Frequency and Effectiveness of Empirical Anti-TNF Dose Intensification in Inflammatory Bowel Disease: Systematic Review with Meta-Analysis

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Abstract: Loss of response to antitumor necrosis factor (anti-TNF) therapies in inflammatory bowel disease occurs in a high proportion of patients. Our aim was to evaluate the loss of response to anti-TNF therapy, considered as the need for dose intensification (DI), DI effectiveness and the possible variables influencing its requirements. Bibliographical searches were performed. Selection: prospective and retrospective studies assessing DI in Crohn’s disease and ulcerative colitis patients treated for at least 12 weeks with an anti-TNF drug. Exclusion criteria: studies using anti-TNF as a prophylaxis for the postoperative recurrence in Crohn’s disease or those where DI was based on therapeutic drug monitoring. Data synthesis: effectiveness by intention-to-treat (random effects model). Data were stratified by medical condition (ulcerative colitis vs. Crohn’s disease), anti-TNF drug and follow-up. Results: One hundred and seventy-three studies (33,241 patients) were included. Overall rate of the DI requirement after 12 months was 28% (95% CI 24–32, I2 = 96%, 41 studies) in naïve patients and 39% (95% CI 31–47, 18 studies) in non-naïve patients. The DI requirement rate was higher both in those with prior anti-TNF exposure (p = 0.01) and with ulcerative colitis (p = 0.02). The DI requirement rate in naïve patients after 36 months was 35% (95% CI 28–43%; I2 = 98%; 18 studies). The overall short-term response and remission rates of empirical DI in naïve patients were 63% (95% CI 48–78%; I2 = 99%; 32 studies) and 48% (95% CI: 39–58%; I2 = 92%; 25 studies), respectively. The loss of response to anti-TNF agents—and, consequently, DI—occurred frequently in inflammatory bowel disease (approximately in one-fourth at one year and in one-third at 3 years). Empirical DI was a relatively effective therapeutic option.

Keywords: inflammatory bowel disease; Crohn’s disease; ulcerative colitis; anti-TNF-α; loss of response; dose intensification

1. Introduction

Biologic therapies have become the mainstay of treatment in inflammatory bowel disease (IBD). Antibodies targeting tumor necrosis factor-alpha (anti-TNF) have become essential in the armamentarium for the treatment of both ulcerative colitis (UC) and Crohn’s disease (CD). TNF is a key proinflammatory cytokine that plays an important role in several autoimmune disorders, including IBD. Elevated stool and mucosal TNF concentrations in UC and CD patients have been shown to correlate with the disease activity [1]. Anti-TNF drugs operate via a multitude of mechanisms: they bind and clear soluble TNF but, also, cell-bound TNF, inducing cytotoxicity on immune cells, like T-cell apoptosis [2]. They are effective at inducing symptom relief, disease remission and mucosal healing and reducing the need for surgery and hospitalizations among patients with moderate-to-severe IBD. The current clinical guidelines recommend anti-TNF agents for patients who are refractory to other treatments [3–6].
However, a considerable proportion of these patients does not respond to induction therapy (primary nonresponse) or lose response over time (secondary nonresponse or loss of response, LOR). In patients who experience LOR to a particular anti-TNF agent, dose escalation or intensification (DI), either by increasing the dose or decreasing the dosing intervals, is commonly used as a rescue strategy to regain the therapeutic effect. Nevertheless, the exact incidence and chronology of this intensification, and its efficacy, are still not well-known.

The aim of this systematic review was to evaluate the incidence of LOR (defined as the need for DI) over time and DI efficacy in regaining both the response and remission in inflammatory bowel disease. The secondary objectives were to identify the possible variables (baseline medical condition, anti-TNF therapy and time of follow-up) influencing the DI requirement and its efficacy.

2. Materials and Methods

2.1. Literature Search and Study Selection

Bibliographic searches were performed in four electronic databases (Medline, Embase, Cochrane Library CENTRAL and CINAHL) from inception up to January 2020. The search strategy (with corresponding keywords in all fields) was: “(inflammatory bowel disease OR Crohn’s disease OR ulcerative colitis) AND (infliximab OR adalimumab OR certolizumab OR golimumab OR antiTNF OR anti-TNF) AND (intensification OR escalation OR optimization OR optimisation)”. Additional hand searches were performed by the cross-referencing of eligible studies in order to identify further relevant publications. Abstracts were screened to discard duplicates. When the literature search yielded two or more studies by the same author assessing the same populations, only the most recent one was chosen, irrespective of the time interval, as it was assumed the latter published would include the most comprehensive and complete data.

The process of study selection is depicted in a flow diagram following the PRISMA statement [7]. The present systematic review was registered in PROSPERO (CRD42017073757). The selection process, data extraction and analyses were performed by two authors (LG and OPN) independently. If discrepancies occurred, consensus was reached by a third reviewer (JPG). The corresponding authors of the studies without sufficient data were contacted for additional information.

2.2. Selection Criteria

Prospective and retrospective studies assessing the LOR to anti-TNF therapy, considered as the need for DI in patients with CD and UC treated for at least 12 weeks with an anti-TNF drug, were selected for inclusion. There were no language restrictions.

Articles in which an anti-TNF was used as the prophylaxis for postoperative recurrence in CD and those where DI was based during therapeutic drug monitoring were excluded. Systematic or narrative reviews, case studies and congress abstracts were excluded from this systematic review.

2.3. Data Extraction and Quality Assessment

A predefined, pre-piloted data extraction form was used to collect the data. The variables recorded were: year of publication; study design (prospective or retrospective); age of the study population (adults ≥ 18 years and children < 18 years); type of inflammatory bowel disease (UC or CD); therapeutic regimens (infliximab (IFX), adalimumab (ADA), certolizumab-pegol, and golimumab); previous anti-TNF treatments (naïve or non-naïve); length of follow-up in months; sample size; and outcome measures (DI requirement and DI efficacy).

The Cochrane risk of bias tool [8] was used to assess the quality of the randomized controlled trials, as they were considered the most reliable method of outcome assessment. The decision was reached post-hoc after performing an exploratory mapping review and confirming the wide range of observational studies in terms of the number and design available in the literature responding to our topic of interest.
2.4. Data Synthesis and Statistical Analysis

All analyses were preplanned a priori. The primary outcomes were the DI requirement measured as the number of patients receiving a DI out of the total of patients studied and DI efficacy in the short term as the number of patients responding out of the total of patients receiving a DI, expressed as the response rate with its standard error. These outcomes were thereafter combined using the inverse variance method, providing 95% confidence intervals (CIs). The statistical significance threshold was set at $p$-value < 0.05. A random effects model was used.

The study heterogeneity was analyzed using the $I^2$ statistic: according to the $I^2$ values, the heterogeneity was considered as: not important ($I^2 < 40\%$), moderate (40–75%) and considerable (>75%). Such interpretations also adjusted for the magnitude of the effect and/or the strength of the evidence given (i.e., $p$-value < 0.1 of the $\chi^2$ test). Begg’s funnel plot [9] was used to estimate the possibility of publication bias.

Post-hoc sensitivity analyses were performed for each meta-analysis subgroup by excluding those studies that were identified as potentially introducing a critical risk of bias that could likely modify the outcome.

Data were analyzed using the Review Manager program (version 5.2).

3. Results

A total of 173 studies (including 33,241 patients) met the inclusion criteria and were finally included in the systematic review and meta-analysis (Figure 1).

![Figure 1. PRISMA flowchart of the screening and selection.](image)

The description of each included study is summarized in Table 1.

There were six randomized, placebo-controlled trials (RCTs) [10–15], 48 prospective open-label observational trials and 119 retrospective studies.

A total of 157 studies assessed the need for DI; the response rate was evaluated in 52 studies, and the remission rate was reported in 33 studies.

One hundred and one studies focused on naïve patients, and 29 evaluated non-naïve patients, while 50 studies included both naïve and non-naïve patients in their assessments. In six studies, prior anti-TNF exposure was not reported. One hundred and seven studies reported the data from IFX users and 92 from ADA users. Only five studies included patients receiving golimumab [16–20], and four studies evaluated patients receiving certolizumab [21–24]; thus, a meta-analysis was not performed.
Table 1. Studies included in the meta-analysis.

| Author and Year | Study Design | Population | Medical Condition | Anti-TNF | Prior Anti-TNF | FOLLOW up (Months) | n | N | DI Rate (%) | Intensification Regimen | Response/Remission | n' | N' | DI Efficacy (%) |
|-----------------|--------------|------------|-------------------|----------|---------------|------------------|---|---|-------------|------------------------|-------------------|----|----|---------------|
| 1 Afif 2009 [25] | P A | UC | ADA | Naïve and non-naïve | 6 | 7 | 20 | 35 |
| 2 Albisi 2019 [26] | R C | CD | ADA | Non-naïve | 12 | 3 | 44 | 7 | ID | Response | 2 | 3 | 67 |
| 3 Armuzzi 2013 [27] | R A | UC | ADA | Naïve and non-naïve | 12 | 31 | 88 | 35 |
| 4 Assa 2013 [28] | R C | UC+CD | IFX+ADA | Non-naïve | - | 20 | 10 | 102 | 10 |
| 5 Baert 2014 [29] | R A | UC | ADA | Non-naïve | 12 | 22 | 73 | 30 |
| 6 Baert 2013 [30] | R A | CD | ADA | Naïve and non-naïve | 14 | 208 | 605 | 34 | RI | Response | 139 | 208 | 67 |
| 7 Baki 2015 [31] | R A | UC | IFX | Naïve and non-naïve | 4 | 17 | 37 | 46 |
| 8 Balint 2018 [32] | P A | UC | IFX | Naïve | 12 | 20 | 61 | 33 |
| 9 Balint 2016 [33] | P A+C | UC | ADA | Naïve and non-naïve | 12 | 13 | 73 | 18 |
| 10 Bhalme 2013 [34] | R A | CD | IFX | Naïve | 13 | 4 | 76 | 5 |
| 11 Black 2016 [35] | R A | UC | ADA | Naïve | 12 | 66 | 155 | 43 |
| 12 Bor 2017 [36] | R A | CD | IFX | Naïve and non-naïve | - | 14 | 48 | 29 | ID | Remission | 3 | 14 | 21 |
| 13 Bortlik 2013 [37] | R A | CD | IFX | Naïve and non-naïve | 24 | 6 | 84 | 7 |
| 14 Bossuyt 2019 [38] | P A | UC | GOL | Naïve and non-naïve | 6 | 8 | 91 | 9 |
| 15 Bouguen 2015 [39] | P A | CD | ADA | Naïve and non-naïve | - | Response | 23 | 42 | 55 |
| 16 Bramuzzo 2019 [40] | R C | UC+CD | IFX | Naïve | 12 | 44 | 172 | 26 |
| 17 Brandes 2019 [41] | R A | UC+CD | ADA | Naïve and non-naïve | 12 | 76 | 502 | 15 |
| 18 Bultman 2012 [42] | P A | CD | ADA | Non-naïve | 12 | 23 | 49 | 47 | - | Response | 20 | 46 | 43 |
| Author and Year            | Study Design | Population | Medical Condition | Anti-TNF | Prior Anti-TNF | FOLLOW up (Months) | n  | N  | DI Rate (%) | Intensification Regimen | Response/Remission | n' | N' | DI Efficacy (%) |
|----------------------------|--------------|------------|-------------------|----------|----------------|-------------------|----|----|-------------|--------------------------|-------------------|----|----|----------------|
| 19 Cameron 2015 [43]       | R C          | UC+CD      | IFX               | Naïve    | Naïve and non-naïve | 23   | 23 | 72 | 32          |                          |                 |    |    |                |
| 20 Casanova 2019 [21]      | R A          | UC+CD      | IFX+ADA+CZP       | Naïve and non-naïve | 18  | 230 | 1122 | 20.5 | RI or ID | Remission | 161 | 230 | 42            |
| 21 Casellas 2015 [44]      | P A          | CD         | ADA               | Naïve    | 36  | 3    | 28   | 11          |                          |                 |    |    |                |
| 22 Castaño 2015 [45]       | R A          | CD         | ADA               | Naïve    | 12  | 9    | 46   | 20          | RI | Remission | 3   | 9   | 33            |
| 23 Caviglia 2007 [46]      | R A          | UC         | IFX               | -        | 24  | 0    | 10   | 0           | RI | Remission | 3   | 9   | 33            |
| 24 Cesarini 2014 [47]      | R A          | UC         | IFX               | Naïve    | 24  | 3    | 40   | 7.5         | RI or ID | Response | 37  | 41  | 90            |
| 25 Chaparro 2011 [48]      | R A          | CD         | IFX               | Naïve    | 41  | 127  | 309  | 43          | RI or ID | Response | 122 | 127 | 96            |
| 26 Chaparro 2012 [49]      | R A          | CD         | IFX               | Naïve    | 22  | 33   | 197  | 17          | - | Remission | 11  | 33  | 33            |
| 27 Cheng, 2017 [50]        | R C          | UC         | IFX               | Naïve    | 24  | 60   | 113  | 53          | RI or ID | Response | 36  | 60  | 60            |
| 28 Choi 2014 [51]          | R A          | CD         | ADA               | Naïve    | 18  | 5    | 36   | 14          | RI | Remission | 10  | 15  | 67            |
| 29 Choi 2017 [52]          | R C          | CD         | IFX               | Naïve    | 16  | 14   | 29   | 48          | RI or ID | Response | 17  | 21  | 80            |
| 30 Church 2014 [53]        | R C          | CD         | IFX               | Naïve    | 16  | 7    | 10   | 70          | RI | Remission | 11  | 33  | 33            |
| 31 Clark 2019 [54]         | R A          | CD         | IFX               | -        | 24  | 10   | 17   | 59          | RI | Remission | 36  | 60  | 60            |
| 32 Cohen 2012 [55]         | R A          | CD         | ADA               | Naïve and non-naïve | 55  | 31   | 75   | 41          | RI or ID | Response | 122 | 127 | 96            |
| 33 Cordero 2011 [56]       | P A          | CD         | ADA               | Non-naïve | 12  | 18   | 25   | 72          | RI, ID | Remission | 65  | 103 | 63            |
| 34 DeRidder 2008 [57]      | R C          | CD         | IFX               | Naïve    | 41  | 40   | 66   | 61          | RI | Response | 24  | 45  | 53            |
| 35 DeBruyn 2017 [58]       | R C          | CD         | IFX               | Naïve    | 19  | 102  | 178  | 57          | RI | Response | 33  | 45  | 73            |
| 36 D’Haens 2018 [10]       | P A          | CD         | IFX               | Naïve    | 12  | 16   | 40   | 40          | RI | Remission | 8   | 13  | 61            |
| 37 Dignass 2019 [17]       | R A          | UC         | IFX               | Naïve    | 24  | 75   | 114  | 66          | RI, ID, RI+ID | Response | 65  | 103 | 63            |
| 38 Dreesen 2018 [59]       | R A          | CD         | IFX               | Naïve    | 24  | 27   | 47   | 57          | RI, ID | Response | 65  | 103 | 63            |
| Author and Year          | Study Design | Population | Medical Condition | Anti-TNF     | Prior Anti-TNF | FOLLOW up (Months) | n  | N   | DI Rate (%) | Intensification Regimen | Response/Remission | n' | N' | DI Efficacy (%) |
|-------------------------|--------------|------------|-------------------|--------------|---------------|-------------------|----|-----|-------------|-------------------------|-------------------|----|----|----------------|
| Dubinsky 2016 [60]      | P            | C          | CD                | ADA          | Naïve and non-naïve | 12               | 35 | 93  | 38          | RI                      | Response          | 20 | 35 | 57            |
|                         |              |            |                   |              | Naïve          | 12               | 18 | 51  | 35          | RI                      | Remission         | 11 | 35 | 31            |
|                         |              |            |                   |              | Non-naïve      | 12               | 17 | 42  | 40          | RI                      | Response          | 7  | 17 | 41            |
| Dumitrescu 2015 [61]    | R            | A          | UC                | IFX          | Naïve          | -                | 65 | 187 | 35          | RI or ID                | Response          | 87 | 157 | 55           |
| Dupont 2016 [62]        | R            | C          | CD                | IFX          | Naïve          | -                | 124| 430 | 29          | RI or ID                | Response          | 99 | 124| 80           |
| Duveau 2016 [63]        | R            | A          | CD                | ADA          | Naïve and non-naïve | -               | 124| 430 | 29          | RI or ID                | Response          | 99 | 124| 80           |
| Echarri 2015 [64]       | P            | A          | CD                | ADA          | Naïve          | 24               | 12 | 68  | 18          | RI                      | Remission         | 9  | 12 | 75            |
| Falaiye 2014 [65]       | R            | A          | UC+CD             | IFX          | Naïve          | 12               | 18 | 29  | 62          | RI or ID                | Response          | 7  | 18 | 39            |
| Fernandes 2019 [66]     | R            | A          | UC+CD             | IFX          | Naïve and non-naïve | 12              | 25 | 149 | 17          | RI or ID                | Response          | 28 | 157| 18            |
|                         |              |            | UC+CD             | IFX          | Naïve and non-naïve | 24              | 38 | 149 | 25.5         | RI or ID                | Response          | 87 | 157| 55           |
| Fernández-Salazar 2015 [67] | R            | A          | UC                | IFX          | Naïve          | 38               | 53 | 144 | 37          | RI or ID                | Response          | 15 | 18 | 83            |
| Fiorino 2017 [68]       | P            | A+C        | UC+CD             | IFX          | Naïve and non-naïve | 3               | 74 | 399 | 16          | RI or ID                | Response          | 15 | 18 | 83            |
| Fortea-Ormaechea 2011 [69] | R            | A          | CD                | ADA          | Naïve and non-naïve | 9               | 57 | 174 | 33          | RI or ID                | Response          | 8  | 18 | 44            |
| Frederiksen 2014 [70]   | R            | A          | UC+CD             | ADA          | No naïve       | 9                | 21 | 57  | 37          | RI or ID                | Response          | 0  | 73 | 55            |
| García bosch 2013 [71]  | R            | A          | UC                | ADA          | Naïve and non-naïve | 12              | 18 | 48  | 37.5        | RI or ID                | Response          | 10 | 15 | 67            |
|                         |              |            | UC+CD             | IFX          | Naïve and non-naïve | 24              | 33 | 112 | 29          | RI or ID                | Response          | 10 | 15 | 67            |
| Ghaly 2015 [72]         | R            | A          | CD                | IFX+ADA      | Naïve and non-naïve | 40              | 73 | 73  | 18          | RI or ID                | Response          | 40 | 73 | 55            |
| Gofin 2019 [73]         | R            | C          | CD                | IFX+ADA      | Naïve          | 19               | 18 | 98  | 18          | RI or ID                | Response          | 0  | 73 | 55            |
| Gonczi 2017 [74]        | P            | A          | UC+CD             | ADA          | Naïve and non-naïve | 12              | 22 | 112 | 20          | RI or ID                | Response          | 10 | 15 | 67            |
| Gonzaga 2009 [75]       | R            | A          | CD                | IFX          | Naïve          | 49               | 56 | 111 | 50          | RI or ID                | Response          | 7  | 13 | 54            |
| González Lama 2008 [76] | R            | A          | CD                | IFX          | Naïve          | 28               | 15 | 114 | 13          | RI or ID                | Response          | 7  | 13 | 54            |
| Author and Year | Study Design | Population | Medical Condition | Anti-TNF | Prior Anti-TNF | FOLLOW up (Months) | n | N | DI Rate (%) | Intensification Regimen | Response/Remission | n’ | N’ | DI Efficacy (%) |
|----------------|-------------|------------|-------------------|----------|--------------|------------------|---|---|-------------|----------------------|-------------------|----|----|-----------------|
| 57 Guerbau 2017 [78] | P | A | CD | IFX | Naive and non-naïve | 12 | 43 | 140 | 30 |
| 58 Guidi 2018 [79] | P | A | UC+CD | IFX | Naive | 3 | 37 | 52 | 71 |
| 59 Ho 2008 [80] | R | A | CD | ADA | Non-naïve | 12 | 13 | 22 | 59 |
| 60 Ho 2009 [81] | R | A+C | CD | ADA | Naive and non-naïve | 12 | 2 | 10 | 20 |
| 61 Hussey 2016 [82] | R | A | UC | ADA | Naive and non-naïve | 19 | 13 | 55 | 24 |
| 62 Hyams 2010 [83] | P | C | UC | IFX | Naive | 30 | 11 | 34 | 33 |
| 63 Hyams 2007 [11] | P | C | CD | IFX | Naive | 12 | 9 | 52 | 17 | ID | Response | 5 | 9 | 56 |
| 64 Iborra 2017 [84] | R | A | UC | ADA | Naive and non-naïve | 12 | 93 | 263 | 35 |
| 65 Inokuchi 2019 [85] | R | A | CD | IFX | Naive | 83 | 54 | 183 | 29.5 |
| 66 Juillerat 2015 [86] | R | A | CD | IFX | Naive | 19 | 13 | 55 | 24 |
| 67 Juliao 2013 [87] | R | A | UC | IFX | Naive | 27 | 4 | 28 | 14 | RI | Response | 4 | 4 | 100 |
| 68 Kang 2016 [88] | P | C | CD | IFX | Naive | 12 | 7 | 72 | 10 |
| 69 Karmiris 2009 [89] | P | A | CD | ADA | Non-naïve | 20 | 102 | 156 | 65 | RI or ID | Response | 73 | 102 | 72 |
| 70 Katz 2012 [90] | R | A | CD | IFX | Naive | - | 77 | 250 | 31 | RI | Response | 37 | 56 | 66 |
| 71 Kelly 2017 [91] | R | A | UC+CD | IFX | Naive | 82 | 143 | 57 |
| 72 Kierkus 2015 [12] | P | C | CD | IFX | Naive | 12 | 16 | 84 | 19 |
| 73 Kiss 2011 [92] | R | A | CD | ADA | Naive and non-naïve | 12 | 33 | 201 | 16 |
| 74 Knyazev 2018 [22] | P | A | CD | CRP | Naive and non-naïve | 24 | 3 | 39 | 8 |
| 75 Knyazev 2016 [93] | R | A | UC | IFX | Naive | - | 5 | 45 | 11 | - | Remission | 4 | 5 | 80 |
| 76 Knyazev 2017 [94] | P | A | CD | ADA | Naive and non-naïve | 28 | 6 | 70 | 9 |
| 77 Kopylov 2011 [95] | R | A | CD | IFX | Naive | RI | Response | 38 | 55 | 70 |
|              |              |            |                   |         |              |                   |    |    |             | ID | Response | 26 | 39 | 67 |
| Author and Year | Study Design | Population | Medical Condition | Anti-TNF | Prior Anti-TNF | FOLLOW up (Months) | n | N | DI Rate (%) | Intensification Regimen | Response/Remission | n’ | N’ | DI Efficacy (%) |
|----------------|--------------|------------|-------------------|----------|---------------|-------------------|---|---|-------------|------------------------|------------------|----|---|--------------|
| Kunovski 2020 [96] | R A | UC | IFX | naïve | 12 | 43 | 396 | 11 |
| Lam 2014 [97] | R A | CD | ADA | naïve | 12 | 34 | 172 | 20 |
| Lees 2009 [98] | R A+C | UC+CD | ADA | non-naïve | 12 | 16 | 30 | 53 |
| Lin 2012 [99] | R A | CD | IFX | naïve | 60 | 34 | 94 | 36 |
| Lindsay 2013 [100] | R A+C | CD | IFX | naïve | 12 | 9 | 380 | 2 |
| Lindsay 2017 [101] | R A | UC | IFX+ADA | naïve | 24 | 19 | 380 | 5 |
| Ling 2018 [102] | R C | CD | IFX+ADA | naïve | 24 | 139 | 538 | 26 |
| Llaó 2016 [103] | P A | UC | IFX | naïve | 24 | 26 | 43 | 60 |
| Lofberg 2012 [104] | P A | CD | ADA | naïve and non-naïve | - | 5 | 131 | 945 | 14 |
| Lopez Palacios 2008 [105] | R A | CD | ADA | non-naïve | 24 | 6 | 22 | 27 |
| Ma 2015 [106] | R A | UC | IFX | naïve | 158 | 36 | 66 | 54 |
| Ma 2014 [107] | R A | CD | IFX | naïve | 139 | 18 | 36 | 50 |
| Ma 2016 [108] | R A | CD | IFX+ADA | naïve | 28 | 23 | 38 | 61 |
| Ma 2014 (bis) [109] | R A | CD | ADA | naïve and non-naïve | - | - | - | - |
| Magro 2011 [110] | R A | CD | ADA | naïve and non-naïve | - | - | - | - |
| Martineau 2017 [111] | R A | CD | GOL | non-naïve | 18 | 51 | 115 | 44 |
| Merras 2016 [112] | P | CD | GOL | non-naïve | 12 | 3 | 35 | 9 |
| Molnar 2012 [113] | R A | CD | ADA | naïve | 12 | 3 | 10 | 30 |
| Moon 2015 [23] | R A | CD | CZP | naïve and non-naïve | 26 | 43 | 358 | 12 |
| Motoya 2018 [114] | P A+C | CD | ADA | naïve and non-naïve | RI | Response | 16 | 28 | 57 |
| CD | ADA | naïve and non-naïve | RI | Remission | 10 | 28 | 35 |
| ADA | naïve | RI | Response | 6 | 9 | 67 |
| ADA | naïve | RI | Remission | 5 | 9 | 56 |
| ADA | non-naïve | RI | Response | 10 | 19 | 53 |
| ADA | non-naïve | RI | Remission | 5 | 19 | 26 |
| Author and Year | Study Design | Population | Medical Condition | Anti-TNF Prior | FOLLOW up (Months) | n | N | DI Rate (%) | Intensification Regimen | Response/Remission | n | N | DI Efficacy (%) |
|----------------|--------------|------------|-------------------|----------------|-------------------|---|---|-------------|------------------------|-------------------|---|---|---------------|
| Moroi 2019 [113] | R | A | CD | IFX | Naïve | 36 | 17 | 62 | 27 |
| Murthy 2015 [114] | R | A | UC | IFX | Naïve | 36 | 0 | 7 | 0 |
| Narula 2016 [115] | P | A | CD | IFX | Naïve | 12 | 39 | 116 | 51 |
| Narula 2016 [115] | P | A | CD | ADA | Naïve | 24 | 9 | 111 | 8 |
| Nedelkopolou 2018 [116] | R | C | UC | IFX | Naïve | 20 | 2 | 10 | 20 |
| Ng 2009 [117] | P | A | CD | ADA | Non-naïve | 12 | 2 | 7 | 29 |
| Nichita 2010 [118] | R | A | CD | ADA | Naïve and non-naïve | 12 | 13 | 55 | 24 |
| Nuti 2014 [119] | R | C | CD | IFX+ADA | Naïve and non-naïve | 36 | 27 | 78 | 35 |
| O’Donnell 2015 [120] | R | A+C | CD | IFX | Naïve | 36 | 133 | 287 | 46 |
| Olivares 2019 [121] | P | A | UC+CD | ADA | Naïve | 18 | 15 | 33 | 45 |
| Orlando 2012 [122] | P | A | CD | ADA | Naïve and non-naïve | 14 | 15 | 110 | 14 |
| Osterman 2017 [123] | R | A | CD | ADA | Naïve | 12 | 42 | 381 | 11 |
| Oussalah 2009 [124] | R | A | CD | ADA | Non-naïve | 36 | 7 | 53 | 13 |
| Oussalah 2010 [125] | R | A | UC | IFX | Naïve | 18 | 36 | 80 | 45 |
| Panaccione 2010 [126] | P | A | CD | ADA | Naïve | 12 | 71 | 260 | 27 |
| Paredes 2020 [127] | P | A | UC+CD | IFX | Naïve | 12 | 2 | 31 | 6 |
| Paredes 2020 [127] | P | A | UC+CD | IFX | Naïve | 24 | 12 | 31 | 39 |
| Pariente 2012 [128] | R | A | UC+CD | IFX | Naïve | 14 | 3 | 31 | 10 |
| Park 2016 [129] | R | A | CD | IFX | Naïve | 36 | 86 | 582 | 15 |
Table 1. Cont.

| Author and Year | Study Design | Population | Medical Condition | Anti-TNF Prior Anti-TNF | FOLLOW up (Months) | n | N | DI Rate (%) | Intensification Regimen | Response/Remission | n' | N' | DI Efficacy (%) |
|-----------------|-------------|------------|-------------------|------------------------|-------------------|---|---|-------------|-------------------|------------------|----|----|----------------|
| 115 Patel 2017 [130] | R | A | CD | IFX+ADA+ CZP+GOL Naïve | 6 | 640 | 4569 | 14 |
| | | | | Naïve | 12 | 1097 | 4569 | 24 |
| | | | | Naïve | 24 | 1553 | 4569 | 34 |
| | | | | Naïve | 36 | 1792 | 4569 | 39 |
| | | | | UC | IFX+ADA+ CZP+GOL Naïve | 6 | 272 | 1699 | 16 |
| | | | | Naïve | 12 | 475 | 1699 | 28 |
| | | | | Naïve | 24 | 680 | 1699 | 40 |
| | | | | Naïve | 36 | 748 | 1699 | 44 |
| 116 Paul 2013 [131] | P | A | UC+CD | IFX | Naïve and non-naïve | ID Remission | 30 | 52 | 58 |
| 117 Peters 2014 [132] | R | A | CD | ADA | Naïve | 24 | 45 | 167 | 27 |
| 118 Peyrin 2007 [133] | P | A | CD | ADA | Non-naïve | 24 | 135 | 271 | 50 |
| 119 Pollinger 2019 [134] | R | A | UC | ADA | Naïve | 12 | 6 | 24 | 25 |
| | | | | Naïve | 12 | 48 | 154 | 31 |
| 120 Preda 2016 [135] | R | A | CD | IFX | Naïve | 36 | 26 | 129 | 20 |
| | | | | Naïve | 20 | 19 | 136 | 14 |
| | | | | UC | ADA | Naïve | 24 | 10 | 75 |
| 121 Qazi 2016 [136] | P | A | UC+CD | IFX | Naïve | 30 | 54 | 108 | 50 |
| | | | | Naïve and non-naïve | RI or ID Response | 41 | 54 | 76 |
| 122 Regueiro 2007 [137] | R | A | CD | IFX | Naïve and non-naïve | 10 | 50 | 118 | 42 |
| | | | | Naïve | 36 | 1 | 58 |
| 123 Reinisch 2013 [138] | P | A | UC | ADA | Naïve and non-naïve | RI Response | 23 | 50 | 46 |
| 124 Renna 2016 [139] | P | A | UC | ADA | Non-naïve | < 6 | 1 | 16 | 6 |
| | | | | Naïve | < 6 | 1 | 17 | 6 |
| 125 Renna 2018 [140] | R | A | UC | ADA | Naïve and non-naïve | RI or ID Response | 23 | 50 | 46 |
| 126 Riis 2012 [141] | R | A | CD | IFX | Naïve and non-naïve | RI | 30 | 20 | 83 | 25 |
| 127 Roblin 2014 [142] | P | A | UC+CD | ADA | Naïve | 20 | 30 | 119 | 25 |
| 128 Roblin, 2016 [143] | P | A | CD | IFX | Naïve | 20 | 10 | 93 | 11 |
| 129 Roblin 2015 [144] | P | A | UC+CD | IFX | Naïve | 20 | 10 | 93 | 11 |
| 130 Rostholder 2012 [145] | R | A | UC | IFX | Naïve | 12 | 27 | 50 | 54 |
| | | | | RI or ID Remission | 5 | 27 | 19 |
| 131 Rubin 2012 [146] | R | A | CD | ANTI TNF | Naïve | 24 | 531 | 1398 | 38 |
| 132 Russo 2009 [147] | R | A | UC | IFX | Naïve | 15 | 2 | 38 | 5 |
| | | | | Naïve and non-naïve | RI or ID Response | 0 | 2 | 0 |
| 133 Rutka 2016 [148] | R | A | UC | ADA | Naïve and non-naïve | RI | 12 | 13 | 73 | 18 |
| 134 Sandborn 2007 [13] | P | A | CD | ADA | Naïve | 12 | 89 | 204 | 44 |
| 135 Sandborn 2016 [149] | R | A | UC | IFX | Naïve | 11 | 166 | 424 | 39 |
| | | | | UC | ADA | 11 | 138 | 380 | 36 |
Table 1. Cont.

| Author and Year | Study Design | Population | Medical Condition | Anti-TNF | Prior Anti-TNF | FOLLOW up (Months) | n  | N  | DI Rate (%) | Intensification Regimen | Response/Remission | n'  | N'  | DI Efficacy (%) |
|-----------------|--------------|------------|-------------------|----------|---------------|-------------------|----|----|-------------|---------------------|-------------------|------|------|-----------------|
| 136 Sands 2004 [14] | P            | A          | CD                | IFX      | Naïve          | 12                | 28 | 96 | 29           | RI                  | Response          | 12   | 21   | 57             |
| 137 Sartini 2018 [150] | R            | A          | UC                | ADA      | Naïve and non-naïve | 24                | 17 | 32 | 53           | RI and ID          | Remission         | 29   | 74   | 39             |
| 138 Sazuka 2012 [151] | R            | A          | CD                | IFX      | Naïve          | 21                | 30 | 74 | 40           | RI                  | Response          | 8    | 14   | 57             |
| 139 Schnitzler 2009 [152] | P            | A          | CD                | IFX      | Naïve          | 55                | 218| 547| 40           | RI                  | Response          | 8    | 14   | 57             |
| 140 Seo 2017 [153] | R            | A          | CD                | ADA      | Naïve and non-naïve | 17                | 45 | 254| 18           | RI                  | Response          | 30   | 35   | 86             |
| 141 Seow 2010 [154] | P            | A          | UC                | IFX      | Naïve          | 14                | 74 | 115| 64           | RI or ID            | Remission         | 29   | 74   | 39             |
| 142 Shapiro 2015 [155] | R            | C          | UC+CD             | IFX      | Naïve          | 12                | 35 | 87 | 40           | RI or ID            | Remission         | 29   | 74   | 39             |
| 143 Sierra 2016 [156] | R            | A          | UC                | ADA      | Naïve and non-naïve | 12                | 16 | 37 | 43           | RI                  | Response          | 29   | 74   | 39             |
| 144 Sprakes 2012 [157] | P            | A          | CD                | IFX      | Naïve          | 24                | 18 | 173| 10           | RI                  | Response          | 29   | 74   | 39             |
| 145 Srinivasan 2018 [158] | R            | A          | CD                | IFX+ADA  | Naïve and non-naïve | 12                | 55 | 423| 13           | RI                  | Response          | 29   | 74   | 39             |
| 146 Stein 2014 [24] | R            | A          | CD                | CZP      | Naïve and non-naïve | 124               | 10 | 87 | 11           | RI                  | Response          | 19   | 36   | 53             |
| 147 Steendholt 2015 [15] | P            | A          | CD                | IFX      | Naïve          | 9                 | 14 | 37 | 43           | RI                  | Response          | 9    | 14   | 64             |
| 148 Sutharsan 2013 [159] | P            | A          | CD                | ADA      | Naïve          | 12                | 36 | 190| 19           | RI                  | Response          | 12   | 9    | 62.5           |
| 149 Suzuki 2015 [160] | P            | A          | CD                | IFX      | Naïve          | 12                | 5   | 17 | 29           | RI                  | Remission         | 2    | 4    | 50             |
| 150 Suzuki 2019 [161] | R            | A          | CD                | ADA      | Naïve and non-naïve | 12                | 14 | 95 | 15           | RI                  | Remission         | 8    | 12   | 67             |
| 151 Suzuki 2017 [162] | P            | A          | UC                | ADA      | Naïve          | 12                | 9   | 78 | 12           | RI                  | Remission         | 5    | 8    | 62.5           |
| 152 Swoger 2010 [163] | R            | A          | CD                | ADA      | Naïve          | 12                | 9   | 78 | 12           | RI                  | Remission         | 2    | 4    | 50             |
| 153 Tajiri 2018 [164] | P            | C          | CD                | IFX      | Naïve          | 12                | 5   | 14 | 36           | ID                  | Remission         | 3    | 5    | 60             |
| 154 Takeuchi 2019 [165] | R            | C          | UC+CD             | IFX      | Naïve          | 12                | 11 | 17 | 65           | ID                  | Remission         | 54   | 79   | 68             |
| 155 Taxonera 2015 [166] | R            | A          | UC                | IFX      | Naïve          | 13                | 16 | 59 | 27           | -                   | Response          | 54   | 79   | 68             |
| 156 Taxonera 2014 [167] | R            | A          | CD                | IFX      | Naïve          | 9                 | 16 | 38 | 42           | -                   | Remission         | 41   | 79   | 52             |
| Author and Year          | Study Design | Population | Medical Condition | Anti-TNF | Prior Anti-TNF | FOLLOW up (Months) | n  | N  | DI Rate (%) | Intensification Regimen | Response/Remission | n' | N' | DI Efficacy (%) |
|-------------------------|--------------|------------|-------------------|----------|----------------|-------------------|----|----|-------------|------------------------|------------------|----|----|-----------------|
| 157 Taxonera 2017 (bis) [168] | R            | A          | UC                | ADA      | Naive          | 24                | 12 | 68 | 18          | RI or ID               | Response         | 7  | 12 | 58             |
|                         |              |            |                   | ADA      | Non-naïve      | 24                | 64 | 116 | 55          | RI or ID               | Response         | 2  | 12 | 17             |
|                         |              |            |                   |          |                |                   |    |     |             | RI or ID               | Response         | 26 | 64 | 41             |
|                         |              |            |                   |          |                |                   |    |     |             | RI or ID               | Response         | 13 | 64 | 20             |
| 158 Taxonera 2017 [169]  | R            | A          | UC                | GOL      | Naive and non-naïve | 12               | 31 | 114 | 27          | RI or ID               | Response         | 22 | 31 | 71             |
| 159 Taxonera 2011 [170]  | R            | A          | UC                | ADA      | Non-naïve      | 12               | 11 | 30 | 37          | RI                     | Response         | 8  | 11 | 73             |
| 160 Tigue 2017 [171]     | R            | A          | UC                | IFX + ADA| Non-naïve      | 12               | 2  | 24 | 8           | RI                     | Response         | 2  | 24 | 8              |
| 161 Tkacz 2014 [172]     | R            | A          | CD                | IFX      | Naive          | 9                | 18 | 106 | 17          | RI                     | Response         | 18 | 18 | 17             |
| 162 Tursi 2018 [173]     | R            | A          | UC                | ADA      | Naïve and non-naïve | 18               | 9  | 56 | 16          | RI                     | Response         | 18 | 18 | 16             |
| 163 Vahabnejad 2014      | R            | A          | CD                | IFX      | Naïve          | 30               | 65 | 89 | 73          | RI or ID               | Response         | 40 | 65 | 62             |
| 164 Vanassche 2012 [175] | P            | A          | UC                | IFX      | Naïve          | 25               | 7  | 13 | 54          | RI or ID               | Response         | 4  | 7  | 57             |
| 165 Vandevondel 2018     | P            | A          | CD                | IFX      | Naïve          | 12               | 6  | 13 | 16          | RI                     | Response         | 6  | 13 | 16             |
| 166 Vatansever 2014      | P            | A          | CD                | IFX + ADA| Non-naïve      | 34               | 40 | 79 | 51          | DI                     | Response         | 19 | 27 | 50             |
| 167 Verstock 2018 [178]  | R            | A          | CD                | ADA      | Naïve          | 12               | 27 | 116 | 23         | RI or ID               | Response         | 12 | 27 | 23             |
| 168 Viazis 2015 [179]    | P            | A          | CD                | IFX + ADA| Naïve          | 28               | 31 | 132 | 23        | RI or ID               | Response         | 16 | 132 | 23            |
| 169 Watanabe 2014. [180] | P            | A          | CD                | ADA      | Naïve and non-naïve | 34               | 40 | 79 | 51          | DI                     | Response         | 16 | 17 | 94             |
| 170 West 2008 [181]      | R            | A          | CD                | ADA      | Naïve          | 12               | 8  | 30 | 27          | RI                     | Response         | 8  | 8  | 100            |
| 171 Wolf 2014 [182]      | P            | A          | UC                | ADA      | No naïve       | 3                | 20 | 123 | 16        | RI                     | Response         | 9  | 20 | 45             |
| 172 Yamada 2014 [183]    | R            | A          | UC                | IFX      | Naïve          | 36               | 17 | 24 | 71          | RI or ID               | Response         | 16 | 17 | 94             |
| 173 Yokoyama 2016 [184]  | R            | A          | CD                | IFX + ADA| Naïve          | 8                | 18 | 107 | 7          | RI or ID               | Response         | 18 | 107| 7              |

DI: Dose intensification. R: Retrospective. P: Prospective. UC: Ulcerative colitis. CD: Crohn’s disease. IFX: Infliximab. ADA: Adalimumab. CZP: Certolizumab pegol. GOL: Golimumab. n: number of patients undergoing dose intensification. N: total number of patients included. ID: Increase of dose. RI: Reduction of the interval of administration. n’: number of patients with a clinical response or remission after dose intensification. N’: total number of patients undergoing dose intensification.
3.1. Dose Intensification Requirements

3.1.1. Twelve-Month Follow-Up

Naïve vs. Non-Naïve Patients

A total of 68 studies with a median follow-up of 12 months were analyzed. In naïve patients, the DI rates ranged from 2% (100) to 80% (165), with an overall pooled rate of 28% (95% CI 24-32, $I^2 = 96\%$, 41 studies) (Figure 2).

In non-naïve patients, the DI rate ranged from 7% (26) to 81% (111), with an overall pooled rate of 39% (95% CI 31-47, $I^2 = 86\%$, 41 studies) (Figure 2).

Figure 2. Dose intensification requirements after the 12-month follow-up in anti-TNF naïve and non-naïve patients.

In non-naïve patients, the DI rate ranged from 7% (26) to 81% (111), with an overall pooled rate of 39% (95% CI 31-47, $I^2 = 86\%$, 18 studies) (Figure 2).
The DI requirement after the 12-month follow-up was statistically higher in non-naïve than in naïve patients (test for subgroup differences: $\chi^2 = 6.13, p = 0.01, I^2 = 83.7\%$).

### Anti-TNF Use by Medical Condition in Naïve Patients

The DI requirement rate after the 12-month follow-up with all the anti-TNF agent data was statistically higher in UC than in CD patients (test for subgroup differences: $\chi^2 = 5.29, p = 0.02, I^2 = 81.1\%$). No other subgroup differences were reported by the medical condition or anti-TNF used (Table 2).

### Table 2. Dose intensification rate after the 12-month follow-up by the anti-TNF agent and medical condition.

| Anti-TNF | UC/CD | DI Requirement (% 95% CI) | I$^2$ (%) | Number of Included Studies |
|----------|-------|---------------------------|-----------|---------------------------|
| IFX UC+CD | 29 (22–36) | 96 | 26 |
| IFX UC | 40 (24–56) | 97 | 8 |
| IFX CD | 21 (15–28) | 92 | 15 |
| ADA UC+CD | 28 (22–34) | 93 | 16 |
| ADA UC | 29 (23–35) | 86 | 6 |
| ADA CD | 28 (17–38) | 94 | 10 |

Anti-TNF: anti-tumor necrosis factor. UC: ulcerative colitis. CD: Crohn’s disease. DI: dose intensification. IFX: Infliximab. ADA: Adalimumab.

### 3.1.2. Thirty-Six Month Follow-Up

A total of 25 studies with a median follow-up of 36 months were analyzed. There was only one study reporting the DI rate in non-naïve patients, and therefore, no subgroup analysis was performed.

The DI rates in naïve patients ranged from 0% (113) to 70% (183), with an overall rate of 35% (95% CI 28–43%, $I^2 = 98\%$, 18 studies) (Figure 3).

### Figure 3. Dose intensification requirements after the 36-month follow-up in anti-TNF naïve patients.

#### Anti-TNF Use by Medical Condition in Naïve Patients

No statistical differences ($p > 0.05$) in the medical conditions or the anti-TNF drug used were found between the subgroups (Table 3).
Table 3. The DI rate after 36-month follow-up by the anti-TNF agent and medical condition.

| Anti-TNF     | UC/CD | DI Requirement (% 95% CI) | I2 (%) | Number of Included Studies |
|--------------|-------|---------------------------|--------|---------------------------|
| IFX          | UC/CD | 38 (30–46)                | 96     | 15                        |
| IFX          | UC    | 48 (34–62)                | 82     | 4                         |
| IFX          | CD    | 35 (26–43)                | 96     | 12                        |
| ADA          | UC/CD | 24 (7–40)                 | 92     | 4                         |
| ADA          | UC    | 34 (3–64)                 | 92     | 2                         |
| ADA          | CD    | 3 (4–11)                  | 80     | 2                         |

Anti-TNF: anti-tumor necrosis factor. UC: ulcerative colitis. CD: Crohn’s disease. DI: dose intensification. IFX: Infliximab. ADA: Adalimumab.

3.1.3. Short-Term Follow up

A total of 17 studies with a median of three to nine months of follow-up were included. The DI rates in naïve patients ranged from 14% (130) to 71% (79) with an overall pooled rate of 29% (95% CI 31–37, I2 = 96%, five studies).

A subgroup analysis evaluating the follow-up time (short-term vs. 12 months vs. 36 months) showed no statistical differences (p > 0.05) in terms of the DI requirements in naïve patients.

3.2. Dose Intensification Efficacy

3.2.1. Response Rate

The response rates ranged from 0% (147) to 96% (48) in naïve patients and from 41% (60) to 75% (181) in non-naïve patients.

The overall rate of the short-term response to the empirical DI was 63% (95% CI: 48–78%, I2 = 99%, 32 studies) and 58% (95% CI: 47–70%, I2 = 68%, nine studies) in the naïve and non-naïve patients, respectively (Figure 4). No statistical differences were found between the groups (p > 0.05).

Figure 4. Response rate after the empirical dose intensification in anti-TNF naïve vs. non-naïve patients.
No statistical differences were found when comparing CD vs. UC patients or the anti-TNF drugs used (Table 4). Neither were found ($p > 0.05$) between different intensification regimens (i.e., intensification of dosing vs. reduction of the interval of administration).

### Table 4. Response rate by the anti-TNF agent and medical condition.

| Anti-TNF | UC/CD Response Rate (%) | $I^2$ (%) | Number of Included Studies |
|----------|-------------------------|-----------|----------------------------|
| IFX UC+CD | 65 (49–80) | 99 | 26 |
| IFX UC | 62 (29–95) | 99 | 8 |
| IFX CD | 67 (59–75) | 91 | 16 |
| ADA UC+CD | 63 (55–70) | 0 | 5 |
| ADA UC | 58 (48–68) | NA | 1 |
| ADA CD | 69 (58–80) | 0 | 4 |

Anti-TNF: anti-tumor necrosis factor. UC: ulcerative colitis. CD: Crohn’s disease. IFX: Infliximab. ADA: Adalimumab.

#### 3.2.2. Remission Rate

The remission rates ranged from 17% (168) to 94% (183) in naïve patients and from 17% (60) to 85% (124) in non-naïve patients. The overall remission rate to empirical DI was 48% (95% CI: 39–58%, $I^2 = 92\%$, 25 studies) and 44% (95% CI: 17–71%, $I^2 = 95\%$, six studies) in naïve and non-naïve patients, respectively (Figure 5). No significant differences were found between the subgroups ($p > 0.05$).

### Table 5. Remission rate by the anti-TNF agent and medical condition in naïve patients.

| Anti-TNF | UC/CD Remission Rate (%) | $I^2$ (%) | Number of Included Studies |
|----------|--------------------------|-----------|----------------------------|
| IFX UC+CD | 46 (34–59) | 93 | 14 |
| IFX UC | 46 (34–59) | 93 | 14 |
| IFX CD | 46 (34–59) | 93 | 14 |
| ADA UC+CD | 46 (34–59) | 93 | 14 |
| ADA UC | 46 (34–59) | 93 | 14 |
| ADA CD | 46 (34–59) | 93 | 14 |

### Figure 5. Remission rates after the empirical dose intensification in anti-TNF naïve vs. non-naïve patients.

No statistical differences were found when comparing CD vs. UC patients or the anti-TNF drugs used (Table 5). Neither were found between the different intensification regimens.
Table 5. Remission rate by the anti-TNF agent and medical condition in naïve patients.

| Anti-TNF | UC/CD   | Remission Rate (%, 95% CI) | I² (%) | Number of Included Studies |
|----------|---------|----------------------------|--------|---------------------------|
| IFX      | UC+CD   | 46 (34–59)                 | 93     | 14                        |
| IFX      | UC      | 50 (25–74)                 | 96     | 7                         |
| IFX      | CD      | 43 (33–53)                 | 60     | 6                         |
| ADA      | UC+CD   | 44 (31–58)                 | 86     | 10                        |
| ADA      | UC      | 17 (07–27)                 | NA     | 1                         |
| ADA      | CD      | 50 (36–64)                 | 79     | 8                         |

Anti-TNF: anti-tumor necrosis factor. UC: ulcerative colitis. CD: Crohn’s disease. IFX: Infliximab. ADA: Adalimumab.

3.3. Pediatric Population

A total of 24 studies reported data on children (<18 years) (Table 1). When compared to the adult population, no statistical differences were found in terms of the DI required or its efficacy. The random-effects pooled DI rate in naïve patients after a 12-month follow-up was 29% (95% CI 21–37%, I² = 81%, n = 9).

3.4. Randomized Controlled Trials

A total of five randomized controlled trials (Table 1) assessed the DI requirements after a 12-month follow-up in naïve patients. The random-effects pooled DI rate was 29% (95% CI 18–41%, I² = 88%, five studies). No statistical differences were found when this subgroup was compared to the group of observational studies.

3.5. Sensitivity Analyses and Risk of Bias

We further investigated potential sources of heterogeneity by excluding studies that included extreme or diverging values in certain subgroups, such as the DI requirements after 12 months [34,100,123,127,147,165] and 36 months [85,113] of follow-up or the response [147] and remission [61,145,168,183] rates. The effects of including different follow-up periods in the same subgroup [34,147,149] or the use of different induction dosing regimens [13,126,138] were also explored. In all cases, the results were stable, with no significant variations after the sensitivity analysis, although the heterogeneity remained considerable.

Among the six RCTs evaluated for a potential risk of bias, five had a low risk of bias for randomization, and four of them reported on the implementation of the random allocation sequence preserving concealment. Four studies also reported the adequate blinding of participants and personnel. Three studies showed low risks of attrition bias; in two of them, the number of excluded patients was not specified, and in the remaining one, there was a difference in the proportion of the outcome data. Finally, none of the studies was considered to show reporting biases. In conclusion, for most of the RCT items assessed, there was a low potential risk of bias detected.

4. Discussion

A LOR to the anti-TNF agents represents a therapeutic challenge to gastroenterologists, as these drugs are usually indicated in severe forms of the disease, and the remaining treatment options in such situations are limited. However, there is no unanimous definition of LOR in the literature [185,186]; it has been defined as an increase in clinical activity (which can be assessed by numerous activity indices) or, alternatively, as the need to modify or discontinue the current treatment. Thus, several authors have proposed that the DI requirement, which has been shown to recapture the response in multiple studies [187], would be a more objective and reliable measure [188] and, therefore, a useful surrogate for the LOR. Several reviews have previously assessed the incidence of a LOR, mainly in CD [185–191]. When compared to previous reviews, our study includes a considerably higher number of studies, up to January 2020, assessing both UC and CD patients and, therefore, conferring more robustness and reliability to our work.
4.1. Prior Anti-TNF Exposure

Several studies have estimated that approximately one-third of inflammatory bowel disease patients experience LOR and require DI, and that occurs more frequently in patients with prior anti-TNF exposure [188–191].

In our study, the overall rate of the DI requirements at a one-year follow-up was 28% in naïve and 39% in non-naïve patients, respectively. This shows no relevant differences with the previous data and constitutes one main finding of our study: dose escalation was needed more often in patients with prior anti-TNF use. In fact, the vast majority of the included studies evaluating both naïve and non-naïve patients showed a greater incidence in the loss of response in those non-naïve [30,34,35,60,81,111,121,132,161,163,168,192,193].

4.2. Time of Follow-Up

Additionally, the time course of LOR remains poorly understood. The median time from the first anti-TNF exposure to the need for a DI varied widely among the studies, from 2.7 to 18 months. However, there is increasing evidence showing that such events occur mostly within the first year of anti-TNF therapy [186].

In our study, no differences were found in the rate of DI for the short term, 12 and 36 months of follow-up, supporting the fact that the LOR and consequent DI occur mainly during the first year of treatment.

4.3. Medical Baseline Condition

Another relevant finding in our study was that a DI was required more frequently in UC than in CD patients. Previous data indicated that some patients with active UC have a higher inflammatory burden and accelerated anti-TNF clearance [194–196]; therefore, they could require a higher drug exposure to achieve a response to TNF antagonists. This could be the rational explanation UC patients need for an earlier and more frequent DI than CD patients [110,120,167]. However, there is also evidence not supporting these results [174]. Further research should be conducted, as no randomized trials have focused on this subgroup of patients; they seem to have the highest DI rate and could benefit the most from alternative treatment strategies.

4.4. Anti-TNF Agent

The comparison between the IFX and ADA DI rates is also a matter of interest. Immunogenicity is believed to be a common cause of LOR due to the formation of antidrug antibodies. Some authors have argued that the chimeric nature of IFX, as opposed to the fully humanized ADA, could render the former more prone to generate an antibody response. However, in our study, we did not find significant differences in the DI rate between IFX and ADA patients, as in previous comparative reports [115].

4.5. Dose Intensification Efficacy

Several clinical trials and open-label cohorts included in a previous review reported DI to restore the response in 50–70% of patients [186]. Billioud et al. also found that DI restored the response in 71% and remission in 40% of the patients [189].

In our study, the response and remission rates to empirical DI in naïve patients were 63% and 48%, respectively. Although no significant differences were reported between the naïve and non-naïve patients, either in the response or remission rates, a trend towards a reduced DI efficacy in the patients with prior anti-TNF exposure was shown.

Our findings support that using all the available treatment options with the first anti-TNF agent through DI (even if it is not based on therapeutic drug monitoring) should be considered before switching to another anti-TNF agent or to another therapeutic target. Nevertheless, it should be noted that almost all studies do assess the DI efficacy in the short term; additional research regarding the long-term response and remission rates after DI should be performed.
4.6. Limitations

Our study had some limitations. First of all, the DI can result in an equivocal interpretation of the LOR if it is done without accurately confirming the disease activity. In addition, there were also some possible predictors for the LOR or DI that were not evaluated in our study, such as the concomitant use of immunomodulators. However, recent guidelines (three) have suggested monotherapy with anti-TNF in patients with long-term remission rather than the use of a combination therapy. Finally, we excluded studies in which the DI was made based on therapeutic drug monitoring, with the aim to assess the effectiveness of empirical DI. In this respect, the current guidelines (three) do not recommend either proactive or reactive therapeutic drug monitoring as a standard clinical practice due to insufficient evidence. Finally, we did not perform a quality assessment of all the included studies given the high heterogeneity of the observational studies encountered in terms of the design and number. It was decided to perform a risk of bias assessment exclusively in RCTs, which represented no more than 1.5% of the total of patients included in our systematic review but, including 512 patients, was a sufficient sample size to drawn robust conclusions. In terms of quality, most studies showed a low risk of bias for the majority of the items assessed, highlighting both an adequate random sequence generation and allocation concealment, as well as blinding; items that were usually preserved. Additionally, a subgroup analysis was performed to control for heterogeneity in terms of study design, and no significant differences in the DI requirement between the RCTs and observational studies were reported.

5. Conclusions

A LOR to anti-TNF agents—and, consequently, DI—occurs frequently in inflammatory bowel disease, with an overall rate of DI requirement of approximately one-fourth at one year and one-third at three years. DI is required more frequently in patients with prior exposure to anti-TNF agents and in UC patients. Empirical DI is a relatively effective therapeutic option, achieving a response in two-thirds and remission in one-half of those patients naïve to anti-TNF treatment.

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