Comparative Efficacy of Anti-TNF in Inducing and Maintaining Remission in Crohn's Disease: *A Systematic Review and Meta-Analysis*

Comment [S1]: Suggest : Comparative Efficacy of Anti-Tumor Necrosis Factor(TNF)Therapy in Inducing and Maintaining remission From Crohn's Disease: a Systematic review and meta-analysis

Abstract

Background: Anti-TNF agents have emerged not only as inducers of remission but have also shown clinical efficacy in the maintenance of remission in patients suffering from Inflammatory Bowel Disease. However, there is limited quantitative evidence of their effectiveness in Crohn's Disease.

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Aim: The current study aims to investigate the relative efficacy of anti-TNF agents in inducing and maintaining remission in Crohn's Disease, by systematically evaluating efficacy outcomes, such as CDAI, SES-CD, and TEAEs.

Methods: A number of digital databases were searched to retrieve relevant literature. This included PubMed, Google Scholar, Cochrane, ClinicalTrials.gov. The PICOS framework was used to systematically select the data. We used the PRISMA framework to synthesize and report the relevant data.

Results: A total of 10 randomized control trials were included in the final sample. Among the anti-TNF agents, adalimumab and infliximab were most frequently used for disease control. Anti-TNF drugs were positively associated with clinical remission OR= 1.31 (95% CI (0.69, 2.10)), p<0.02; improved SES-CD scores (>50% reduction in endoscopic lesions), 1.65 (95% CI (1.44, 1.87)), p<0.0001; sustained CD remission significantly, -25.65 (95% CI (-33.22, -18.07)), p<0.001; and showed a relatively insignificant impact in lowering the incidence of treatment-emergent adverse effects 0.84 (95% CI (0.69, 1.03)), p=0.10.

Conclusion: Infliximab and adalimumab should be taken into consideration as first-line alternatives for maintaining remission in Crohn's disease due to their better efficacy and set-up safety profiles.

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Introduction

Over 500,000 individuals in the US suffer from Crohn's disease (CD), a chronic inflammatory bowel disease (IBD) with an increasing worldwide incidence [1]. In the groundbreaking study by Crohn et al. from 1952 [2], it was acknowledged as a distinct disease from ulcerative colitis (UC), even though previous studies had described it as "regional ileitis" or "regional enteritis [Smith]." Extra intestinal manifestations of Crohn's disease are mostly due to systemic inflammation and include arthritis, uveitis, pericholangitis, and renal disorders [3]. These conditions may appear before the intestinal manifestations. Systemic amyloidosis is a rare, late sequela. Over the past fifty years, there have been significant advancements in our comprehension of the immuno-pathogenesis of CD, which has led to better pharmacological treatments. These advancements have allowed doctors to recognize the potential benefits of disrupting the immuno-inflammatory pathway [4]. Our paradigms have changed over time, moving from symptom treatment to endoscopic and clinical remission to minimize long-term corticosteroid use and avoid long-term consequences and impairment. Several drugs and surgical procedures are available to treat Crohn's disease: each having a different efficacy and possible side effects. Although they sometimes have unfavorable side effects including headaches and diarrhea, aminosalicylates (5-ASAs) like mesalamine are useful in mild-to-moderate cases of gastrointestinal tract inflammation [5]. Corticosteroids, such as prednisone, are effective anti-inflammatory medications for brief flare-ups, prolonged use can result in weight gain, bone loss, and an increased risk of infection [6].

A large family of proteins and receptors involved in immune control includes human TNF [7]. To reduce inflammation, biological therapies—which include anti-TNF drugs like infliximab, adalimumab, etrolizumab, and ustekinumab—target particular proteins in the immune system. Treating inflammatory bowel disease with infliximab, a genetically modified chimeric immunoglobulin Ig-G1 anti-human tumor necrosis factor agent, was the first application of a biological response modifier [5]. It is capable of fixing complement, lysing cells that express TNF-alpha membrane-bound and inducing downregulation of inflammatory processes throughout the mucosal layer. To make the Crohn's Disease Endoscopic Index of Severity (CDEIS) simpler, the Simple Endoscopic Score for Crohn's Disease (SES-CD) was created. SES-CD score has been used in many research to characterize treatment response or disease severity. While some of them defined severity grades using specific cutoff values, others used the SES-CD score as a continuous variable [8]. Experts empirically chose all SES-CD cutoff values provided in published clinical trials. No study employs score 0 to predefine inactivity,

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although in most of the studies that utilized SEC-CD scoring to define disease severity, a score <3 reflected inactive illness. Score 0 was used in studies that employed SES-CD to define response to treatment. The ideal SES-CD cut-off for endoscopic remission does not exist [9]. In clinical practice, it is crucial to utilize a clinical activity index, such as the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) assessment score or the Crohn's Disease Activity Index (CDAI) [10]. The index that is most commonly used to evaluate the clinical condition of CD patients is the CDAI, which is constructed from eight independent factors. The European Crohn's and Colitis Organization and the American College of Gastroenterology define CDAI as follows: < 150, 250–220, 220–450, and > 450, respectively, indicating remission, mild disease activity, moderate disease activity, and severe disease activity [11].

The current study is a comprehensive review and meta-analysis of the relative efficacy of anti-TNF agents and their role in the induction of CD therapy. Moreover, their role in the maintenance of remission, and effectiveness in preventing recurrence can further be investigated by incorporating different dosing regimens, alternating the routes of administration, and further elaborating the long-term clinical remission and response rates through different drugs within the group.

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Rationale

A patient's quality of life can be improved and remission can be maintained with proper long-term management of Crohn's disease, a chronic inflammatory bowel illness. Anti-TNF medications, including golimumab, certolizumab pegol, adalimumab, and infliximab, are frequently used to bring about and sustain remission in Crohn's disease. Although these medications are successful, there is a lack of comparable data about their ability to sustain remission for prolonged periods. It is essential to comprehend the relative effectiveness of these treatments to optimize therapeutic approaches and enhance patient outcomes. By methodically assessing the effectiveness of different anti-TNF medications in preserving remission in Crohn's disease, this study seeks to close this research gap.

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Objectives

The primary objective of this research is to conduct a systematic review and meta-analysis on the relative effectiveness of several anti-TNF drugs, such as golimumab, certolizumab pegol, adalimumab, and infliximab, in helping Crohn's disease patients maintain in remission. Assessing the rates of durable remission, analyzing safety profiles, and determining variables that can affect treatment outcomes are some of the specific goals. The purpose of this thorough research is to offer evidence-based insights to support professional judgment and enhance patients' long-term treatment plans for Crohn's disease.

Methodology

Eligibility Criteria

The PRISMA framework and the PICOS (Population, Intervention, Comparison, Outcome, and Study design) scheme was followed to establish the inclusion and exclusion criteria [12]. Papers that were published in 2020–2024 were deemed suitable for inclusion. The target population included: (i) patients with a diagnosis of Crohn's disease confirmed after CDAI scores (>200-400 for diagnosis), (ii) patients who presented one or more chronic symptoms or complications after conventional treatment; (iii) patients with treatment-resistant variants of CD (defined as Harvey-Bradshaw Index [HBI] score <5, fecal calprotectin<150 µg/g, and C-reactive protein <10 mg/L) for at least 9 months on a stable dose of 40 mg subcutaneous adalimumab; (iv) patient with a sustained clinical remission after initial treatment.

Studies were considered for inclusion if they presented quantifiable data about efficacy outcomes with anti-TNF (as discussed previously). The details of the eligibility criteria are further provided in the table below (Table 1).

Criteria	**Inclusion**	**Exclusion**
Language	Studies published in English	Others
Duration	Publications from 2020-2024	All literature before 2020
Methodology	Randomized Control Trials Quantitative Qualitative Observational Studies (Prospective and Retrospective)	Protocols Reviews Case series Grey Literature
Location	Global	-
Target Population	Patients with a diagnosis of CD confirmed from patient CDAI scores (>220-400) Patients with treatment-resistant variants of CD (defined as Harvey-Bradshaw Index [HBI] score <5, fecal calprotectin<150 µg/g, and C-reactive protein <10 mg/L)	Individuals with any form of ostomy or ileoanal pouch, symptomatic bowel stricture, abdominal or perianal abscess, and small bowel syndrome were not eligible. Neither were individuals with ulcerative or indeterminate colitis. -

Follow-up	Between 4 weeks to 54 weeks	More than 54 weeks
Context	Studies investigating various efficacy and safety outcomes, such as reduction in CDAI scores, SES-CD scores, TEAEs, and FC levels.	Studies investigating non-efficacy outcomes. Studies with no quantitative data for pre-test and post-test analysis.

Table 1: Eligibility Criteria for the Systematic Review

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Information Sources

We looked through several digital databases to obtain relevant literature. Among these are ClinicalTrials.gov, PubMed, Google Scholar, and Cochrane. There were more resources available, such as independent journals. The information was compiled using databases as well as journals such as "*LANCET Gastroenterology and Hepatology*," "*JAMA*," and others.

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Search Strategy

Using the PICOS technique (discussed below), the search strategy was developed to find relevant information in digital databases. Ten studies (out of a total sample of n = 211) in the final sample satisfied the eligibility requirements. A PubMed search query was created that included the following terms: "(("Crohn Disease"[Mesh] OR "Crohn's Disease" OR "Crohn Disease") AND ("Anti-TNF Agents" OR "TNF Inhibitors" OR "Tumor Necrosis Factor Inhibitors" OR "Infliximab" OR "Adalimumab" OR "Certolizumab Pegol" OR "Golimumab") AND ("Remission Induction" OR "Remission Maintenance" OR "Disease Remission" OR "Maintenance Therapy" OR "Long-term Treatment") AND ("Comparative Efficacy" OR "Head-to-Head Comparison" OR "Effectiveness" OR "Efficacy" OR "Comparative Study"))."

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Selection Process

The study approach was developed based on a comprehensive review of pertinent literature published in peer-reviewed journals. After carefully reviewing the literature that met our established inclusion criteria, a thorough analysis was conducted using the PICOS technique. To lessen publication bias, we carried out a comprehensive examination of the literature and closely considered peer-reviewed publications with high impact factors. To speed up the screening of primary and secondary literature, all chosen papers were assessed using the specialist screening tool Rayyan.ai[13]. A group of researchers worked together to define the papers that met the criteria and those that did not. Only 10 studies could be collected for analysis after the results were evaluated. Studies that did not meet the eligibility requirements were marked as 'disputed' or 'excluded'. A panel consisting of three researchers resolved disagreements and concluded. The studies were disregarded if they mentioned a different demographic, had a wrong methodological design, measured wrong outcomes, or had a high risk of bias. Some of the studies may have more than one of the previously mentioned features.

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Data Items

After finalizing the secondary screening process, we assessed the overall sample size (n=10) of the selected literature. To create a PRISMA flow chart that follows the rules of Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [14], we used articles from reputable journals and other sources.

A number of measures were taken to reduce bias in the analysis: (1) a strict selection of the best research materials; (2) a requirement that peer reviewers declare any conflicts of interest; and (3) a preference for meta-analyses over traditional review articles. We purposefully excluded the narrative and systematic reviews in order to maintain the integrity of the study.

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Assessment of Research Quality

-*Systematic review:* We performed a thorough examination of bias in each primary study that was chosen for a quality assessment. For this, it was necessary to examine the demographics of the population, the features of the interventions, and the geographical area in which the study was carried out. First, a thorough literature search in electronic databases was used to find relevant studies that fit the inclusion criteria. Predetermined qualifying criteria, such as study design, population characteristics, and result of interest, were used to choose studies. Data extraction was then carried out to gather details regarding the overall sample size and number of events (e.g., CDAI scores, SES-CD index, etc.) in each study.

-*Meta-analysis:* To evaluate the degree of bias in the chosen studies, we used a range of digital and web-based resources. We investigated domains that are prone to prejudice in depth [15]. In order to minimize bias, the following steps should be taken: (1) create a random sequence; (2) keep allocations secret; (3) blind staff and participants; (4) blind outcome assessments; (5) address attrition bias; (6) avoid selective reporting; and (7) identify and mitigate other biases. Out of 10, 9 studies reported dichotomous and continuous data for the studied outcomes. The data were included in the statistical meta-analysis. In addition, Review Manager (RevMan version 5.4) was used to create a "forest plot" for the meta-analysis. RevMan (3.5.1) made it straightforward to do a meta-analysis of the 10 original inquiries. For the analytical tool, three researchers gathered comparable and poolable data [16].

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All of the data in the investigation were available as Dichotomous as well as Continuous variables. Statistical heterogeneity was assessed using the I^2 statistic, with values above 50% indicative of substantial heterogeneity.The pre-test and post-test interventions were extracted for dichotomous outcomes. Due to a lack of paired t-test data, n *(frequency of events)*/ N *(Total number of events),*and Mean ± Standard Deviation (SD) were used independently in crossover studies. Numerical value estimation from graphical data was attempted. In meta-analyses, a number of statistics were used to assess the heterogeneity of the included papers. The impact sizes varied amongst studies, as indicated by the tau square (τ^2), which is an indication of the within-study variance. Degrees of freedom (df) represented the number of independent

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comparisons required to calculate the pooled effect size. If detected differences in effect sizes between studies were more than what would be expected by random chance, it was determined by the chi-square (χ^2) test. If the chi-square value was significant, then heterogeneity was positive. The fraction of total variation that can be attributable to heterogeneity rather than random variation was assessed by the I-square (I^2). Elevated figures suggested increased variability and offered an intuited sense of the extent of disparity across research findings.

Statistical Analysis

A univariate, linear, meta-analysis was performed with RevMan 5.4.1 software. The Odds Ratio [OR] and its Confidence Interval (CI) were estimated using dichotomous and continuous data. The synthesis of results from many pieces of research investigating the prevalence of neurological outcomes in a sample of 3032 patients was made possible by this methodology. Using the relevant formulae, the OR and its CI were determined from the retrieved data. The odds ratio is represented by the symbol [OR], which indicates the degree and direction of the relationship between exposure and result. Conversely, CI measures the precision or level of uncertainty in the effect size estimate. The *DerSimonian* and *Laird* random-effects model was then used to do the meta-analysis, which takes into account both within-study and between-study variability. With this method, an overall summary effect size in terms of the Odds Ratio (OR) and its associated confidence interval (CI=95%) could be estimated. A forest plot was used to visually represent the results, showing the overall pooled estimate as well as the point estimates and confidence ranges of the various investigations. Greater precision and hence more trustworthy estimations are indicated by a smaller CI.

Interpretation of statistical significance involved assessing whether the observed effect size was likely to have occurred by chance alone. The calculated effect size and its matching confidence interval (CI) were compared to achieve this. The effect size was deemed statistically insignificant if the confidence interval (CI) contained 0, indicating that there was not enough data to reject the null hypothesis. Stated differently, there was no indication of a significant correlation between the two variables. On the other hand, if the confidence interval (CI) did not include zero, the impact size was statistically significant, suggesting that anti-TNF and efficacy in CD remission were related.

Results

Study Selection

PubMed, Science Direct, and MedLine were searched to identify all articles evaluating the prevalence of neurological complications among patients of CD, irrespective of the patient demographics. RevMan 5.4 software was used to do statistical analysis. Following thorough

investigation across all databases, 211 articles were retrieved. The total number of studies was lowered to 152 after duplicates were eliminated, and then to 120 after additional screening. During this screening process, review articles and papers unrelated to the results of the study were eliminated. Following an examination of the abstract and title, 37 full-text publications were included; after additional editing, these articles made up the final ten in this systematic review. The results of the screening protocol are summarized in the figure below. (Figure 1) [17].

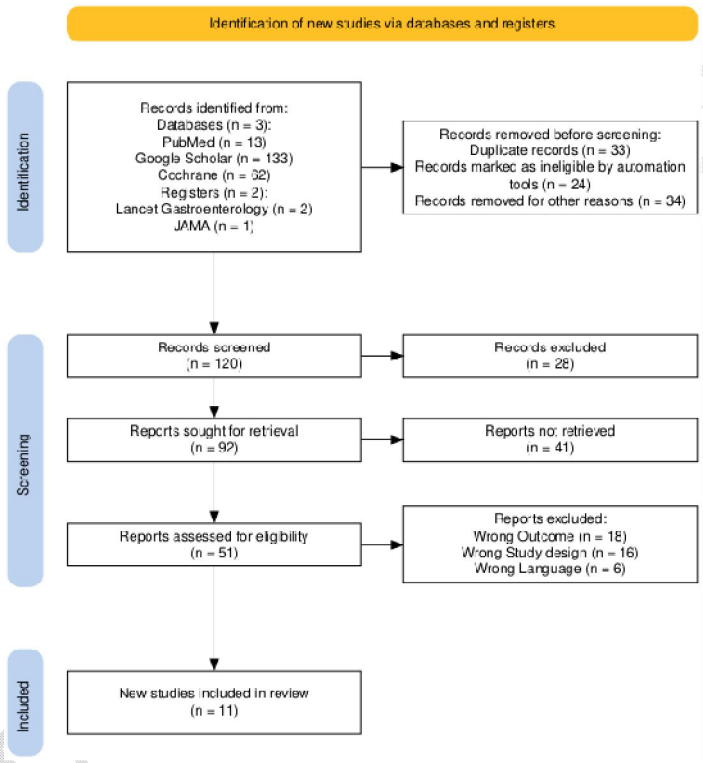

Figure 1: PRISMA flow diagram for the Literature Review

Baseline Characteristics

In the current study, two important confounders were disease status as well as the specific drug therapy employed. These factors influenced the treatment regimens, and subsequently, determined the patient response to the treatment provided. The data for specific patient characteristics at baseline are mentioned in the patient characteristics table provided below. It is important to consider these factors when discussing the efficacy outcomes of anti-TNF agents. (Table 2)

Study ID	*Location*	*Sample Size*	*Mean Age*	Follow-up	Drug Used	Disease Status
Van Linschoten RCA et al. 2023 [18]	Netherlands	174	>18years	24, 48 weeks	Adalimumab	Stable remission
Schreiber S et al. (2024) [19]	UK	136	>18years	34, 54 weeks	CT-P13 (biosimilar of Infliximab)	Active (post-clinical remission)
Cheifetz AS et al. (2022) [20]	USA	103	13	46 weeks	Infliximab	Active responders
Sands BE et al. (2022) [21]	USA	386	>18years	52 weeks	Ustekinumab vs Adalimumab	Treatment resistant
D'Haens GR et al. (2022) [22]	Multi-national	479	34 (18–71)	44 weeks	Adalimumab	Treatment resistant
Strik AS et al. (2020) [23]	Netherlands	80	38 (29–51)	52 weeks	Infliximab	Clinical Remission
Narula N et al. (2022) [24]	Multi-national	420	38.6	6 weeks induction and 54 weeks maintenance	CT-P13 (biosimilar of Infliximab)	Clinical Remission
Syversen SW et al. (2021) [25]	Norway	411	44.7 [SD, 14.9]	6 weeks induction and 54 weeks maintenance	Infliximab	Treatment resistant
Syversen SW et al. (2021b) [26]	Norway	458	46.7 (12.3)	7 weeks induction and 54 weeks maintenance	Infliximab	Treatment-resistant
Sandborn WJ et al. (2023) [27]	Multi-national	385	39.7	14 weeks and 52 weeks	Etrolizumab	Corticosteroid resistant

Table 2: Patient characteristics at baseline[18-27]

Study Characteristics

Out of a total sample of n=211, 10 studied met the inclusion criteria for the final sample. All of the primary studies were randomized, parallel-group, trials. 2/10 studies were in phase 2a and 3b respectively; whereas, 2/10 studies were post-hoc analysis of previous studies. Further, 1 study

was an open-label, double-blind, study. The sample sizes ranged from as small as N=80 and as high as N=458. The data estimation and patient follow-up points ranged from 4 weeks to 64 weeks. The data points for induction of remission were calculated at 4 and/ or 6 weeks follow-up. However, the maintenance of remission was calculated at 52 weeks, and 64 weeks of follow-up. Quantitative data were available for both phases of the treatment regimen. Out of a total sample of 10 studies, 4 studies investigated the role of infliximab independently, 2 studies explored the efficacy of CT-P13, 2 discussed the efficacy of adalimumab in comparison with a control group, 1 study demonstrated relative efficacy of adalimumab with ustekinumab, and lastly, 1 study investigated the role of etrolizumab (a relatively newer anti-TNF agent).

Adalimumab

Adalimumab is the most commonly used drug for induction as well as maintenance of remission. At normal concentrations, its efficacy is comparable to that of Ustekinumab. However, at a higher dosing regimen, it was associated with improved clinical remission in the induction phase. No significant changes were reported in the maintenance phase of the treatment. Further, clinically adjusted doses are less frequently associated with sustained disease remission, as compared to TDM. In juvenile CD patients, switching from subcutaneous to IV infusion also showed significant improvements in CDAI and SES-CD scores. Further, it is important to consider a potential disease flare-up when increasing the concentration of adalimumab, aimed at targeted remission.

Infliximab

Infliximab was employed in 4 trials, as monotherapy and combination therapy. In the study conducted by Narula N et al. 2022 [24], for "biologic-naïve" CD patients, infliximab and ustekinumab seem to work similarly in terms of efficacy and onset time. Similar to adalimumab, in juvenile CD patients, higher post-induction infliximab concentrations are linked to both short- and, long-term beneficial clinical outcomes, according to a study conducted by Cheifetz AS et al. (2022) [20]. For a comparative overview, infliximab is superior to adalimumab in treatment-resistant CD. Consequently, adalimumab is the preferred mode of treatment in patients who are in stable remission.

Sr. No.	Study ID	Location	Study Design	Participant Characteristics	Intervention	Outcomes	Main findings	Conclusion

The results of the systematic review are provided in the table below. (Table 3)

1	Van Linschoten RCA et al. 2023 [18]	Netherlands	open-label, non-inferiority, randomised controlled trial	Random assignments (2:1) were made to place patients (N = 174) in the intervention group (N = 113) or control group (N = 61).	Adalimumab dose intervals were increased for patients assigned to the intervention group to 40 mg every three weeks at baseline, then to every four weeks if they continued to experience clinical and biochemical remission.	Incidence of persistent flare; Adverse events	When compared to the control group, the intervention group's incidence of persistent flares (three [3%] out of 109) was not inferior.	There is a trade-off between the chance of a flare-up and the individual benefit of extending the intervals between adalimumab doses and the chance of the disease returning, and patient preferences for treatment should be considered.
2	Schreiber S et al. (2024) [19]	UK	Post hoc analysis of a randomized trial	50 (76.9%) and 57 (86.4%) of the 136 patients who were enrolled in the CT-P13 IV and CT-P13 SC groups, respectively, finished the entire study.	The CT-P13 SC arm (also known as the "SC maintenance group") was randomly assigned to patients, who were subsequently given CT-P13 SC every two weeks until W54 (120 mg/240 mg for patients with a body weight of <80 kg/≥80 kg).	SIBDQ; TEAEs; SES-CD	In CD patients, SES-CD scores considerably improved (p = 0.01). Regarding the SIBDQ score (p = 0.0006), there was an additional noteworthy increase in HRQoL between W30 and W54 in the IV-to-SC transition group.	The formulation change from intravenous to subcutaneous infliximab maintenance therapy was well received and may yield further therapeutic benefits.
3	Cheifetz AS et al. (2022) [20]	USA	post hoc analysis of the REACH trial	Children with moderate to severe CD who underwent infliximab induction therapy at a dose of 5 mg/kg at weeks 0 through 6 made up the trial cohort.	All comprised 103 pediatric patients receiving infliximab treatment for moderate to severe CD. At week 10, participants were randomized to receive infliximab 5 mg/kg every eight or twelve weeks until week 46.	PCDAI (clincal remission), Long-term clinical response (LTCR)	Higher week 10 infliximab concentrations were linked to both LTCR at week 30 (OR: 1.62; 95%CI: 1.12-2.36; p=0.010) and CR at week 10 (odds ratio (OR): 1.54; 95% confidence interval (CI): 1.06-2.22; p=0.022).	In juvenile CD patients, higher post-induction infliximab concentrations are linked to both short- and long-term beneficial clinical outcomes.
4	Sands BE et al. (2022) [21]	USA	double-blind, parallel-group, active-	A total of 386 individuals were enrolled and 633 patients had their eligibility evaluated between June 28, 2018, and	randomized to receive either adalimumab (n = 195) or ustekinumab (n = 191). Using an interactive web response system, eligible patients were randomized 1:1 to receive either	CDAI, TEAEs	The occurrence of the primary outcome did not differ significantly between the ustekinumab and adalimumabgroups.Of the 191 patients in the ustekinumab group and the 195 patients in the	Adalimumab and ustekinumabmonotherapies both shown remarkable efficacy in this group of patients who had never used biologics.

			comparato	December 12, 2019.	ustekinumab (about 6 mg/kg intravenously on day 0 and 90 mg subcutaneously once every 8 weeks) or adalimumab (160 mg on day 0, 80 mg at 2 weeks, and 40 mg subcutaneously once every 2 weeks) until week 56.		adalimumab group, four (2%) and five (3%) respectively had serious infections.	
5	D'Haens GR et al. (2022) [22]	Multi-national	, randomized, double-blind, multicenter tria	Individuals were randomly assigned to either the conventional induction regimen (adalimumab 160 mg at week 0 and 80 mg at week 2; n ¼ 206) or the higher induction regimen (adalimumab 160 mg at weeks 0, 1, 2, and 3; n ¼ 308).	Adalimumab 160 mg was given to participants with HIR at baseline, as well as at weeks 1, 2, and 3. For SIR, patients were given 160 mg of adalimumab at baseline, 80 mg of adalimumab at week 2, and a placebo at week 3.	CDAI; TEAEs; Mayo Score: HRQoL; SEC-CD	At week 12, 62.3% of patients in the HIR group and 51.5% of patients in the SIR group had reached clinical remission (P ¼.008); In the maintenance phase, comparable percentages of patients in the TDM and CA groups met the 56 efficacy end points (all exploratory) every week.	The efficacy and safety of higher induction dosage matched those of the authorized standard induction dosage. Maintenancedose adjustment largely by blood adalimumab levels was not more efficacious than clinically adjusted dosage
6	Strik AS et al. (2020) [23]	Netherlands	a randomized controlled trial	Following screening of 186 IBD patients on IFX maintenance therapy, 80 individuals were randomized, with 40 patients in each treatment group.	Patients were randomized (1:1) to either continue receiving IFX maintenance medication without modifications to the dose and/or treatment interval (conventional dosing group; CG) or receive dashboard-driven IFX dosing (precision dosing group; PG).	CR (4 weeks/ 52 weeks); AEs	During a one-year follow-up period, driven IFX dosing led to a greater percentage of patients experiencing prolonged clinical remission in comparison to standard dose. Two individuals in the PG were found to have pneumonia; one of them required hospitalization in order to get intravenous antibiotics."	We showed that IFX dosing using a Bayesian dashboard, as opposed to traditional dose, decreased the incidence of LOR in IBD maintenance medication.

7	Narula N et al. (2022) [24]	Multi-national	post hoc analysis of UNITI-2 and IM-UNITI CD trials	the 420 CD patients who were not yet treated with biologics. We investigated differences in the percentages of patients who achieved clinical remission by week six, clinical response, and calprotectin normalization.	"Infliximab (5 mg/kg intravenously at weeks 0 and 2) and ustekinumab (6 mg/kg intravenously at week 0) were the standard dose induction therapies used."	CR (6weeks); LTCR	Comparably more patients (44.9% [96 of 214] vs. 37.9% [78 of 206]) achieved CR with infliximab by week 6 as opposed to ustekinumab.	For "biologic-naïve" CD patients, infliximab and ustekinumab seem to work similarly in terms of efficacy and onset time.
8	Syversen SW et al. (2021) [25]	Norway	Randomized, parallel-group, open-label clinical trial	198 in the TDM group and 200 in the standard therapy group) received their randomized intervention and were included in the full analysis set.	Patients were randomized 1:1 to receive standard infliximab therapy without drug and antibody level monitoring (standard therapy group; n = 204) or proactive TDM with dose and interval changes based on scheduled monitoring of blood drug levels and antidrug antibodies (TDM group; n = 207).	CR (30 weeks); AEs	In the TDM and standard treatment groups, 100 (50.5%) of 198 patients and 106 (53.1%) of 200 patients, respectively, had reached clinical remission at week 30 (adjusted difference, 1.5%; 95% CI, −8.2% to 11.1%; P =.78).	Over a 30-week period, proactive therapeutic medication monitoring did not considerably increase clinical remission rates as compared to usual therapy.
9	Syversen SW et al. (2021) [26]	Norway	Randomized, parallel-group, open-label clinical trial	Total 458 participants were screened and CD patients were identified and segregared. The TDM group; n = 228, and standard therapy group; n = 230, respectively.	Patients were randomized 1:1 to either standard infliximab therapy without drug and antibody level monitoring or proactive TDM with dose and interval modifications based on scheduled monitoring of serum drug levels and antidrug antibodies.	sustained disease control; AEs	127 patients (55.9%) in the standard treatment group and 167 patients (73.6%) in the TDM group both showed the primary outcome of sustained disease management without illness deterioration.	When it came to maintaining disease management without the condition getting worse, proactive TDM was more beneficial than treatment without TDM.

10	Sandborn WJ et al. (2023) [27]	Multi-national	randomised, placebo-controlled, double-blind, phase 3 study	385 patients (209 [54%] male and 326 [85%] white) were randomly assigned in induction cohort 3 to receive placebo (n=97), 105 mg etrolizumab (n=143), or 210 mg etrolizumab (n=145).	Patients received 105 mg of etrolizumab subcutaneously every 4 weeks (at weeks 0, 4, 8, and 12) or 210 mg of etrolizumab subcutaneously every 4 weeks (at weeks 0, 2, 4, 8, and 12) according on a random assignment (2:3:3).	CR; SES-CD; Aes	28 (29%) of 96 patients in the placebo induction group and 48 (33%) of 145 patients in the 210 mg induction etrolizumab group were in clinical remission at week 14 (adjusted treatment difference: 3·8% [95% CI -8·3 to 15·3]; p=0·52).	Compared to placebo, etrolizumab dramatically increased the percentage of patients with moderately to highly active Crohn's disease who experienced clinical remission and endoscopic improvement.

Table 3: Results of the Systematic Review[18-27]

Risk of Bias Plot

A traffic lights plot was created to represent the risk of bias domains. Further, the individual biases in each domain were also represented by relative labels “high”, “low”, or “moderate”. The risk of bias and the summary plot for the selected studies are mentioned in the figures below. (Figure 2, 3).

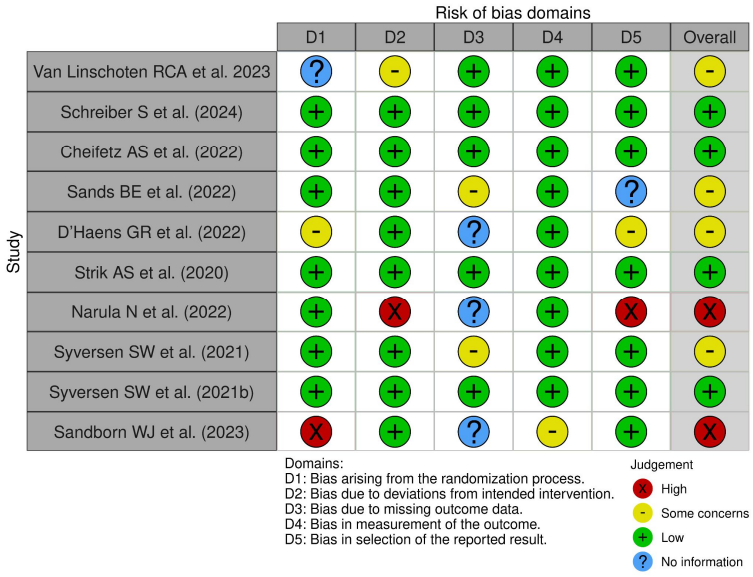

Figure 2: ROB2 tool for Risk of Bias assessment

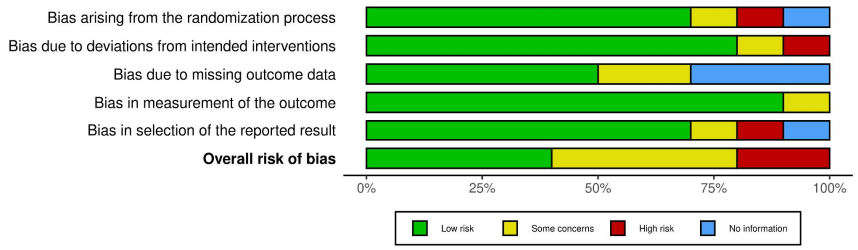

Figure 3: Summary plot for individual domains

Forest Plots

It is important to note that all patients were biologically naïve and had active CD (Crohn's Disease Activity Index [CDAI] score 220–450), that had not responded to conventional therapy. Efficacy assessments conducted pre-dose at all study visits, CDAI score (CD patients), C-reactive protein (CRP) level, and fecal calprotectin (FC) level, assessed on continuous scales. Baseline fecal calprotectin level >250 mcg/L and week 6 fecal calprotectin level <250 mcg/L, n (%) across all patient populations. All patients need to have been on an immunomodulator therapy (thiopurines or methotrexate) for at least 8 weeks to be included in the study. Clinical remission was defined as achieving a partial Mayo score of ≤1 point (UC patients) or an absolute CDAI score of <150 points (CD patients).

Using a dichotomous [Number of events/Total sample] and continuous [Mean(SD)] approach, data from 10 studies were combined to create a forest plot with the primary outcome represented by the Odds Ratio (OR). The OR was computed using a fixed-effects model. The green/ blue squares represented the point estimations, and the horizontal axis showed the confidence interval (CI=95%). Lack of influence, or a state that was "no-effect," was shown by the central vertical line.

1. **Clinical Remission**

For the primary endpoint of CR, 5/10 studies provided quantifiable data. All experimental groups contained different dosing regimens of Adalimumab, infliximab, and Ustekinumab. The control group represented standard therapy (normal dosing). All 5/5 studies reported improved response rates after initiating anti-TNF therapy in both the induction as well as maintenance phases. The combined effect size for all individual studies was found to be OR= 1.31 (95% CI (0.69, 2.10)). The heterogeneity was estimated to be Chi^2=5.44, df=4. And I^2=26%. The test for overall effect was, hence, Z=2.30, p-value=0.02. The evidence deduced that anti-TNF drugs were significantly associated with clinical remission in all eligible patients. The forest plot for the analysis is provided in the figure below. (Figure 4)

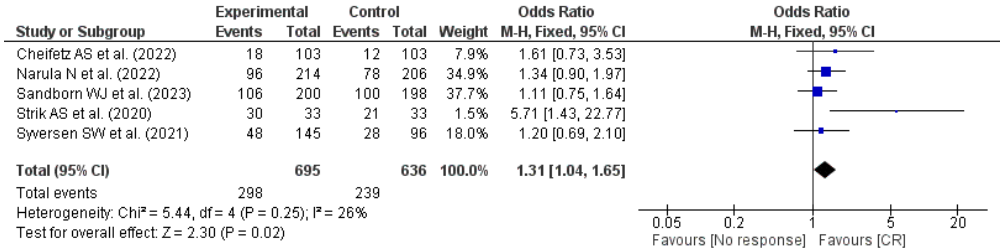

Figure 4: Forest plot for CR rates with Anti-TNF therapy[20][23][24][25][27]

2. SES-CD Scores

The centrally read endoscopic evidence of mucosal inflammation is defined as SES-CD 6 or 4 for isolated ileal disease, excluding the presence of the narrowing component. This signifies the correlation between the clinical disease activity and the severity of endoscopic lesions. A score of SES-CD <4 indicated a 50% reduction in the endoscopic lesions, which directly was associated with clinically improved outcomes for the patients.

As evident from the forest plot, all 3/3 studies concluded a significant improvement in SES-CD scores. However, SES-CD scores were more prominently associated with the maintenance phase (between week 30 and week 54). The overall effect was estimated to be 1.65 (95% CI (1.44, 1.87)). The heterogeneity in the analysis was found to be Chi^2=1.99, df=2, and I^2=0%. The association between the studied variables was significant (p-value< 0.00001). (Figure 5)

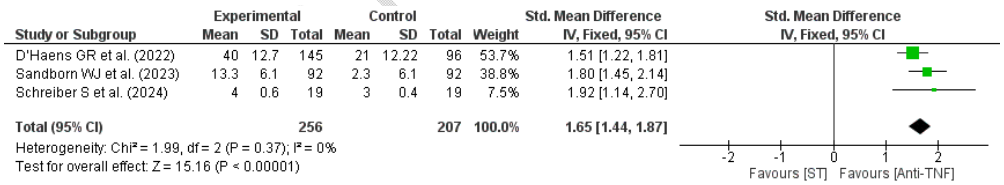

Figure 5: Forest plot for CDAI scores in clinically sustained CD remission[19][22][27]

3. CDAI Scores

For the secondary endpoint, the quantitative data was scarce. As mentioned above, the CDAI scores indicated a sustained remission of the disease. 2/10 studies, D'Haens GR et al. 2022 [22] and Schreiber S et al. 2024 [19], provided continuous data for relative differences in CDAI scores. Predictably, all the studies advocated for anti-TNF. Both studies demonstrated a stable

remission of the disease through adalimumab and infliximab. The total estimated effect size was found to be -25.65 (95% CI (-33.22, -18.07)). The analysis had significant variability: Chi^2=6.21, df=1, and I^2=84%. The test for overall effect was found to be Z=6.64, p-value < 0.0001. (Figure 6)

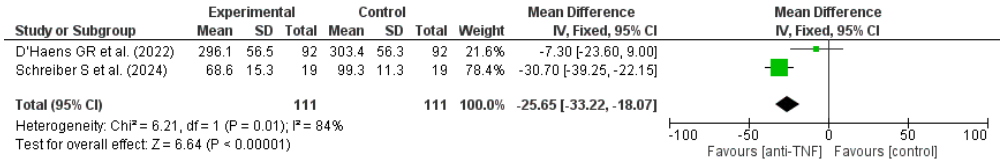

Figure 6: CDAI scores after induction treatment [19][22]

4. Treatment-Emergent Adverse Effects (TEAEs)

The safety of the anti-TNF was also investigated in the current study. This was calculated as the difference between TEAEs as occurred during and after the initial treatment regimen with anti-TNF agents. As evident from the forest plot, 5/7 studies showed a reduction in AEs with anti-TNF drugs. On the other hand, 2/7 studies, D'Haens GR et al. 2022 [22] and Sandborn WJ et al. 2023 [27] revealed a negative association between the studied variables. These concluded that treatment-emergent AEs were more prominent after TNF agents. The overall effect size was estimated to be 0.84 (95% CI (0.69, 1.03)). The heterogeneity in this analysis was comparable to other outcomes. However, the p-value was large (p=0.10), even though the individual effect did not vary significantly among the studies. Another reason for a relatively larger p-value is large is because the effect sizes are small, and the statistical limitation of the studies. The forest plot for the analysis is provided in the figure below. (Figure 7)

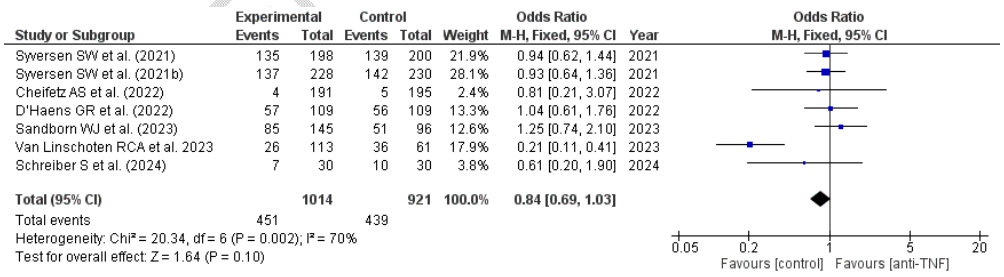

Figure 7: TEAEs after anti-TNF therapy[18][19][20][22][25][26][27]

Discussion

Chronic gastrointestinal tract irritation is a hallmark of Crohn's disease, which makes maintaining long-term remission extremely difficult. Anti-TNF (tumor necrosis factor) pharmacies, in addition to adalimumab, golimumab, certolizumab pegol, and infliximab, have completely changed how this condition is treated. The goal of this systematic review and meta-analysis was to provide a thorough evaluation of these drugs with a focus on sustained remission costs, safety profiles, and treatment outcome-influencing factors. Our data showed different phases of different anti-TNF drugs' effectiveness in maintaining CD remission. The only drugs that showed efficacy in induction and maintenance of remission as compared to other treatments were infliximab and adalimumab. However, one study also showed that there were no significant differences between adalimumab and ustekinumab when compared for their clinical remission rates. This result is consistent with other research showing that the first-generation anti-TNF drugs, infliximab, and adalimumab, have a more significant impact on the long-term management of CD [28]. Particularly infliximab has undergone extensive research and is frequently regarded as the gold standard for induction and preservation therapy [29]. Because adalimumab is completely humanized, there is a lower possibility of immunogenicity, which could explain why it continues to work so well.

In the study conducted by Syversen SW et al. (2021) [25], an improved strategy of drug administration was tested. Therapeutic Drug Monitoring (TDM) is a proactive form of drug administration that offers subcutaneous or IV forms of drug based on patient's evaluation and serum levels of FC, HBI scores, and other biochemical indices. TDM, when compared with clinically adjusted dosage, performed significantly better [30]. It also showed improved rates of sustained disease management and maintained remission. In another study conducted by Narula N et al. (2022) [24], Comparably more patients (44.9% [96 of 214] vs. 37.9% [78 of 206]) achieved CR with infliximab by week 6 as opposed to ustekinumab.

Safety is a critical factor in the long-term use of anti-TNF dealers. Our evaluation shows that all four marketers have similar safety profiles, with damaging results in most cases which include infections, injection web page reactions, and infusion-associated reactions. However, diffused variations exist. Infliximab and adalimumab, because of their intravenous and subcutaneous routes of administration respectively, present distinct safety concerns [31]. Infliximab's infusion-related reactions, together with acute allergic reactions, require close tracking throughout the administration. Adalimumab's subcutaneous injections are usually highly tolerated however can cause local injection site reactions. Among all the patient cohorts, erythema and injection site reactions were the most commonly occuring AEs. Several factors have an effect on the efficacy and safety of anti-TNF sellers in retaining remission. Patient-related factors, together with age, disorder duration, and former remedy history, play a vital function. Younger sufferers and people with a shorter ailment length often reply better to anti-TNF remedy. Prior publicity to anti-TNF sellers can result in the improvement of antibodies, reducing the efficacy of next remedies.

Therefore, the sequencing of remedy and cautious patient choice are essential for optimizing results.

Treatment success is also influenced by pharmacokinetic and pharmacodynamic factors. TDM, or therapeutic drug monitoring, has become a valuable tool for enhancing anti-TNF treatment. Anti-drug antibodies and drug trough range measurements can be used to inform dose adjustments, improving efficacy and reducing the risk of negative outcomes. Compared to certolizumab pegol and golimumab, infliximab and adalimumab have more established TDM techniques because of their longer medical use. It has been demonstrated that combination therapy with immunomodulators, such as methotrexate or azathioprine, increases the effectiveness of anti-TNF retailers. This technique can improve medication durability and lessen immunogenicity. However, a vigilant threat-gain appraisal is required because of the increased risk of infections and cancers. According to our analysis, people with competitive disease or those with advanced antibodies against anti-TNF retailers benefit most from aggregate therapy.

The findings of this systematic evaluation and meta-analysis have crucial scientific implications. Infliximab and adalimumab should be taken into consideration as first-line alternatives for maintaining remission in Crohn's disease due to their better efficacy and set-up safety profiles. Long-term, real-global research is needed to verify the sturdiness of remission and lengthy-time period safety of those sellers. Additionally, exploring personalized remedy methods primarily based on pharmacogenomics and biomarkers ought to enhance therapeutic effects. This comprehensive assessment underscores the superior efficacy of infliximab and adalimumab, whilst highlighting the need for similar studies on other similar agents. Optimizing treatment techniques through TDM, mixed strategy, and customized techniques might be critical in improving long-term results for sufferers of CD.

Limitations

Although the study investigated the right outcomes and measures for analysis and assessment, it had several limitations. Firstly, despite rigorous screening and quality assessment, some studies included in the review had a “high” risk of bias. Secondly, we used study characteristics in consideration but did not consider methodological characteristics of studies. One of the limitations of the study was the significant variations in sample sizes. A high incidence reported for a study with a small sample size, and vice versa, offers a greater variability in the studies, which affects the heterogeneity, ultimately decreasing the reliability and the accuracy of the statistical tests applied. Several studies have demonstrated that the results of the final analysis can be significantly altered when population demographics are sub-grouped into effect sizes. Within-group comparisons were established regardless of patient age, race, and ethnicity. The test for variability among the studies also yielded large values for heterogeneity. This was due to the statistical limitation of the individual studies and the possible overlap of patient populations in multiple studies. Finally, the data was taken globally and not from one region.

Conclusion

The current study investigated the efficacy and safety of anti-TNF agents among CD patients by synthesizing data from 10 randomized studies through systematic review and meta-analysis. The results show that there is a wide range of outcomes, such as CDAI scores, CR, SES-CD, and TEAEs. Further research is required for future research goals, clinical management techniques, and policy development by offering evidence-based guidelines for the epidemiology and clinical outcomes of these problems.

Comment [S17]: weak and general

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