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Aliment Pharmacol Ther. Author manuscript; available in PMC 2021 May 01.

Published in final edited form as:

Aliment Pharmacol Ther. 2020 May ; 51(9): 831–842. doi:10.1111/apt.15685.

SYSTEMATIC REVIEW AND META-ANALYSIS: EFFICACY AND SAFETY OF EARLY BIOLOGIC TREATMENT IN ADULT AND PAEDIATRIC PATIENTS WITH CROHN'S DISEASE

Ryan Ungaro[1], **Saurabh Aggarwal**[2], **Ozlem Topaloglu**[2], **Wan-Ju Lee**[3], **Ryan Clark**[3], **Jean-Frederic Colombel**[1]

[1]The Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, United States

[2]NOVEL Health Strategies, Bethesda, MD, United States

[3]AbbVie Inc., Health Economics and Outcomes Research, North Chicago, IL, United States

SUMMARY

Background—There is an increasing body of evidence showing that earlier use of biologics improves clinical outcomes in Crohn's disease (CD).

Aim—To perform a systematic review and meta-analysis to assess the impact of early biologic use in the treatment of CD.

Methods—PubMed and Embase databases were searched for English language papers and conference abstracts published through April 30, 2019. Studies were selected for inclusion if patients initiated biologics within 2 years of a CD diagnosis or if earlier biologics use (top-down) was compared to a conventional step-up strategy. Random-effects meta-analyses were conducted to compare clinical remission (CR), relapse and endoscopic healing rates between early biologic treatment (<2 years of disease duration or top-down treatment strategy) and late/conventional treatment (biologic use after >2 years of disease duration or conventional step-up treatment strategy).

Results—A total of 3,069 records were identified, of which 47 references met the selection criteria for systematic review. A total of 18,471 patients were studied, with a median follow-up of 64 weeks (range 10–416). Meta-analysis found that early use of biologics was associated with higher rates of clinical remission (OR 2.10 [95% CI: 1.69–2.60], n=2763, P<0.00001), lower relapse rates (OR 0.31 [95% CI: 0.14–0.68], n=596, P=0.003) and higher mucosal healing rates (OR 2.37 [95% CI: 1.78–3.16], n=994, P<0.00001) compared to late/conventional management.

Correspondence: Ryan Ungaro, 17 E 102nd St 5th Floor, New York, NY 10029, ryan.ungaro@mssm.edu.

AUTHORSHIP

Guarantor of article: Ryan Ungaro

Author contributions: Dr. Ungaro, Dr. Lee, Dr. Clark, and Dr. Colombel evaluated the literature review and meta-analysis results and provided revisions/comments to the manuscript content. Dr. Aggarwal supervised the literature review and meta-analysis execution and reviewed revisions/comments to the manuscript content. Dr. Topaloglu conducted the literature review and meta-analysis and addressed revisions/comments to the manuscript content. All authors approved the final version of the article, including the authorship list.

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Conclusions—Early biologic treatment is associated with improved clinical outcomes in both adult and paediatric CD patients, not only in prospective clinical trials but also in real-world settings.

Keywords

Crohn's disease; meta-analyses; biologics; inflammation; outcomes research

INTRODUCTION

Crohn's disease (CD) is a chronic, disabling, and progressive inflammatory disease of the gastrointestinal tract[1–3]. Chronic inflammation is associated with accumulation of tissue damage that can lead to disease complications such as strictures, fistulae and surgical resections[4–6]. Up to half of patients with CD will experience a disease complication requiring surgery within 10 years of diagnosis[7].

The treatment paradigm has shifted to a treat-to-target approach in CD in which endoscopic healing is paramount in order to improve remission rates and long-term risk of complications[8]. Despite their higher efficacy, biologics are often used as a later line of therapy for Crohn's disease (CD), after steroids, 5-ASA or thiopurines[9,10]. There is an increasing volume of evidence suggesting that early use of biologics can improve rates of remission and disease complications[11–17]. Despite these data, the rates of early adoption of biologic therapy are quite low in real world practice[18]. Therefore, we conducted a systematic review and meta-analysis of the current available data on the impact of early biologic use in CD.

MATERIALS AND METHODS

Study Identification

A systematic review of English language abstracts in the following databases was performed per a pre-specified and clearly defined PRISMA guidelines-based protocol through April 30, 2019: Medline, Medline In-Process and Embase. Search terms comprised combinations of free-text and medical subject heading (MeSH) terms. The criteria for screening of the articles were as follows:

- Population: All patients with Crohn's disease (e.g. "Crohn's Disease" [MeSH])
- Interventions of interest: Adalimumab, Infliximab, Certolizumab pegol, Natalizumab, Vedolizumab, Ustekinumab, or any combinations of these treatments
- Early treatment related terms: "early treatment", "earlier treatment", "disease duration", "late treatment", "top down"
- Study type of interest: All types of studies except case reports and case series
- Relevant conference proceedings, Internet resources and backward snowballing (bibliographic reference lists of any identified systematic reviews and meta-analyses were searched)

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Study Selection

Studies were excluded if they did not include patients with disease duration less than 2 years. All titles and abstracts were reviewed by two co-authors to determine if they met the study screening criteria (Level 1 screen); those selected in the first screen underwent a full text review for relevance (Level 2 screen). For quality control, a third individual manually checked the screening criteria based on titles and abstracts for all included and excluded studies. For each eligible study, the relevant data were extracted in duplicate and independently verified with the original sources. Outcomes included clinical remission (CR), corticosteroid free clinical remission (CSFR), deep remission, endoscopic healing, relapse rate, hospitalization rate, complications (defined as progression to strictures and/or fistulas/abscess), IBD-related surgeries, cost effectiveness and safety in adult and paediatric populations.

Meta-Analysis

A random-effects meta-analysis (Cochrane RevMan 5.3) was conducted to compare efficacy of early with late or conventional treatment with biologics. Early biologic treatment was defined as treatment initiated within 2 years of disease diagnosis or “top-down” therapy where biologics were initiated prior to oral immunosuppressants. Late/conventional treatment was defined as treatment initiated after 2 years of disease duration or conventional step-up management (i.e., use after oral immunosuppressants). Data from clinical trials and observational studies were pooled and analysed in meta-analysis if similar criteria were used to define study populations, outcomes and measurement timing. The late/conventional group data was pooled if there were data for two or more disease durations (e.g. 2–5, 5–10 and >10 years). For efficacy, pooled odds ratios (OR) for CR, relapse rates and mucosal healing (MH) rates were assessed using the Mantel Haenszel (M-H) method. The analysis was conducted for overall, adult and paediatric patient groups, respectively, as appropriate. Sensitivity analyses were conducted by excluding observational studies and use of biologics in combination with immunomodulators (IM) or immunosuppressants (IS). Inter-study heterogeneity was assessed with Cochrane Q and I^2 tests (with significant heterogeneity indicated by $P<0.10$ or $I^2 \geq 50\%$). A quality assessment for observational studies and post hoc analyses was conducted for studies included in the meta-analysis using the New-Castle Ottawa Scale[19]. For RCTs, risk of bias assessment was conducted using the tool developed by UK’s National Institute for Health and Care Excellence (NICE; https://www.nice.org.uk/process/pmg24/chapter/clinical-effectiveness).

RESULTS

Search Results

A total of 3069 records were identified and screened. Forty-seven studies were included after applying inclusion and exclusion criteria including three randomized controlled trials (RCTs) (n=499 patients, Table 1A), 12 post hoc analyses of RCTs (n=6758 patients, Table 1A), 31 observational studies (n=14237 patients, Table 1B) and one cost-effectiveness analysis model met the inclusion criteria (Figure 1). Among the 31 observational studies, eight were prospective studies (n=3905 patients), 18 were retrospective studies (n=5797 patients), and five studies (n=4535 patients) lacked details of study design. A total of 18,471

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patients were studied, with a median follow-up duration of 64 weeks (range 10–416). Twenty-eight studies were conducted in adult patients, 16 studies were conducted in paediatric patients and three studies were conducted in adult and paediatric patients. In most studies, use of biologics within 1 year or 2 years of disease diagnosis was defined as "early" biologic use. Seven studies were conducted in newly diagnosed patients. Of the 47 studies that met inclusion/exclusion criteria, sixteen studies met the criteria for meta-analysis (based on comparative design, outcomes definitions, follow up period). The range of quality assessment score for observational studies and post analyses included in the meta-analysed study was 5–8 (out of maximum score of 8), indicating a high quality of the included studies (Supplementary Table S6). The two RCTs included in the meta-analysis also were of relatively high quality (Supplementary Table S7).

Systematic Review Results: Efficacy Outcomes

Efficacy in Adults—Eight studies reported higher clinical remission rates (Table 2) with early treatment (38%−81.5%) versus late/conventional treatment (14% −80%)[11,12,15,17,20–23]. In an RCT, the CR rates for early versus late/conventional were 60.6% vs. 35.9% (p=0.0062)[15]. In a large pooled post hoc analysis of ten trials, the CR rates were significantly higher in the shorter disease duration groups (<1 year: 45.8%, ≥1–<2 years: 31.0%; 2–≤5 years: 23.1%; >5 years: 23.6%, p = 0.026)[21]. In two other post hoc analyses, the CR rates in early versus late treatment groups were 56% vs 58% (n=945, <2 vs 2–5 years at 20 weeks, CR was defined as HBI≤4)[20] and 46% vs 28% (n=777, <2 vs 2–≤5 years at 26 weeks)[11]. Two large observational studies reported similar trend in higher remission rates in early versus late/conventional treatment group[22,23].

Two studies reported deep remission rates of 33–36.9% with early biologic treatment compared to 10–23% with late/conventional management[16,24,25]. In a 3-year follow up study, patients with early CD who had deep remission were less likely to have disease progression[24].

Nine publications showed that early treatment leads to better mucosal healing rates (29.0–72.0%) compared to late/conventional treatment (12.9–62.2%)[15,17,23,26–31]. In an RCT the rate of mucosal healing was 45.9% vs 30.3% (n=244, p=0.010) in tight control vs conventional treatment group[29]. In a long term follow-up of an RCT, significantly higher MH rates of 72.0% compared to 28.6% were observed in early versus late/conventional treatment group[30]. Similar trends were observed in five observational studies in a real-world setting[23,26,28,31].

In a post-hoc analysis of hospital admissions (measured week 4 through week 56), hospitalization-free rates were higher although not significant, in patients with shorter disease duration (<2 yr 93%; 2–5 yr 90%; >5 yr 86%)[11]. One study reported significantly lower relapse rates in early versus late/conventional treatment group[32]. Three studies observed that compared to late/conventional treatment, early treatment with biologics reduced bowel strictures and damage[33–35]. One RCT, six observational studies and one post-hoc analysis showed significantly lower rates of intestinal surgery in early versus late/conventional treatment group[15,34,36–40]. However, one study showed that early treatment did not reduce the rate of IBD complications in early versus late/conventional treatment group[41].

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Four additional studies showed potential value of early treatment with lower loss of efficacy[42], decreased time to treatment failure[43], slower rate of disease progression[44] and improvement in mean HBI scores[45]. A small study showed 91% CR rate in an early treatment group[46]. *See* Supplementary Table S1 *for efficacy in adults*.

Efficacy in Paediatric Patients—Five studies in paediatric patients reported significantly higher CR rates in early treatment groups (62%−85%) versus late/conventional treatment (45.5–60.3%) (Table 3)[47–51]. Three studies reported lower relapse rates in early (16.1%−23.1%) versus late/conventional treatment groups (50.0%−61.5%)[52–54]. Two small studies reported mucosal healing rates of 45% vs 32%[48] and 65% vs 62%[28] when comparing early versus late/conventional treatment group. Two studies reported surgery outcomes, one showed lower rates at 1 year with early biologics compared to early immunosuppressants (2.94% vs 1.61%)[53] and the other study showed that 10-year risk for first bowel surgery was 26%[55]. Two studies provide evidence for lowering risk of penetrating complications with early biologic treatment[49,55], though one study showed that early treatment might not lower risk of stricturing complications[49]. Five studies showed value of early treatment for loss of response[56], better height[57], higher PCDAI score[58], prolonged response rate[59] and sustained primary response[60]. In one observational study outcomes were similar with accelerated step-up and conventional management[61]. *See* Supplementary Table S2 *for efficacy in paediatric patients*.

Cost Effectiveness Outcomes—One study was found that assessed cost effectiveness of early (within 2 years of CD diagnosis) versus late (more than 2 years after diagnosis) treatment with biologics[62]. In a Canadian setting, a Markov model was developed to simulate the progression of a hypothetical cohort of patients with CD after the initiation of either infliximab or adalimumab. The model compared the lifetime cost-effectiveness of early versus late initiation of anti-TNF therapy using published loss of response rates. The model results show that over a patient's lifetime, early initiation of infliximab yielded an additional 1.02 quality-adjusted life years (QALYs) and saved $18,054 compared to late initiation of infliximab. Similarly, early initiation of adalimumab yielded an additional 0.74 QALYs and saved $18,526 compared to late initiation of adalimumab. At a willingness-to-pay threshold of $50,000 per QALY, early initiation of both infliximab and adalimumab had a 68% chance of being cost-effective, while late initiation had a 32% chance of being cost-effective (Supplementary Table S3).

Safety—In a large pooled analysis (n=2207), the overall rate of adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation and malignancies were similar between disease duration groups[21]. Serious infection rates were lower in those treated early versus patients treated within 2–5 yrs and >5 yrs of CD diagnosis (4.2 vs 8.7 and 8.3/100 PY)[21]. In an open label 2-year randomized control trial, the rate of serious adverse events were similar in early combined immunosuppression and conventional management groups (30.8% versus 25.3%, p=1.0)[15]. In a post hoc analysis of an RCT, the incidence of serious adverse events was lowest with disease duration less than 2 years (14% in <2 years group, versus 22.7% and 22.0% in 2–5 years and ≥5 years group, respectively)[11]. In a post hoc analysis of a randomized maintenance trial there were more serious adverse

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events with increasing disease duration (SAEs < 1 year: 0%, ≥1 to <2 years: 0%, ≥ 2 to <5 years: 6.7% and ≥ 5 Years: 6.8%)[12]. Overall across studies, the serious infection or malignancy rates were similar or better in early compared to late biologic groups. *See* Supplementary Table S4 *for safety outcome*s.

Meta-Analysis: Efficacy Outcomes

Clinical Remission—Eight publications reporting clinical remission in adult[12,15,17,21,23] and paediatric[47,50,51] patients were included for meta-analysis. Overall higher rates of CR at 26–52 week ranged from 48–78% in early biologic treatment compared to 35–57% for late or conventional management or step-up (Figure 2). The overall pooled remission rates in adult patients at 26 week were 62.3% (95% CI: 58.2%−66.2%) and 34.2% (95% CI: 32.2% −36.3%) in early biologic treatment versus late/conventional, respectively (n=2763). For the overall patient population, the OR for remission with early biologic treatment was 2.10 (95% CI: 1.69–2.60, n=2763, P<0.00001, Figure 2) compared to the late/conventional treatment. The results were similar in adult and paediatric patient subgroups. In adults, the OR for remission at 26 week with early biologic treatment was 1.99 (95% CI: 1.59–2.50, n=2546, P<0.00001, Figure 2). In the paediatric patient subgroup, the OR for remission at ~52 week with early biologic treatment was 3.07 (95% CI: 1.59–5.94, n=217, P=0.0009, Figure 2). The OR were similar for studies using only biologics (no IM/IS; Supplementary Figure 2) and using only RCTs (Supplementary Figure 3). Of the publications that included clinical remission, three reported CSFR in adult and paediatric patients[15,23,47]. The OR for CSFR with early biologic treatment was 3.83 (95% CI: 2.60–5.63, n=720, P<0.00001, Supplementary Figure 1).

Relapse Rate—Four publications reporting relapse rates in adult[32] and paediatric [52–54] patients were included for meta-analysis. For the overall patient population, the OR for relapse with early biologic treatment was 0.31 (95% CI: 0.14–0.68, n=596, P=0.003, Figure 3) compared to late/conventional treatment. In the paediatric patient subgroup, the OR for relapse at 1 year with early biologic treatment was 0.18 (95% CI: 0.07–0.43, n=105, P=0.0001 Figure 3). Subgroup analysis for adults was not feasible because only one study reported relapse rates comparing early versus late treatment.

Mucosal Healing Rate—Seven publications reporting mucosal healing (MH) rates at 12 week to 4 years in adult[15,17,23,27,29,31] and paediatric[28] patients were included for meta-analysis. For the overall patient population, the OR for MH rate with early biologic treatment was 2.37 (95% CI: 1.78–3.16, n=994, P<0.00001, Figure 4) compared to late/ conventional treatment. In the adult patient subgroup, the OR for MH rate with early biologic treatment was 2.44 (95% CI: 1.82–3.27, n=981, P<0.00001, Figure 4). Subgroup analysis for paediatrics was not feasible because only one study reported MH rates comparing early versus late treatment. The results for overall OR were similar for only RCTs (Supplementary Figure 4).

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DISCUSSION

To our knowledge, this is the most comprehensive systematic review and meta-analysis on outcomes of early biologic use in CD. The meta-analysis findings confirm our hypothesis that early use of biologics in patients with moderate-severe CD leads to statistically and clinically better clinical remission (OR 2.10 [95% CI: 1.69–2.60], n=2763, P<0.00001), relapse (OR 0.31 [95% CI: 0.14–0.68], n=596, P=0.003) and mucosal healing (2.37 (95% CI: 1.78–3.16, n=994, P<0.00001) rates compared to late/conventional treatment. We observed that early biologic treatment is associated with improved clinical outcomes (clinical remission, corticosteroid free remission, mucosal healing, relapse rate, hospitalization rate, complications and surgeries) not only in prospective clinical trials but also in real-world settings. Lower rates of hospitalizations and surgery suggest there may be decreased resource use with early use of biologics with one study suggesting that early biologic use is cost-effective.

Furthermore, multiple sensitivity analyses using data only from RCTs, studies with CSFR and by excluding studies that used biologics in combination with IM/IS confirmed our hypothesis of value of early treatment with biologics in CD. Using data only from RCTs, the OR for clinical remission with early use of biologics was 1.95 (n=564, 95% CI:1.52–2.49, P<0.00001) versus late/conventional treatment. The OR was similar for mucosal healing rates in RCTs (OR 2.21 [95% CI: 1.34–3.64], n=241, P=0,002). Using studies without any combination treatment with IM/IS, the OR for clinical remission was 2.09 (n=2033, 95% CI:1.56–2.80, P<0.00001). The OR for pooled CSFR rate for early biologic use versus late/conventional treatment was 3.83 (n=146, 95% CI:2.60–5.63, P<0.00001).

A review comparing trials in early CD and rheumatoid arthritis (RA) suggests that the concept of early intervention in other immune-mediated diseases such as RA is well established and there might be lessons to learn from other chronic inflammatory diseases[63]. This systematic review and meta-analysis supports findings and hypotheses from several other narrative reviews and overviews[3,63–69].

Despite this evidence, the real-world utilization of biologics is still low in early disease CD patients[18]. There is a need to educate clinicians, policymakers and payer stakeholders to improve access and utilization of biologics in early disease settings, especially for patients with moderate to severe CD. Though our study supports early use of biologics, there are some limitations of our review. First, the outcome definitions slightly differed across some studies. Second, the follow up duration varied across trials. Third, the vast majority of data were on anti-TNF agents alone so our results may not be generalizable to other therapies. There are still limited data on longer-term outcomes such as prevention of complications, bowel damage, disability, and durability on drug. Further studies should continue to understand if early intervention with a more treat to target / tight control approach impacts long term outcomes, and if the improved response rates with shorter disease duration applies to all classes of biologics/targeted agents.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENT

Declaration of personal interests

Jean-Frederic Colombel has served as a consultant or advisory board member for AbbVie, Amgen, Boehringer-Ingelheim, Celgene Corporation, Celltrion, Enterome, Ferring, Genentech, Janssen and Janssen, Medimmune, Merck & Co., Pfizer, Protagonist, Second Genome, Seres, Shire, Takeda, Theradiag; a speaker for AbbVie, Ferring; speaker's bureau for Amgen. Dr. Colombel has received research grants from Takeda, Johnson and Johnson, and is a stockholder of Intestinal Biotech Development and Genefit.

Ryan Ungaro is supported by a Career Development Award from the Crohn's and Colitis Foundation and an NIH K23 Career Development Award (K23KD111995-01A1). He has served as an advisory board member or consultant for Janssen, Pfizer, and Takeda and received research grants from AbbVie, Boehringer Ingelheim, and Pfizer.

Saurabh Aggarwal and Ozlem Topaloglu are employees of NOVEL Health Strategies, which received payment from AbbVie to assist with the literature review.

Ryan Clark and Wan-Ju Lee are employees of AbbVie and may hold AbbVie stock.

Declaration of funding interests

Financial support for the study was provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication. All authors contributed to the development of the publication and maintained control over the final content.

Medical writing support was provided by Sushil Kumar, of NOVEL Health Strategies, Columbia, MD, USA; this support was funded by AbbVie.

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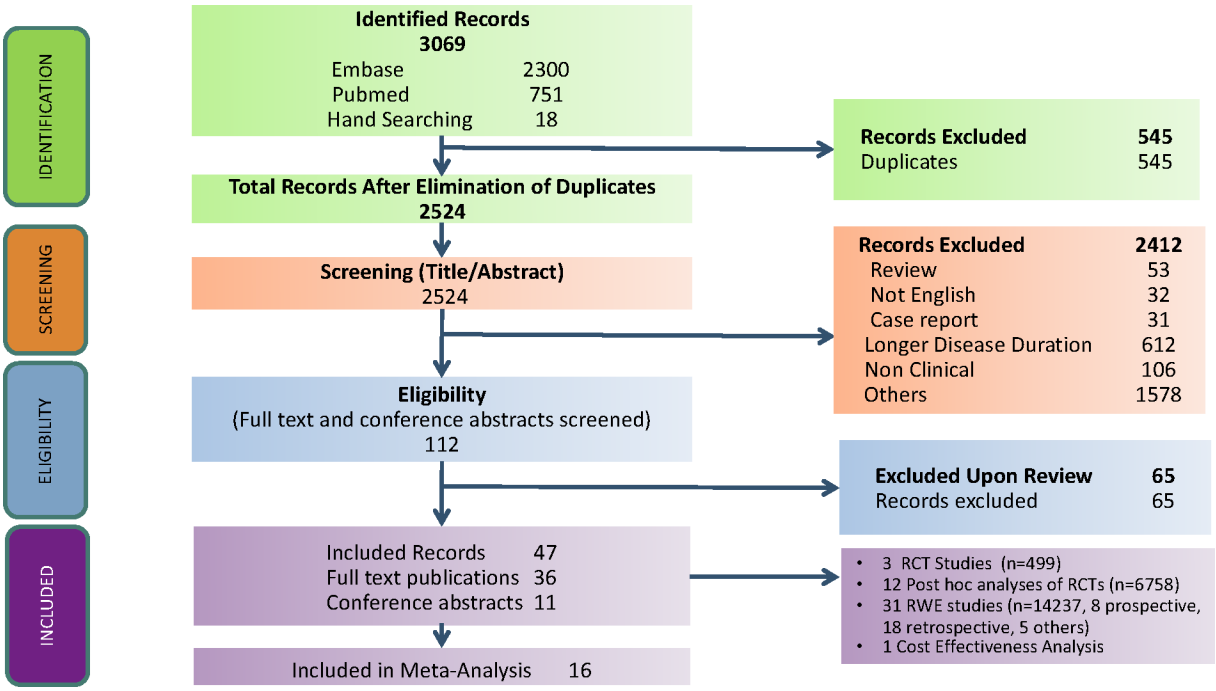

Figure 1.
PRISMA Diagram of Study Screening and Selection

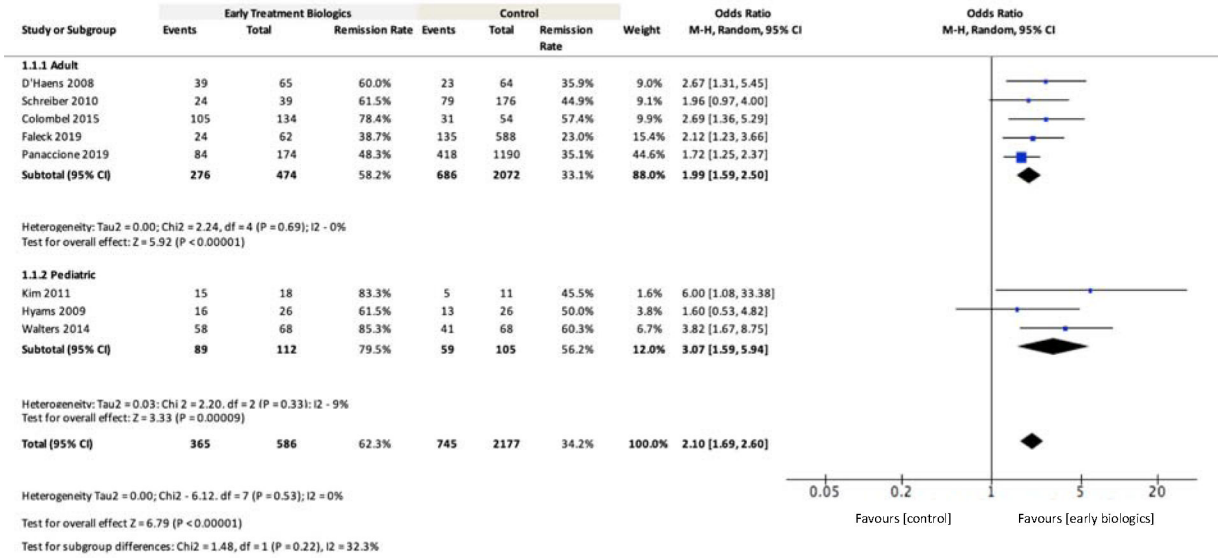

Figure 2.

Meta-Analysis Comparing Clinical Remission Rates for Early Biologic versus Late/ Conventional Treatment

Notes: Definition of clinical remission: three studies used CDAI<150[12, 17,21]; one study used CDAI<150 plus no bowel resection and no steroid use[15]; two studies used PCDAI≤10[50,51]; one study used corticosteroid free remission and PCDAI ≤10 at 1 year after diagnosis without luminal resection[47]; one study did not provide definition of clinical remission[23]

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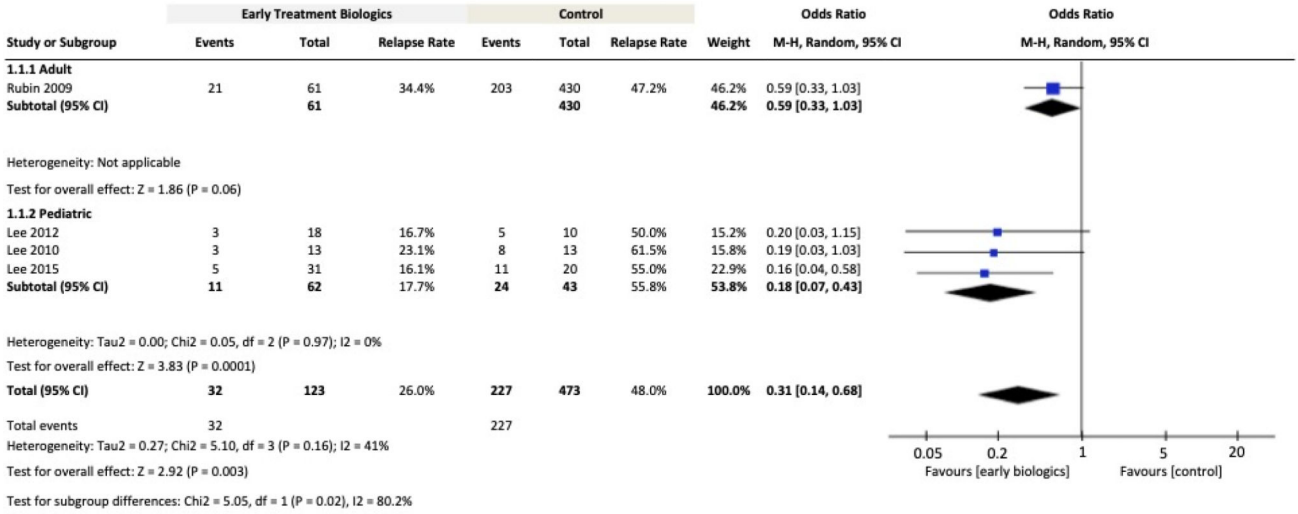

Figure 3.

Meta-Analysis Comparing Relapse Rates for Early Biologic versus Late/Conventional Treatment

Definition of disease relapse: One study used increase in CDAI≥70 and an absolute CDAI>220[32]; three studies used PCDAI>10[52–54]

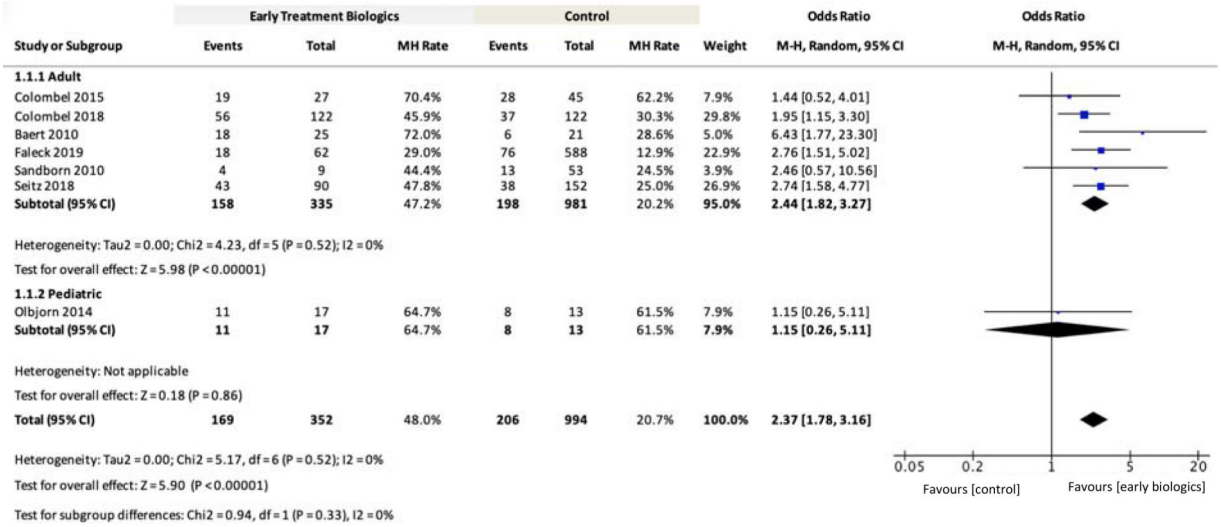

Figure 4.

Meta-Analysis Comparing Mucosal Healing (MH) Rates for Early Biologic versus Late/ Conventional Treatment

Definition of endoscopic healing: one study used SES-CD=0[15]; one study used CDEIS<4 and absence of deep ulcers[29]; one study used absence of any mucosal ulcers (including aphthous ulcers)[17]; one study used absence of mucosal ulceration[27]; one study used absence of ulcers and/or erosions[23]; one study used disappearance of ulcerations, multiple erosions, bleeding and friability (grade 0 or 1)[28]; one study did not report definition[31]

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Table 1A

Study Characteristics (RCT and Post-hoc Analysis of RCTs)

Author Journal/ Conference Year	Study type	Patient	Size	Study Duration	Intervention(s)	Disease Duration Definitions for Evaluating Early Biologic Use
Panaccione, J Crohns Colitis 2019[21]	Post hoc analysis	Adult	2207	NR	ADA	< 2 yrs, 2 to 5 yrs, >5 yrs
Dulai, ECCO, 2019[39]	Post hoc analysis	Adult	1253	7 yrs	VDZ	≤2 vs. >2, ≤3 vs. >3, and ≤5 vs. >5 yrs
Reinisch, ECCO, 2009[20]	Post hoc analysis	Adult†	945	20 wks	ADA	<2 yrs, 2 to 5 yrs, >5 yrs
Schreiber, J Crohns Colitis., 2013[11]	Post hoc analysis (RCT and open label extension)	Adult	777	3 yrs	ADA	<2 yrs, 2 to <5 yrs, ≥5 yrs
Rubin, DDW, 2009[32]	Post hoc analysis	Adult	491	48 wks	ADA, PBO	2 yrs, ≥2 yrs
Schreiber, Am J Gastroenterol., 2010[12]	Post hoc analysis	Adult	425	26 wks	CER	<1 year, ≥1 to < 2 yrs, ≥2 to <5 yrs, ≥5 yrs
Colombel, Lancet, 2018[29]	RCT	Adult	244	48 wks	ADA	≤2 yrs, >2 yrs
Colombel, Aliment Pharmacol Ther., 2015[17]	Post hoc analysis	Adult	188	26 wks	AZA, IFX and AZA +IFX	≤18 mon, >18 mon
D'Haens, Lancet, 2008[15]	RCT	Adult	129	2 yrs	IFX+AZA vs AZA	Newly diagnosed
Feagan, Gastroenterology, 2014[43]	RCT	Adult	126	50 wks	IFX+MTX, IFX +PBO	<2 yrs
Yzet, ECCO, 2019[24]	Post hoc analysis	Adult	122	3.02 yrs	ADA	≤2 yrs, >2 yrs
Sandborn, DDW, 2010[27]	Post hoc analysis	Adult	123	1 year	ADA, PBO	<2 yrs, 2 to 5 yrs, >5 yrs
Hyams, ECCO, 2009[51]	Post hoc analysis	Paediatric	112	54 wks	IFX+IM	<2 yrs, ≥2 yrs
Colombel, Clin Gastroenterol Hepatol., 2014[16]	Post hoc analysis	Adult	69	1 year	ADA	<2 yrs, 2 to 5 yrs, >5 yrs
Baert, Gastroenterology., 2010[30]	Extension study (follow up of an RCT)	Adult	46	2 yrs	IFX+AZA vs AZA	Newly diagnosed

ADA: adalimumab, IFX: infliximab; PBO: placebo; AZA: azathioprine; CER: certolizumab; IM: immunomodulators; IS: immunosuppressants NR: Not reported, VDZ: Vedolizumab; yrs: years.

†Assumed to be adult.

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Table 1B

Study Characteristics (Observational Studies)

	Author Journal/ Conference Year	Design	Patient	Size	Study Duration	Intervention(s)	Disease Duration Definitions for Evaluating Early Biologic Use
	Rubin, Inflamm Bowel Dis., 2012[36]	Observational	Adult	3750	2 yrs	'Step-Up', IS-to-TNF', 'Early-TNF'	≤30 days
	Loftus, Inflamm Bowel Dis., 2019[45]	Observational study	Adult	1980	1 year	ADA	<2 yrs, 2–<5 yrs 5–<10 yrs, ≥10 yrs
	Ogata, J Crohns Colitis., 2016[22]	Observational	Adult	1693	24 wks	ADA	<2, 2 to 5, 5–10, 10–20, >20 yrs
†	Kerur, CGH 2018[55]	Observational	Paediatric	1442	10 yrs	Anti-TNFs	<3 months
	Kugathasan, Lancet., 2017[49]	Observational	Paediatric	913	3 yrs	IFX, ADA, IM	Newly diagnosed
	Faleck, CGH, 2019[23]	Observational	Adult	650	6 months	VDZ	≤2 yrs, >2–≤5 yr, >5 yrs
	Walters, Gastroenterology., 2014[47]	Observational	Paediatric	552	1 year	Anti-TNF or IM (not specified)	Newly diagnosed
	Safroneeva, Aliment Pharmacol Ther., 2015[33]	Observational	Adult	540	15 mon	IM and/or TNF antagonists	<2 yrs
	Oh, PLoS One., 2017[37]	Observational	Adult	507	NR	Anti-TNF or IM	<2 yrs
	Safroneeva, ECCO, 2013[34]	Observational	Adult	450	15 mon	IM or Anti-TNF	<2 yrs (adjusted for diagnostic delay)
	Seitz, UEG 2018[31]	Retrospective chart review	Adult	242	2 years	Anti-TNFs	<2 and >2 years
	Church, Inflamm Bowel Dis., 2014[57]	Observational	Paediatric	195	8 yrs	IFX	Median 1.6 (0.6–3.0) yrs
	Ma, Inflamm Bowel Dis., 2016[38]	Observational	Adult	190	154 wks§	IFX, ADA	<2 yrs
	Kotze, Digestion., 2015[42]	Observational	Adult	175	NR	ADA, IFX	<2 yrs
	Chambrun, ECCO, 2015[40]	Observational	Adult‡	153	44 mon (mean)	IFX	< 18 mon
	Yu, Mediators Inflamm., 2015[26]	Observational	Adult and Paediatric	106	10 wks	IFX	22.2 mon (remission group)
	Wauters, Inflamm Bowel Dis., 2017[61]	Observational	Paediatric	91	5 yrs	Anti-TNF (not specified)	0.2 (0.1–0.5) yrs
	Panchal, DDS 2019[44]	Retrospective chart review	Adult and Paediatric	88	NR	Anti-TNFs w/o IM	< 2, 3–10, 11–20, 21–30 and >30 yrs
	Nuij, J Crohns Colitis., 2015[41]	Observational	Adult and Paediatric	85	41.4 mon§	IFX, IFX+ADA, ADA	Newly diagnosed, <16 mon
†	Bolia, J Pediatr Gastroenterol Nutr., 2017[56]	Observational	Paediatric	73	1 year	IFX w/o IM in early versus non-early CD	Time interval between diagnosis and introduction of IFX (mon): Loss of response group: 28 (4–90); No loss of response group: 12.5 (1–121)
	Lee, J Pediatr Gastroenterol Nutr., 2015[53]	Observational	Paediatric	51	3 yrs	AZA+IFX (top-down) versus step-up	10.8 ± 9.0 (step-up) mon vs 1.0 ± 0.5 (top-down) mon

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	Author Journal/ Conference Year	Design	Patient	Size	Study Duration	Intervention(s)	Disease Duration Definitions for Evaluating Early Biologic Use
†	Kato, Gut Liver., 2011[46]	Observational	Adult	43	14 wks	IFX	3.26±5.63 mon
	Ling, DDS, 2018[60]	Retrospective chart review	Paediatric	43	48 months	IFX	<3 months and ≥ 3 months
†	Nuti, J Crohns Colitis., 2015[48]	Observational	Paediatric	37	2 yrs	IFX, ADA	13 ± 16 (0.5–63) mon
†	Olbjørn, Scand J Gastroenterol., 2014[28]	Observational	Paediatric	36	2 yrs	IFX	Newly diagnosed
	Lee, World J Gastroenterol., 2010[54]	Observational	Paediatric	36	2 yrs	AZA+IFX, AZA	Newly diagnosed
	Kim, Acta Paediatr., 2011[50]	Observational	Paediatric	29	1 year	AZA+IFX (top-down) vs step-up	Step-up: 11.5 ± 7.4; Top-down: 0.8 ± 0.6
	Lee, Pediatr Gastroenterol Hepatol Nutr., 2012[52]	Observational	Paediatric	28	3 yrs	AZA+IFX (top-down) versus step-up	Duration from the initial diagnosis to IFX infusion: Step-up: 49.6±5.2; Top-down: 1.8±2.4 wks
†	Wewer, J Pediatr Gastroenterol Nutr., 2006[59]	Observational	Paediatric	24	3 yrs	IFX (episodic)	26 (range 0.7–93) mon
	Lionetti, Aliment Pharmacol Ther., 2003[58]	Observational	Paediatric	22	18 wks	IFX	<1 year
	Echarri, DDW 2011[35]	Observational	Adult	13	6 mon	ADA, IFX	<2 yrs
	Beilman, CGH, 2018[62]	Model	Adult	N/A	Lifetime	ADA, IFX	<2 yrs

ADA: adalimumab, IFX: infliximab; PBO: placebo; AZA: azathioprine; CER: certolizumab; IM: immunomodulators; IS: immunosuppressants NR: Not reported, VDZ: vedolizumab.

Studies marked

† were not comparative studies

‡ Assumed to be adult

§ Median follow up.

Note: Nuij 2015 had 66 Crohn's disease [CD], 16 ulcerative colitis [UC], 3 inflammatory bowel disease unclassified [IBDU]) patients, NR is not reported

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Table 2

Clinical Remission in Adults

Study (year)	N	Outcome	Timepoint	Results
Panaccione 2019[21]	2207	CR (CDAI<150)	26 weeks	<1 year: 57.8% (n=45) ≥1–<2 years: 35.8% (n=67) 2–≤5 years: 34.2% (n=196) >5 years: 33.7% (n=768) p=0.013
Ogata 2016 †[22]	1693	CR (CDAI < 150)	24 weeks	<2 versus 2 to <5 years: OR 0.84 (0.26–2.65) p=0.76 <2 versus 5 to <10 years: OR 0.28 (0.10–0.80) p=0.02 <2 versus 10 to <20 years: OR 0.27 (0.10–0.75) p=0.01 <2 versus >20 years: OR 0.24 (0.08–0.71) p=0.01
Schreiber 2010[12]	425	CR (CDAI ≤ 150)	26 weeks	<1 Year: 68.4% (n=19) ≥1 to <2 years: 55.0% (n=20) ≥2 to <5 years: 46.7% (n=45) ≥5 Years: 44.3% (n=131)
Faleck 2019[23]	650	CR (complete resolution of all CD related symptoms) And CSFR (tapering off steroids completely, achieving clinical remission, and no repeat steroid prescription within 4 weeks of tapering)	26 weeks	CR ≤ 2 years vs >2 years: 38% vs 23% (p<0.05) CSFR ≤ 2 years vs >2 years: 43% vs 14% (p<0.05)
Schreiber 2013[11]	777	CR (CDAI < 150)	26 weeks	<2 years: 46% (n=56) ≥2 to <5 years: 28% (n=95) ≥5 years: 32% (n=366)
			52 weeks	<2 years: 43% (n=56) ≥2 to <5 years: 30% (n=95) ≥5 years: 28% (n=366)
Reinisch 2009[20]	945	CR (HBI ≤ 4)	20 weeks	<2 years: 58% (n=62/107) 2–5 years 56% (n=121/217) >5 years 50% (n=309/621)
Colombel 2015[17]	188	CR (CDAI < 150) and Composite Outcomes	26 weeks	IFX+AZA Combination early versus non-early: CR: 81.5% vs 80.0% p<0.05 CR+MH: 63% vs 53.3% p<0.05 CR+CRPnorm: 76.5% vs 55.6% p>0.05 CR+MH+CRPnorm: 64.7% vs 44.4% p<0.05
D'Haens 2008[15]	129	CSFR (CDAI < 150 and absence of corticosteroid treatment, and no intestinal resection)	26 weeks	Early combined immunosuppression group vs conventional management: •60.6% (n=39/65) vs 35.9% (n=23/64) •Δ=24.1% (95% CI 7.3–40.8, p=0.0062)
			52 weeks	Early combined immunosuppression group vs conventional management: •61.5% (n=40/65) vs 42.2% (n=27/64) •Δ=19.4% (95% CI 2.4–36.3, p=0.0278)

† Study only reported odds ratios.

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Table 3

Clinical Remission in Paediatric Patients

Study (year)	N	Outcome	Timepoint	Results
Kim 2011[50]	29	CR (PCDAI<10)	1 year	Step-up: 5 of 11 Top-down: 15 of 18
Hyams 2009[51]	52	CR (PCDAI≤10)	54 weeks	<2 years: 62% (n=26) ≥2 years: 50% (n=26)
Walters 2014[47]	136	CR (Corticosteroid free and PCDAI≤10)	1 year	Early anti-TNF: 85% (n=68) Early IM: 60% (n=68)
Nuti 2015[48]	37	CR (absence of symptoms related to CD and PCDAI ≤10)	2 year	Early (<1 year) group: 70.6% Late (>1 year) group: 70%
Kugathasan 2017[49]	175	Corticosteroid free remission rate	26 weeks	71% (124/175)