-related reactions, or hepatic events, and no cases of progressive multifocal leukoencephalopathy were reported. Out of the ten deaths (four in UC patients and six in CD patients), two were considered drug-related to be by local investigators (West Nile virus infection-related encephalitis and hepatocellular carcinoma) [16]. Continuous treatment with vedolizumab sustained long-term clinical response, with 33% of UC patients and 28% of CD patients in clinical remission at 400 weeks of treatment.

A recent retrospective evaluation at Leuven University Hospital examined mucosal healing following vedolizumab treatment in patients from the GEMINI LTS study [18]. The study included 58 patients (34 with UC and 24 with CD) who had previously been treated with anti-TNFα therapy and were monitored via endoscope for multiple years (median = 3.2). Mucosal healing, adjusted for non-responder imputation, was observed in 50% of UC patients and 29% of CD patients. Additionally, 32.4% of UC patients and 20.8% of CD patients achieved histological healing. Mucosal and histological healing were significantly correlated in UC and CD patients [18].

Vedolizumab presents a promising new treatment option for patients with UC and CD who do not respond to conventional therapies or TNFα inhibitors. Safety and efficacy of vedolizumab in treating IBD were established in the GEMINI study. However, the specific inclusion and exclusion criteria used in the study design restrict the direct application of clinical trial findings to patients encountered in everyday clinical practice. The patients included in the RCTs are only partially representative of the IBD population encountered in clinical practice [19]. Numerous studies have confirmed vedolizumab's efficacy in

real-world clinical practice and have assessed its long-term outcomes. Although significant heterogeneity in study designs limits the interpretation of data, series of real-world experiences provide relevant evidence.

Mucosal healing is linked to reduced rates of needing to go the hospital, surgeries related to IBD, bowel injury, and colonic dysplasia [20,21]. As there is more evidence demonstrated that mucosal healing can impact IBD progression, the long-term mucosal healing rates observed with vedolizumab, as described by Noman, are notably impactful, and consistent with the 1-year mucosal healing outcomes from the GEMINI 1 trial and the US VICTORY study consortium [18].

In conclusion, vedolizumab has been shown to be effective and safe in patients who have not responded to TNF-α inhibitors, positioning it as a viable second-line and maintenance therapy for this patient group. Furthermore, vedolizumab is recommended as a potential first-line treatment for steroid-dependent and refractory patients, as well as for other biologic drugs and for patients who are unresponsive to immunosuppressants. Vedolizumab may be better for patients who prefer to avoid systemic toxicity (those at high risk of chronic disease or the elderly population).

2.3. Ustekinumab

Ustekinumab is a monoclonal antibody targeting the p40 subunit of IL-12 and IL-23. Its efficacy for induction and maintenance therapy in IBD was evaluated in the UNITI trials for CD and UNIFI trials for UC [22,23]. The UNITI trials were phase 3 randomized, double-blind, placebo-controlled trials. They consisted of two induction trials (UNITI-1 and UNITI-2) that lasted for eight weeks and one maintenance trial (IM-UNITI) that lasted for 44 weeks, totaling 52 weeks of treatment and observation [22,23].

The UNITI research program used a randomized withdrawal design with only the patients who showed treatment response in the induction trials being re-randomized in the maintenance trial. Treatment response at week 6 was the primary efficacy endpoint in UNITI-1 and UNITI-2 and was defined as a decrease of at least 100 points from the baseline CDAI score or a total CDAI score below 150 points. In IM-UNITI, the primary efficacy endpoint was clinical remission at week 44, defined as a CDAI score below 150 points [22,23].

The randomized withdrawal design is an important limitation of the IM-UNITI trial. Patients who were evaluated in the randomized trial for the maintenance phase were already responsive to the experimental agent at baseline [22,23]. These patients could represent a subpopulation of CD patients who have underlying disease biology (histopathological or molecular) conferring treatment response. This overestimates the efficacy of ustekinumab for maintenance therapy and limits the applicability of the study findings to induction responders. Furthermore, the efficacy endpoint was less stringent in the induction trials (clinical response) than in the maintenance trial (clinical remission). This could have also led to an overestimation of the efficacy of ustekinumab for induction therapy [22,23].

Patients included in the UNITI induction trials were adult patients with moderately–severely active CD (baseline CDAI score $\geq$ 220 and $\leq$450) for at least three months [22,23]. In UNITI-1, participants had a previous history of non-response, loss of response, or adverse effects to at least one TNF antagonist. UNITI-2 participants were patients who showed treatment failure to conventional therapy (corticosteroids, azathioprine, methotrexate, and 6-mercaptopurine) [22,23]. The requirement of a history of treatment failure could be a source of selection bias. Patients in the trials had longer disease durations, were possibly refractory to medical treatment, and could have benefitted from surgical interventions.

UNITI-1 enrolled 741 patients with 33 (4.5%) drop-outs, while UNITI-2 enrolled 628 patients with 23 (3.6%) drop-outs. The primary population in the IM-UNITI included 397 patients who showed treatment response in the induction trials, with 36 (9.1%) patients discontinuing in this phase [22,23]. The sample size in UNITI-1 and UNITI-2 was computed to detect a 15 and 17 percentage point difference in clinical response, respectively, between the placebo and treatment groups at a power of at least 90% and two-sided significance level

of 0.05. Drop-out rates were low and did not exceed the anticipated rate (10%) used in the sample size calculation [22,23]. Although most groups in the induction trials were able to meet the calculated sample size, the placebo-treated group in UNITI-2 was two participants below the required sample size. Although these were not counted as clinical response or remission, the loss of participants could contribute to underreporting of safety endpoints, such as adverse events.

In UNITI-1 and UNITI-2, the treatment groups received a single intravenous administration of fixed dose of 130 mg ustekinumab, a weight-range-based dose of 6 mg/kg ustekinumab, and a placebo. The dosages were based on the results of the phase 2, trial showing the efficacy of 1, 3, and 6 mg/kg doses for induction therapy [21,22]. However, it should be noted that there are differences in the actual doses received by each patient. In the 130 mg group, the dose ranges from 1 to 3 mg/kg ustekinumab. In the 6 mg/kg group, the dose ranges from 4.6 to 7.1 mg/kg [22,23]. These might have contributed to the treatment response in the drug groups.

In the maintenance phase, patients who responded to induction therapy were randomized to subcutaneous 90 mg ustekinumab every eight weeks (q8w), subcutaneous 90 mg ustekinumab every 12 weeks (q12w), or placebo [22,23]. However, dose escalation was allowed in the maintenance trial if the loss-of-response criteria (CDAI score $\geq$ 220 and a 100-point increase in CDAI score from baseline) was met. The numbers of patients who met these criteria were 29, 28, and 51 in the ustekinumab q8w group, the ustekinumab q12w group, and the placebo-treated group, respectively [22,23]. The intention-to-treat principle was nevertheless applied in the analyses. Although these participants were not counted as clinical response or remission, this could potentially have confounded other efficacy and safety endpoints.

Randomization was performed with a computer-generated schedule and the concealment of allocation was ensured. Participants and outcome assessors were blinded to treatment allocation. Randomization was generally successful, with no statistically significant differences across the treatment groups in any of the trials. However, several nominal differences can be observed at the baseline. Patients in UNITI-1 had higher CDAI scores and longer disease duration than patients in UNITI-2. In UNITI-1, the 130 mg group had a lower median fecal calprotectin and higher glucocorticoid use. The placebo-treated group in this trial also had a higher proportion of males. In UNITI-2, the duration of disease was longer, and the TNF antagonist history was lower in the placebo-treated group [22,23]. These factors could have affected the results, particularly with respect to the placebo, as discussed below.

In UNITI-1, the clinical responses at week 6 were 34.3%, 33.7%, and 21.5% for the ustekinumab 130 mg group, the ustekinumab 6 mg/kg group, and the placebo-treated group. This indicated an absolute difference of 12.8 (95% CI 5.0–20.7) and 12.3 (95% CI 4.5–20.1) in the ustekinumab 130 mg and ustekinumab 6 mg/kg groups, respectively, when compared to the control. Higher rates of clinical response were observed in UNITI-2, with clinical response at week 6 of 51.7%, 55.5%, and 28.7%, respectively. The absolute difference compared to placebo was 23.0% (95% CI 13.8–32.1) and 26.8% (95% CI 17.7–35.9) in the ustekinumab 130 mg and ustekinumab 6 mg/kg groups, respectively [22,23]. In the IM-UNITI trial, clinical remission was seen in 35.9% of patients in the placebo-treated group. Treatment with 90 mg ustekinumab q8w resulted in a clinical remission rate of 53.1% (absolute difference compared to placebo 17.2%; 95% CI 5.32–29.17), while treatment with 90 mg ustekinumab q12w induced clinical remission in 48.8% of patients (absolute difference compared to placebo 13.0%; 95% CI 1.05–24.87) [22,23].

The relative probabilities of remission in the ustekinumab-treated groups compared to the placebo-treated group can be computed and were at most 1.59, 1.93, and 1.48 in UNITI-1, UNITI-2, and IM-UNITI, respectively [22,23]. These results suggest that patients in UNITI-2 responded better to induction therapy, probably due to decreased disease activity and duration at baseline. Furthermore, the efficacy of ustekinumab in patients with

CD who previously failed treatment (to TNF antagonist or conventional therapy) was not exceptionally high.

This possible attenuation in treatment effect could be due to high treatment response in the placebo-treated groups (>20%). One plausible cause for the improvement of participants who received placebo was concomitant therapy. For all trials, stable doses of immunosuppressants, mesalamine, antibiotics, and oral corticosteroids were allowed. For UNITI-2, 31.4% of patients had a history of TNF antagonist use [22,23]. These patients were not excluded if the TNF antagonist was administered prior to an eight-week washout period and there was no history of non-response, loss of response, or adverse effects. Although these variables were not statistically different across groups, the potential for a confounding effect could not be ruled out. For the maintenance phase, ustekinumab administration in the induction phase could have bleed-over effects that cannot be ruled out, resulting in a high treatment response to placebo. Lastly, although this was a multicenter project, a majority of the participants in the UNITI trials were white (84%) [22,23]. This could preclude the applicability of the results to individuals in other ethnic groups.

The UNIFI trial was a phase 3 randomized, placebo-controlled trial to evaluate the efficacy of ustekinumab for UC. It employed the same trial design (randomized withdrawal design from induction to maintenance therapy), the same ustekinumab dose, and similar inclusion criteria (moderate-to-severe UC with previous treatment failure) as in the UNITI trials [22,23]. However, the UNIFI trial differs from UNITI in the use of clinical remission as the primary endpoint for both induction and maintenance and a stronger therapeutic effect of ustekinumab.

UC patients who were involved in the UNIFI and had received ustekinumab at 130 mg doses/6 mg per kilogram doses had higher rates of clinical remission at week 8 compared to those who received placebos (15.6% for those receiving 130 mg doses, 15.5% for those receiving 6 mg per kilogram doses, and 5.5% for those receiving the placebo, $p < 0.001$) [23]. Also, those who receiving the treatment had higher rates of histo-endoscopic mucosal healing/major secondary end points compared to the placebo-treated group at week 8 [23]. Some patients receiving the treatment, but not having a response by week 8, were given an additional 90 mg subcutaneous dosage and 59.7% of these individuals had a delayed treatment response at week 16 [23]. In terms of overall remission at week 44, 38.4% of those receiving 90 mg doses every 12 weeks had remission, as did 43.8% of those who received the same dosages every 8 weeks; those were compared to the placebo-treated group who had 24.0% ($p = 0.002$, and $p < 0.001$ for the respective groups and their comparison with the placebos) [23]. Patients on ustekinumab also discontinued their corticosteroid usage faster than the placebo-treated group.

2.4. Nutrition and Its Role Alongside Biologics

In addition to the increasing and emerging evidence on the role of biologics in treating IBD, manifested as CD and UC, it is also important to briefly consider and acknowledge the increasing amounts of evidence that changes to diet can have on improving outcomes and inducing remission. Prior reviews have summarized the evidence for exclusive enteral nutrition (EEN) in managing CD [24–27]. It has been demonstrated that such an intervention can potentially be effective, but issues relating to tolerance and adverse events (thus, adherence) remain an issue [25].

Due to issues with EEN, different dietary interventions, such as the Crohn's Disease Exclusion Diet (CDED) for CD patients, are increasingly being proposed to improve outcomes for patients [28]. The CDED involves providing patients with 6 weeks of partial enteral nutrition for 50% of the nutrients they consume, followed by 25% of their calories for the next 6 weeks, and then increased flexibility for eating thereafter [28]. The diet has been shown in clinical trials to have comparable efficacy to EEN but is notably more tolerable for patients [28–30]. For example, one randomized control trial on children with CD showed that CDED were approximately 13.92 times more likely have tolerance compared to patients

on EEN (OR = 13.92, 95% CI 1.68–115.14) [30]. A 13-week randomized control trial with CD therapeutic dietary interventions is currently underway [31].

Based on the existing evidence for the role of dietary interventions in IBD, the American Gastroenterological Association has provided a clinical practice update emphasizing the need for tailored dietary interventions, which include the role of enteral liquid nutrition for patients with CD [32]. There has also been a strong recommendation for the role of dietitians in the care of these patients [32].

Currently, increasing numbers of studies are continually being conducted, with emerging evidence for the role of plant-based diets in inducing remission, with recommendations being made for conducting clinical trials to assess their role further [33]. Interventions may also be developed to provide microbiome therapies in the future [34]. Additionally, very recently emergent studies have provided evidence that combined treatments of biologics, along with dietary interventions such as EEN and partial enteral nutrition (PEN), may show superior effectiveness compared to biologics-only approaches [35,36]. For example, in a retrospective cohort study, those on combination therapy had higher clinical response rates compared to those who were only on biologics (95.0% response compared to 66.0% response) at week 16. They also had higher rates of clinical remission (87.0% compared to 52.6%) and endoscopic response (91.4% compared to 47.4%) [36]. At week 52, these results persisted, with combination patients having higher clinical responses at this time point (84.7% compared to 49.1% on biologics only), and higher clinical remission (77.8% compared to 38.6%), endoscopic response (69.2% compared to 32.6%), and mucosal healing (51.9% compared to 18.6%) [36]. There is also reason to believe that using biologics may further help with nutritional status, which can further justify evaluating combinatory approaches in the future. A prospective cohort study has demonstrated that the usage of ustekinumab resulted in an overall improvement in nutritional status in CD patients, including improvements in total body water body mass index [37]. Thus, by focusing on both biologic therapies and nutritional interventions, the benefits from either single approach may combine to provide even more benefits to patients and their quality of life.

3. Discussion

Each of the three biologics discussed in this paper, which are vedolizumab, ustekinumab, and golimumab, have been shown to demonstrate effectiveness in improving the outcomes for IBD patients. There are numerous strengths and limitations for all of these trials which need to be taken in consideration when providing guidance for clinical and treatment purposes. However, it is important that these trials, and their respective trials, are not considered or evaluated in isolation from other studies conducted or studies that are ongoing.

Aside from the major clinical trials that have been discussed and analyzed thoroughly in this review, there is the continual emergence of evidence regarding the effectiveness of these forms of biologic therapies. For example, a study published in late 2023 demonstrated that, for more than 13,000 patients receiving at least one form of biologic therapy, vedolizumab was shown to be superior in terms of drug effectiveness over a five-year timespan in comparison to those who were given anti-tumor-necrosis drugs ($p = 0.006$). The study also demonstrated that vedolizumab was also more effective than adalimumab and infliximab [38]. The ENTERPRET randomized control trial, which was published in May 2024, evaluated the dose optimization of vedolizumab in UC patients for those who were initially unresponsive to the therapy. The clinical trial showed that a proportion of patients who showed initial unresponsiveness to vedolizumab (along with high drug clearance) benefitted from continual treatment with this drug irrespective of whether or not dose optimization occurred [39]. These studies add to the existing evidence for the safety and effectiveness of this treatment.

With regard to golimumab, there is also the continual emergence of evidence for its effectiveness in treating patients with IBD. The in-TARGET two-phase trial showed that approximately a third of patients with UC who were treated with golimumab achieved a

continuous clinical response and endoscopic remission at the one-year mark [40]. After the de-escalating of the golimumab treatment, approximately 60% of patients who had remitted at the one-year point had maintained deep remission by the two-year point [40]. A smaller-scale multicenter prospective study of 159 patients showed that those with active UC classified as moderate-to-severe being given golimumab treatment experienced improvements in both disease activity and inflammatory biomarkers; they also demonstrated significant improvements in health-related quality of life [41]. Importantly, these improvements in quality of life were demonstrated at weeks 24 and 48 of management and were greater based on increased disease activity [41].

For ustekinumab, a recently published systematic review thoroughly analyzed and assessed a total of 17 studies published on the treatment's effectiveness for UC (which included 1 randomized control trial, 13 observational studies, and 3 long-term extensions); it was demonstrated that clinical remission at induction occurred between 24% and 61% of the time, and remission occurred in 33% to 79% of patients during follow-up at 52 weeks [42]. Notably, adverse events occurred in 2.6% to 77% of studies, though serious adverse events only occurred in 3.7% to 6.0% of cases [42]. Overall, this review has highlighted the effectiveness of ustekinumab clinically for patients in diverse settings. However, a recently published clinical trial from July 2024 has recently also compared the effectiveness and safety of risankizumab in comparison to ustekinumab for CD patients; the randomized control trial showed that risankizumab was noninferior to ustekinumab for inducing clinical remission at week 24, and superior in inducing endoscopic remission at week 48 [43]. The authors have emphasized the need for further study to determine the comparative effects of these treatments, and to continue to guide clinical practice.

Alongside these findings regarding biologic therapies as forms of management, the crucial role of nutrition management in IBD needs to be considered, and there is emerging evidence of the impact of nutritional therapies for patients on biologics. A retrospective observational study has shown that, for CD patients who were no longer responsive to biologics, clinical remission, transmural response, and improved nutritional status occurred at higher rates for those who had PEN and escalated biologics [35]. Preliminary data for a study on CD patients demonstrated that there were better responses to blood and inflammatory markers of the gut for patients on the biologic adalimumab and PEN, compared to those only on adalimumab [44]. Similarly, another prospective cohort study showed that adalimumab combined with enteral nutrition resulted in better Crohn's disease activity index scores, as well as for endoscopic and clinical remission, in comparison to those on adalimumab alone [45]. Patients with moderate-to-severe CD on vedolizumab and 16 weeks of EEN showed improved overall clinical and endoscopic outcomes in comparison to those only on vedolizumab [46].

It is evident that nutritional status needs to be considered for management of IBD, and this should continue to be the case when patients may be placed on biologic therapies, especially as there is also evidence that nutritional status can serve as a predictor of achieving remission [47]. Overall, there remains a need for clinical trials to better demonstrate the impact of a combination approach of nutritional interventions with biologics (and of nutritional interventions more generally) in IBD, and it needs to be acknowledged that there is clear potential in the combination approach. The future development of relevant clinical guidelines for these combination approaches may become of high value as part of the larger goal of improving overall outcomes for IBD patients.

4. Conclusions

IBD remains a major health burden across the globe. With the emergence of biologic therapies, there have been overall improvements in the management of IBD. Golimumab is one such form of therapy; the PURSUIT-SC trial has provided evidence of its efficacy. A newer biological drug, vedolizumab, has also shown effectiveness for severe cases of UC, and for cases in which the disease is refractory to standard medications. Furthermore, ustekinumab, a monoclonal antibody, was assessed in the UNITI trials, which were

conducted to determine its effectiveness against CD; the UNIFI trials were conducted to determine its effectiveness against UC. In this review, we have synthesized and critically analyzed the literature regarding the existing evidence for these forms of treatment in IBD. We have evaluated specific trials, as well as the larger evidence base from recently emerging studies. Lastly, we have discussed the importance of dietary and nutritional approaches in addressing forms of IBD.

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