Biologics in Focus: A Comprehensive Review of Current Biological and Small Molecules Therapies for Crohn’s Disease in the United Arab Emirates (UAE)

Laith Alrubaiy 1,2,* L., Louise Christine Pitsillides 3,4, Thomas O’Connor 4,5, Matilda Woodhill 4,6, Harry Higgins 7, Thaer Khaleel Swaid 8, Doa’a Alkhader 9 and Zaher Koutoubi 9

1 Healthpoint Hospital, Abu Dhabi 112308, United Arab Emirates
2 Department of Medicine Health and Life Sciences, Singleton Bay Campus, Swansea University School of Medicine, Swansea SA2 8PP, UK
3 East of England Foundation School, Victoria House, Capital Park, Fulbourn, Cambridge CB21 5BQ, UK;
lpitsillides@hotmail.com
4 Imperial College London Gastroenterology and Hepatology Department, London SW7 2AZ, UK;
thomas.oconnor4@nhs.net (T.O.); matildawoodhill@gmail.com (M.W.)
5 School of Physiology, Pharmacology and Neuroscience, University of Bristol, Bristol BS8 1QU, UK
6 Leeds General Infirmary, Leeds Teaching Hospital Trust, Leeds LS1 3EX, UK
7 Sunshine Hospital, Furlong Road, St Albans, Melbourne, VIC 3021, Australia; harryphiggins@gmail.com
8 Sheikh Shakhbout Medical City, Abu Dhabi 112301, United Arab Emirates; dr_t_haer@hotmail.com
9 Cleveland Clinic Abu Dhabi, Abu Dhabi 112308, United Arab Emirates;
alkhadd@clevelandclinicabudhabi.ae (D.A.); koutouz@clevelandclinicalabudhabi.ae (Z.K.)

* Correspondence: l.alrubaiy@swansea.ac.uk

Abstract: Introduction: The management of Crohn’s disease (CD) in the Middle East, like in other parts of the world, is rapidly evolving with the introduction of novel advanced medical and biological therapies. In the United Arab Emirates (UAE), several biological therapies are used to achieve remission in severe and resistant cases of CD. We carried out a literature search to analyze the effectiveness and safety of biologic treatments currently licensed in the UAE. Methods: We searched the PubMed, Embase and Cochrane library databases from inception to January 2020 to identify relevant studies. Search terms were generated using established treatment guidelines for CD. We also manually searched the bibliographies of relevant literature to obtain additional papers. Results: Biologic and small molecule agents for CD include four core drug classes: anti-tumor necrosis factor-α agents (TNF-α), integrin receptor antagonists, Janus kinase (JAK) inhibitors and IL-12/IL-23 antagonists. All drug classes showed good efficacy and safety in managing patients with CD. Some drug classes had distinguishable side effect profiles. This included an increased lymphoma and tuberculous risk for TNF-α and integrin receptor antagonists. Many trials supported the effectiveness of these licensed drugs. Biologic agent intolerance was common; one-third of patients receiving TNF-α treatment will develop intolerance to that specific drug. Conclusions: Advanced medical therapies licensed in the UAE have proven to be safe and efficacious. Additional research is required to evaluate the safety and efficacy of newer biologics and biosimilars.

Keywords: Crohn’s disease; inflammatory bowel disease; biologics; Anti-TNF; JAK2 inhibitor; Middle East; United Arab Emirates

1. Introduction

Crohn’s disease (CD) is a chronic inflammatory disease characterized by inflammation of the gastrointestinal system. A well-established pattern of transmural, asymmetric, granulomatous inflammation is a hallmark feature of CD [1]. Strictureing, penetrating disease and other complications are present in one-third of patients at the time of diagnosis [1]. Current British Society of Gastroenterology (BSG) guidelines recommend a ‘step up’ management; medical management is escalated if the patient’s CD increases in severity or...
becomes refractory to current treatment [2]. Corticosteroids are the first-line treatment for inducing remission in mild to moderate CD. Patients then transition to immunomodulator therapies such as azathioprine (AZA) or mercaptopurine for CD maintenance therapy.

Traditionally, biologics are reserved for those with refractory CD despite being on optimal immunomodulator therapy [3]. They are licensed for use in moderate-to-severe CD. BSG guidelines now recommend the early induction of biologics for patients with aggressive CD, which can offer effective treatment for those with poor prognostic factors [2].

Biologic agents were first licensed in the late 1990s, revolutionizing the management of moderate and severe CD [4]. Three biological drug classes have since been established: anti-tumor necrosis factor agents (anti-TNFα), integrin receptor antagonists and IL-12/IL-23 antagonists [2–4].

Efficacy is measured by assessing clinical response and remission. Clinically, remission is often classified using scores derived from clinical symptoms and biological parameters [2–5]. The Crohn’s Disease Activity Index (CDAI) score of <150 is often quoted by literature as a threshold for remission [5]. Endoscopic remission is determined by measures such as mucosal healing [6]. Establishing a biological agent’s side effect profile is essential to quantifying the risks and benefits of administering a certain drug.

The aim of our review was to accumulate and present the current literature on the efficacy and safety of biological therapies currently licensed for the treatment of CD in the United Arab Emirates (UAE) based on the clinical trials reviewed by regulatory authorities such as the FDA. Furthermore, the review will provide an assessment of biological agents that can be used to aid clinicians in providing evidence-based care. Our search focused on randomized control trials (RCTs), meta-analyses and systematic reviews—the highest level of evidence (grade A) as per SIGN guidelines [7].

2. Results
2.1. Anti-TNFα Agents

Anti-TNF agents are human IgG1 monoclonal antibodies that bind against TNF alpha to neutralize it and prevent interactions with TNFα receptors, which would normally activate a release of cytokines, acute phase reactants of inflammation and other damaging molecules [8]. Established but rare serious adverse effects for anti-TNFα therapies include reactivation of latent tuberculosis (TB), lymphoma and opportunistic infections [9].

2.1.1. Infliximab

Infliximab (IFX) was the first successful biologic therapy to be developed; it has been licensed to treat moderate-to-severe CD since 1999 [10,11]. The standard dosage is 5 mg/kg IV at 0, 2 and 6 weeks, and every 8 weeks thereafter to maintain remission [10,11]. In refractory cases, dosage levels can increase and time between infusions can decrease.

Multiple RCTs have assessed the safety and efficacy of IFX. A summary of these findings, along with relevant statistical information, can be found in Table 1. Targan et al. [12] found IFX to be effective in rapidly inducing clinical remission with a single infusion, a finding that D’Haens et al. [13] confirmed was also effective at an endoscopic level. Primary non-response to therapy is 13–40% [14].

IFX is effective as a maintenance therapy in patients with successful IFX induction therapy [15,16]. If, after the second dose, no clinical response (defined as a ≥70-point decrease in CDAI) is seen, then it is unlikely any further treatment with IFX will be effective, and alternative therapies should be considered. A recent meta-analysis [17] identified a loss of response in 34% of patients over a median follow-up time of 54 weeks; however, no strong predictors for this loss of response have been identified [18].

The most commonly reported side effects are nausea and headache; however, IFX is generally considered well tolerated (Table 1). One severe adverse event is infusion reactions, which subsequently cause treatment failure. These often occur in the presence of anti-IFX antibodies, which are more likely to be found in patients undergoing episodic maintenance
therapy [19]. To reduce the likelihood of an infusion reaction, patients can be treated with 100 mg IV hydrocortisone prior to each infusion [20].

Long-term safety was addressed by The TREAT study, which analyzed the long-term risk of IFX and found no independent increased risk of severe infection compared to placebo ($p = 0.97$) [21]. However, due to the increased risk of TB, patients should be tested for latent TB and subsequently treated before initiating IFX treatment [22].

The use of IFX as part of a combination therapy has also been studied. The addition of AZA has been shown to reduce immunogenicity and, therefore, the proportion of patients withdrawing from treatment [15,23]. Although a pilot study showed promise that coadministering methotrexate might also increase remission rates, the subsequent RCT by Faegan et al. [24] indicated that it was not superior to IFX monotherapy. Prolonged concomitant immunosuppressant therapy beyond 6 months, even if an initial benefit was seen, also has no further benefit over IFX monotherapy [25].

Most recently, subcutaneous administration of IFX has been shown to be more convenient and user-friendly mode of administration [26]. The subcutaneous administration of IFX (IFX-SC) has been shown to have stable, consistently higher levels of the drug and significantly lower immunogenicity [26,27] while maintaining high clinical response and safety [27]. Studies have shown that IFX induction and maintenance are associated with higher rates of response and remission in CD-perianal fistula healing as well as higher treatment persistence compared to ADA [28].
### Table 1. Summary of RCTs evaluating the safety and efficacy of infliximab to induce or maintain remission in CD [10,12,13,15,18,23–25,29].

<table>
<thead>
<tr>
<th>Author, Trial Name (Year)</th>
<th>Participants</th>
<th>Regimen</th>
<th>Follow-Up (Weeks)</th>
<th>Primary Outcome Results (%)</th>
<th>Safety/Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inclusion Criteria</td>
<td>Number of Participants (n=)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D’Haens (1999) [13]</td>
<td>Moderate–severe CD a</td>
<td>30</td>
<td>Single IFX infusion: 5 mg/kg</td>
<td>4</td>
<td>CDEIS d score change (mean)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Single IFX infusion: 10 mg/kg</td>
<td></td>
<td>10.6 to 4.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Single IFX infusion: 20 mg/kg</td>
<td></td>
<td>13.3 to 6.9</td>
</tr>
<tr>
<td>Rutgeerts (1999) [10]</td>
<td>Previous IFX induction response. Moderate–severe CD a</td>
<td>73</td>
<td>10 mg/kg IFX every 8 weeks, 4 infusions total</td>
<td>44</td>
<td>Clinical response e (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hanaeur, ACCENT I (2002) [18]</td>
<td>CDAI &gt; 220</td>
<td>573</td>
<td>SDRi b and SDRm c</td>
<td>30</td>
<td>Clinical remission f (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SDRi b then 10 mg/kg IFX every 8 weeks</td>
<td></td>
<td>Clinical remission f (%)</td>
</tr>
<tr>
<td>Sands, Accent II (2004) [29]</td>
<td>Fistulizing CD</td>
<td>282</td>
<td>SDRi b and SDRm c</td>
<td>54</td>
<td>Median time to loss of response g (weeks)</td>
</tr>
<tr>
<td>Targan (1997) [12]</td>
<td>Moderate–severe CD a</td>
<td>108</td>
<td>Single IFX infusion: 5 mg/kg</td>
<td>48</td>
<td>Clinical response e (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Single IFX infusion: 10 mg/kg</td>
<td></td>
<td>48</td>
</tr>
<tr>
<td>Van Assche, IMID (2008) [25]</td>
<td>6 months of controlled disease with IFX and an immunosuppressive</td>
<td>80</td>
<td>SDRm c Immunosuppressive continued (vs. SDRm c Immunosuppressive stopped)</td>
<td>104</td>
<td>Change required in IFX dose or interval (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- **SDRi b:** Single dose remission b
- **SDRm c:** Multiple dose remission c
- **CDEIS d:** Clinical Disease Activity Index d
- **Clinical remission e:** Percentage of patients achieving clinical remission e
- **Median time to loss of response g:** Median time to loss of clinical remission g
- **Safety/Adverse Events:** AE: Adverse Events; MCAE: Major Clinical Adverse Event; SAE: Serious Adverse Event.
## Table 1. Cont.

<table>
<thead>
<tr>
<th>Author, Trial Name (Year)</th>
<th>Participants Inclusion Criteria</th>
<th>Regimen</th>
<th>Follow-Up (Weeks)</th>
<th>Primary Outcome Results (%)</th>
<th>Safety/Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colombel, SONIC (2010) [23]</strong></td>
<td>Moderate–severe disease a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>508</td>
<td>AZA group: 2.5 mg/kg daily AZA + Plc infusions</td>
<td>30</td>
<td>Steroid-free clinical remission d (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IFX group: SDRm c + daily oral Plc</td>
<td></td>
<td>44.4</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Combination Group: SDRm c + 2.5 mg/kg daily AZA</td>
<td></td>
<td>56.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colombel, SONIC (2010) [23]</td>
<td>Steroid dependent disease + stable AZA/6-MP dose or naïve to AZA/6-MP</td>
<td>113</td>
<td>SDRI a + AZA/6-MP (vs Plc + AZA/6-MP)</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>LeMann (2006) [15]</td>
<td>Steroid therapy initiated within previous 6 weeks due to active disease</td>
<td>126</td>
<td>5 mg/kg IFX IV at weeks 1, 3, 7, 14, then SDRm c + either methotrexate 10 mg/week escalating to 25 mg/week OR Plc</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Steroid-free clinical remission d (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IFX: infliximab, Plc: placebo, AZA: azathioprine, AE: adverse event, MCAE: most common adverse event, SAE: severe adverse event. a = CDAI 220–450; b = Standard Dose Regimen Induction dose: 5 mg/kg IV over 2 h, at weeks 0, 2 and 6; c = Standard Dose Regimen Maintenance dose: 5 mg/kg IV over 2 h, every 8 weeks; d = CDEIS (Crohn’s Disease Endoscopic Index of Severity): <3 considered remission; e = clinical response: ≥70-point decrease in CDAI; f = clinical remission: CDAI < 150 g = loss of response: increase in disease severity/activity, need for additional therapy or discontinuation of medication owing to perceived lack of efficacy.
2.1.2. Adalimumab

The following RCTs are summarized in Table 2. The optimal induction dose of adalimumab (ADA) is 160 mg, then 80 mg, two weeks apart [30,31]. A dose of 40 mg of ADA weekly or every other week is equally effective in maintaining remission in patients with CD [32]. ADA is superior to placebo in patients who are intolerant or who have lost response to IFX [33]. The EXTEND trial also found ADA is superior to placebo in terms of mucosal healing and had higher endoscopic and clinical remission rates [33,34].

Table 2. Summary of RCTs evaluating the safety and efficacy of adalimumab to induce or maintain remission in CD [30–34].

<table>
<thead>
<tr>
<th>Author, Trial Name (Year)</th>
<th>Participants Inclusion Criteria</th>
<th>Number of Participants (n=)</th>
<th>Adalimumab Regimen</th>
<th>Follow-Up Length (Weeks)</th>
<th>Primary Outcome</th>
<th>Primary Outcome (%)</th>
<th>Safety/Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanauer, Classic I (2006) [30]</td>
<td>Moderate–severe disease native to anti-TNF therapy</td>
<td>299</td>
<td>Injections at week 0 and week 2: 1.40 mg/20 mg 2.80 mg/40 mg 3.160 mg/80 mg</td>
<td>4</td>
<td>Rates of clinical remission at week 4, CDAI &lt; 150</td>
<td>1. 18 2. 24 3. 36</td>
<td>1.0.36 2.0.06 3.0.001</td>
</tr>
<tr>
<td>Colombel, CHARM (2007) [31]</td>
<td>Moderate–severe disease</td>
<td>778</td>
<td>1. week 4–40 mg eow 2. week 4–40 mg weekly</td>
<td>26 and 56</td>
<td>Rates of clinical remission at weeks 26, 56</td>
<td>1. week 26: 36 2. week 26: 47 56 weeks: 26 weeks: 17 56 weeks: 12</td>
<td>&lt;0.001 &lt;0.001</td>
</tr>
<tr>
<td>Rutgeerts, EXTEND (2012) [34]</td>
<td>Moderate–severe disease</td>
<td>135</td>
<td>weeks 0 and 2–160 and 180 mg week 4–40 mg row</td>
<td>12 and 52</td>
<td>1.Mucosal healing at weeks 12 and 52 2.Remission rates CDEIS at weeks 12 and 5 3.Clinical remission at weeks 12 and 52</td>
<td>1. week 12: 27; week 52: 74 2. week 12: 52; week 52: 28 3. week 12: 47; week 52: 33 1. week 12: 23; week 52: 12 2. week 12: 22; week 52: 12 3. week 12: 22; week 52: 12</td>
<td>AE: (66.7%) MCAE: headache (10.4%) SAE: 14.8%</td>
</tr>
</tbody>
</table>

ADA: adalimumab, Plc: placebo, eow: every other week, AE: adverse event, MCAE: most common adverse event, SAE: severe adverse event

The above trials reported an incidence of around 5% of serious adverse events and serious infections. Common adverse events include injection site complications, nausea, headache and infections. A 2014 meta-analysis concluded that, overall, ADA generally has a favorable safety profile [35].

One problem with biologic therapies is the loss of efficacy due to immunogenicity. The DIAMOND trial, the only RCT comparing ADA monotherapy with ADA/AZA combination therapy, determined that there is no significant difference in achieving clinical remission between groups [36]. However, a follow-up study of the GAIN and ADHERE trials deemed ADA/AZA combination therapy beneficial to those who were intolerant or had lost response to IFX [33]. A recent meta-analysis concluded that this therapy is not superior to monotherapy in the induction and maintenance of CD despite being associated with lower immunogenicity [37]. Combination therapy was also associated with a small but statistically significant increased risk for serious and/or opportunistic infections, a higher risk of lymphoma and an increased risk of malignancy compared to monotherapy and other therapies [38–40].

ADA showed efficacy in stricture disease of the small bowel in the CREOLE study [41]. Two small studies have also suggested ADA appears effective in preventing post-operative
recurrence [42,43]. The CHARM study showed that complete fistula closure at week 56 was significantly greater in patients on ADA compared with placebo (33%-vs.-13%) [32]. Data from the ADHERE and CHARM studies deemed ADA more effective than placebo in inducing fistula healing and maintaining it [44]. The CHOICE trial assessed the quality of life in patients with fistula disease who had previously failed IFX therapy. It demonstrated ADA was effective in inducing complete fistula healing in 39% of patients [45]. The best outcomes have been achieved when surgical and medical therapies have been used in conjunction. The insertion of draining setons along fistula trajectories prior to the institution of infliximab therapy improves early and long-term remission rates [46].

2.2. Integrin Receptor Antagonists

Vedolizumab

Vedolizumab (VDZ) is a relatively new biologic therapy licensed for use in treating CD in Europe [47]. It acts as a gut-selective integrin blocker and consists of monoclonal IgG-1 that binds to α4β7 integrin on T-helper lymphocytes, preventing their translocation from blood to gut tissue [48]. Its selectivity was demonstrated in Wyant et al. [49] after VDZ reduced the response to antigens administered orally but not parenterally. A more recent study suggested that VDZ causes changes in innate rather than adaptive immunity, affecting gut macrophage populations to reduce local inflammation [50].

The standard dosing regimen includes an induction period of 300 mg intravenous VDZ infusions at weeks 0, 2 and 6, followed by maintenance therapy of 300 mg every 8 weeks [51]. However, a recent review concluded that further studies are needed regarding VDZ dose optimization [52].

VDZ was first tested in the seminal GEMINI trials (Table 3), which demonstrated that up to 39.0% of patients were in remission after one year compared to 21.6% with placebo [53]. They also suggested that VDZ would be more effective in biologic-naïve patients and that increasing the dosing frequency could improve outcomes in patients who lose response [53–58]. Many larger studies have since been carried out to assess the real-world safety and efficacy of VDZ, demonstrating similar results to the GEMINI studies [53–60]. A Scottish cohort study showed a 52.5% reduction in hospitalizations in the 12 months after VDZ treatment (compared to the previous 12 months) [61]. VISIBLE 2 phase 3 clinical trials examined SC VDZ in patients with CD and demonstrated that SC VDZ is both effective and safe in VDZ-naïve IBD patients [62].

Over 152 weeks, the drug was shown to be comparably safe to other available biologics, with long-term benefits to health-related quality of life [63,64]. Although serious adverse events and infections were slightly more common in VDZ users than placebo, many of these were associated with exacerbation or complications of Crohn’s [63]. The most common other adverse event was nasopharyngitis, rates of which have been included in Table 5. Multiple other studies have demonstrated a favorable safety profile for extended and preoperative treatment [65].
Table 3. Summary of RCTs evaluating the safety and efficacy of vedolizumab to induce or maintain remission in CD [47,48,54].

<table>
<thead>
<tr>
<th>Author, Trial Name (Year)</th>
<th>Participants</th>
<th>Number of Participants (n=)</th>
<th>Regimen</th>
<th>Follow-Up (Weeks)</th>
<th>Primary Outcome Results (%)</th>
<th>Safety/Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inclusion Criteria</td>
<td></td>
<td></td>
<td></td>
<td>Outcome</td>
<td>Drug</td>
</tr>
<tr>
<td>Sandsborn. (2013) [48]</td>
<td>Moderate–severe CD&lt;sup&gt;a&lt;/sup&gt; plus one other indication of CD</td>
<td>461</td>
<td>300 mg IV VDZ, every 4 or 8 weeks PI.</td>
<td>52</td>
<td>Clinical remission&lt;sup&gt;f&lt;/sup&gt;</td>
<td>36.4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sands, GEMINI II&amp;III (2017) [47]</td>
<td>Moderate–severe CD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1476</td>
<td>300 mg IV VDZ, every 8 weeks PI.</td>
<td>52</td>
<td>Clinical remission&lt;sup&gt;d,f&lt;/sup&gt;</td>
<td>48.9</td>
</tr>
<tr>
<td>Vermiere, GEMINI LTS (2017) [54]</td>
<td>Moderate–severe CD&lt;sup&gt;a&lt;/sup&gt; (HBI 8–18)</td>
<td>1349</td>
<td>300 mg IV VDZ, every 4 weeks PI.</td>
<td>152</td>
<td>Clinical remission (HBI)</td>
<td>89.0</td>
</tr>
</tbody>
</table>

CD: Crohn’s disease, VDZ: vedolizumab, IV: intravenous, PI: post-induction, Plc: placebo, SAE: severe adverse event, SI: serious infection, HBI: Harvey–Bradshaw Index, a = CDAI 220–450; b = dose every 4 weeks; c = dose every 8 weeks; d = in TNF-naïve patients; e = in patients previously failing anti-TNF treatments; f = clinical remission, CDAI < 150.
VDZ has been shown to be particularly effective when used in conjunction with initial concomitant steroid treatment or another immunomodulator; however, this increases the risk of adverse events [66]. Treatment will likely have a greater effect on patients with CD for less than 2 years [66]. Interestingly, VDZ treatment was not only associated with a 45–75% improvement in extra-intestinal manifestations but also with paradoxical skin manifestation and inflammatory arthralgia/arthritis in patients who previously did not express this [67]. Early response to VDZ treatment may be a good indicator of inducing remission beyond one year [68]. Vedolizumab may be effective in treating extra-intestinal manifestations related to luminal disease activity (e.g., type 1 peripheral arthritis and erythema nodosum) but has not shown biochemical improvement in primary sclerosing cholangitis [69].

Although most studies proposed VDZ as a suitable alternative to anti-TNFα biologics, the reported percentages of patients showing clinical remission or response vary and are often low. This may be because VDZ is frequently given after multiple other treatment failures and only to those with moderate–severe disease [70].

Based on the evidence assessed in this review, the best use of VDZ would be as long-term maintenance therapy for those responsive at 6 weeks and used in conjunction with corticosteroids only in the early stages of treatment.

2.3. IL-12 and IL-23 Antagonists

2.3.1. Ustekinumab

Ustekinumab (UST) is an IgG1 antibody that targets the P40 subunit of interleukins 12 and 23 [71]. Originally approved for the treatment of psoriasis and psoriatic arthritis, it was approved for the treatment of moderate-to-severe CD after the seminal UNITI trials (Table 4) [71,72]. Within CD pathogenesis, UST targets the Th-1 and Th-17 pathways [73,74].

The UNITI phase 3 trials demonstrated a clinical response to UST after 6 weeks of treatment in patients for whom conventional or anti-TNFα therapy had failed [71]. Many real-world observational studies have since been carried out to assess the safety and efficacy of UST. Initial clinical response rates have been reported to be 38.9–84.0% [71,72]. Dose escalation has been reported as effective in up to 73.0% of patients losing response to UST treatment. A small number of studies have reported UST to be effective in patients with aggressive fistulizing or perianal disease for whom other treatments have been ineffective [71,72].

UST has a good safety profile, and most adverse events reported have been complications of CD due to a lack of treatment response. A Cochrane review found 67% had at least one adverse event compared to 73% of placebo patients [74,75]. The UNITI trials found varying adverse effects to be the most common, notably arthralgia, headaches and infections [71]. In these trials, adverse and serious adverse effects were more common in the placebo use than in UST [72].
Table 4. Summary of RCTs evaluating the safety and efficacy of ustekinumab to induce or maintain remission in CD [71,72].

<table>
<thead>
<tr>
<th>Author, Trial Name (Year)</th>
<th>Participants</th>
<th>Primary Outcome Results (%)</th>
<th>Safety/Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inclusion Criteria</td>
<td>Number of Participants (n=)</td>
<td>Regimen</td>
</tr>
<tr>
<td>Feagan, UNITI I, (2016) [71]</td>
<td>Moderate–severe CD a</td>
<td>741</td>
<td>130 mg UST IV single dose</td>
</tr>
<tr>
<td>Feagan, UNITI II, (2016) [71,72]</td>
<td>Moderate–severe CD a</td>
<td>628</td>
<td>130 mg UST IV single dose</td>
</tr>
<tr>
<td>Feagan, IM-UNITI, (2016) [71–73]</td>
<td>Moderate–severe CD a</td>
<td>397</td>
<td>90 mg SC UST every 8/12 weeks</td>
</tr>
</tbody>
</table>

CD: Crohn’s disease, UST: ustekinumab, IV: intravenous, SC: subcutaneous, Plc: placebo, AE: adverse event, SAE: severe adverse event, SI: serious infection, MCAE: most common adverse event. a = CDAI 220–450; b = CDAI < 150; c = CDEIS score of 4 or less d = decrease in CDAI from baseline ≥100.
2.3.2. Risankizumab

Risankizumab-rzaa is a humanized IgG1 monoclonal antibody that selectively binds to the p19 subunit of human IL-23 cytokine and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses. Risankizumab-rzaa inhibits the release of pro-inflammatory cytokines and chemokines [76]. The efficacy and safety of risankizumab were evaluated in three multicenter, double-blind, placebo-controlled Phase 3 clinical studies: two replicate induction studies (Advance and Motivate) and a maintenance study (FORTIFY) [77–79].

Significantly more patients receiving risankizumab achieved the coprimary endpoints of CDAI clinical remission and endoscopic response at week 12 compared to those receiving placebo. At week 52, the proportion of patients in FORTIFY achieving CDAI < 150 clinical remission was 52% for risankizumab 360 mg vs. 41% for withdrawal/placebo.

2.3.3. Janus Kinase (JAK) Inhibitors

JAKs are intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes, including inflammatory responses, hematopoiesis and immune surveillance. The JAK family of enzymes contains four members: JAK1, JAK2, JAK3 and TYK2, which work in pairs to phosphorylate and activate signal transducers and activators of transcription (STATs) [80].

Upadacitinib, a novel Janus kinase (JAK) inhibitor, has been recently used in the management of CD. The JAK family of kinases plays an important role in mediating signaling pathways downstream of various cytokine receptors implicated in immune response modulation. It is one of the licensed medications for CD in United Arab Emirates based on the coming study results [80–82].

The mechanism of action of upadacitinib in the treatment of CD emerges from its ability to modulate key pathways involved in its pathogenesis, mainly by selectively inhibiting JAKs. Upadacitinib has the ability to decrease the production of pro-inflammatory cytokines, like interleukins (IL-6, IL-12, IL-23 and interferons (IFN-γ)), which are crucial to the maintenance of chronic inflammation in CD. This approach holds promise for achieving remission and improving patient quality of life, particularly for those who do not respond to other treatment modalities for CD and its known complications [83].

As described in many clinical trials, patients with moderate-to-severe CD responded favorably to upadacitinib induction and maintenance medication compared to a placebo, and the benefit-to-risk ratio was deemed favorable [84–87].

In two phase 3 induction trials (U-EXCEL and U-EXCEED), patients with moderate-to-severe CD were randomly assigned to receive 45 mg of upadacitinib or placebo (2:1 ratio) once daily for 12 weeks. In the U-ENDURE maintenance trial, patients who had a clinical response to upadacitinib induction therapy were randomly assigned to receive 15 mg of upadacitinib, 30 mg of upadacitinib, or placebo (1:1:1 ratio) once daily for 52 weeks [80–82].

The primary endpoints for induction (week 12) and maintenance (week 52) were clinical remission (defined as a Crohn’s Disease Activity Index score of <150 [range, 0 to 600, with higher scores indicating more severe disease activity]) and endoscopic response (defined as a decrease in the Simple Endoscopic Score for CD [SES-CD; range, 0 to 56, with higher scores indicating more severe disease] of >50% from baseline of the induction trial [or for patients with an SES-CD of 4 at baseline, a decrease of ≥2 points from baseline]).

A total of 526 patients underwent randomization in U-EXCEL, 495 in U-EXCEED and 502 in U-ENDURE. A significantly higher percentage of patients who received 45 mg upadacitinib than those who received placebo had clinical remission (in U-EXCEL, 49.5% vs. 29.1%; in U-EXCEED, 38.9% vs. 21.1%) and an endoscopic response (in U-EXCEL, 45.5% vs. 13.1%; in U-EXCEED, 34.6% vs. 3.5%) (p < 0.001 for all comparisons). At week 52 in U-ENDURE, a higher percentage of patients had clinical remission with 15 mg upadacitinib (37.3%) or 30 mg upadacitinib (47.6%) than with placebo (15.1%), and a higher percentage had an endoscopic response with 15 mg upadacitinib (27.6%) or 30 mg upadacitinib (40.1%) than with placebo (7.3%) (p < 0.001 for all comparisons).
Herpes zoster infections occurred more frequently in the 45 mg and 30 mg upadacitinib groups than in the respective placebo groups, and hepatic disorders and neutropenia were more frequent in the 30 mg upadacitinib group than in the other maintenance groups. Gastrointestinal perforations developed in four patients who received 45 mg upadacitinib and in one patient each who received 30 mg or 15 mg upadacitinib [80].

2.4. Biosimilars

For IFX, there are three biosimilars currently licensed: Infliximab-dyyb/CT-P13 (Inflectra and Remsima), Infliximab-abda/SB2 (Renflexis in the US and Flixabi in the EU), and infliximab-qbtx/GP1111 (Zessly) [87–92]. Multiple studies have shown that these biosimilars are no less effective or safe than the original IFX, and there is a wealth of anecdotal evidence to further support this. The safety profiles of all IFX biosimilars are also all comparable.

When a biosimilar becomes licensed for use in one condition, it also becomes licensed for any other indications of the original drug. Thus, some of these drugs do not have any CD-specific trials to assess efficacy and safety. This includes the four licensed biosimilars for ADA (Humira): Amgevita, Imraldi, Hyrimoz and Hulio.

3. Discussion

NICE guidelines recommend the use of IFX and ADA as the first-line biological therapy for patients with refractory CD [3]. The efficacy and safety of IFX and ADA has been well documented. A comparator study has found no significant differences in efficacy. However, Kennedy et al. [17] identified a lower immunogenicity in those taking ADA than IFX (28.5% vs. 62.8%). Despite higher immunogenicity being associated with higher rates of infusion reactions and, thus, higher treatment failure rates, this does not seem to affect the overall efficacy rates or proportions of adverse events when comparing the two. Switching from IFX to ADA is associated with a loss of tolerance and efficacy within a year [93]. However, the subcutaneous administration of ADA means that it is preferable for some patients [93].

One-third of patients do not respond to a specific anti-TNFα agent, and some develop long-term intolerance [70]. Transferring drug classes can overcome these challenges. UST has frequently been compared to VDZ as a potential treatment for patients with CD unresponsive to anti-TNFα drugs. One study found no significant difference in the efficacy or safety between the two drugs [89]. Another suggested that VDZ is associated with a higher postoperative complication and ileus rate (p = 0.009, p = 0.015 respectively). A 2018 review suggested that patients with more severe disease or with prior anti-TNFα exposure were more likely to respond to UST than VDZ [94]. IL-12 and IL-23 antagonists constitute an important treatment addition for the treatment of moderate-to-severe CD with a trusted safety profile.

Accurate prognostic measurements at diagnosis would allow for a more effective, personalized approach to treatment; however, effective predictors have yet to be elucidated and, therefore, must be further investigated [5]. With recent research supporting the early utilization of biological therapies in patients with aggressive CD, the ‘top-down’ managerial approach should be considered in the next revision of NICE guidelines.

The search strategy benefited from an extensive range of keywords, allowing relevant literature to be obtained. Manually identifying appropriate papers from bibliographies expanded our range of suitable evidence. However, we recognize some limitations in the approach. Further search terms such as: “Inflectra” and “Amgevita” could have identified biosimilar-specific papers. Furthermore, the keywords “Tuberculosis”, “Progressive multifocal leukoencephalopathy” and “Lymphoma” that target individual adverse events commonly associated with biologics could have enhanced the search effectiveness.
4. Materials and Methods

We searched Embase, PubMed and Cochrane databases to obtain relevant literature. Search terms are shown in Table 5. Results from database inception to 5 January 2020 were selected after title and abstract analysis. Papers studying pediatric, obstetric or non-human populations were excluded.

Table 5. Terms used in literature search of databases.

- ‘Crohns disease’, ‘Crohns’, ‘IBD’, and ‘inflammatory bowel diseases’

After title and abstract analysis, our search generated 63 relevant papers. Bibliographies of relevant literature were hand-searched to obtain further appropriate papers.

5. Conclusions

Licensed drugs discussed in this review have been proven to be safe and efficacious. Some have shown particular benefits within specific populations. Advanced medical therapies have shown efficacy and safety rates and should, therefore, be considered for inclusion in future treatment pathways to offer a more diverse range of biological therapies for the treatment of CD in the UAE.

Funding: This research received no external funding.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were generated for this study.

Conflicts of Interest: The authors declare no conflict of interest.

References


74. Ge, W.S.; Fan, J.G. Integrin antagonists are effective and safe for Crohn’s disease: A meta-analysis. World J. Gastroenterol. 2015, 21, 4744–4749. [CrossRef]


**Disclaimer/Publisher’s Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.