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Review

Biologics in Focus: A Comprehensive Review of the Current Biological Therapies for Ulcerative Colitis in the United Arab Emirates (UAE)

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Abstract: Background: Ulcerative colitis (UC) is a relapsing–remitting inflammatory condition that has an increasing incidence across the world, including in the Middle East. Biological monoclonal antibody drugs (biologics) have been shown to be advantageous in treating UC. We undertook a review of the currently available biological and small-molecule therapies, with a particular emphasis on those currently licensed in the United Arab Emirates (UAE). Methods: We conducted a literature search for studies on biological therapies using the PubMed, MEDLINE, and Embase databases using a list of keywords that were generated following referral to existing treatment guidelines for UC. Papers looking at biological and small-molecule treatments for UC in adult populations were included. Pediatric, pregnancy, and cost-effectiveness studies were excluded. Results and Discussion: There are currently three classes of biologics (anti-tumor necrosis factors (anti-TNFs), anti-integrins, and anti-interleukins) and one class of small-molecule therapy (Janus kinase (JAK) inhibitor) licensed for UC treatment in the UAE. Within the anti-TNF class, three medications have been approved: infliximab, adalimumab, and golimumab. For JAK inhibitors, there are two: tofacitinib and upadacitinib. There is only one licensed medication in the remaining classes: vedolizumab (anti-integrin) and ustekinumab (anti-interleukin). The length of studies varied from 6–8 weeks for induction studies and 52 weeks for maintenance studies. The studies demonstrated increased efficacy in these medications compared to placebos when clinical response, clinical remission, and other secondary measures such as mucosal healing were assessed following the induction and maintenance phases. Biosimilars of infliximab and adalimumab are also available for treating UC, and their safety and efficacy were compared to their biologic originators. Conclusions: The introduction of biologics has been proven to be beneficial for the treatment of UC. This review summarizes the efficacy and safety of each biological class in the treatment of the disease; however, biological drug registries and further studies are required to offer more insight into the comparative efficacy and safety of these agents.

Keywords: biologics; ulcerative colitis; United Arab Emirates; infliximab; tofacitinib

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1. Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) that is characterized by symptoms of bloody diarrhea and rectal urgency [1]. Its incidence has increased in Western Europe and North America over the past century, and more recently in Asian nations [2,3]. The multifactorial etiology of UC is not clearly defined. The contributing factors

to chronic colonic inflammation include gastrointestinal dysbiosis, genetic susceptibility, and environmental factors [4].

The aim of pharmacological treatment is to reduce mucosal inflammation and maintain remission, with a step-up approach recommended by the current guidelines. Typically, 5-Aminosalicylic acids (5-ASAs) are used for induction and maintenance of remission [5,6]. Conventionally, when the 5-ASA response is limited, corticosteroids are employed for induction and thiopurines are used for maintenance. Recently, the range of available biologics has grown. As their costs have decreased, they are often favorable due to their decreased toxicity and increased tolerability [5]. This review explores the biological and small-molecule therapies that are currently licensed for UC treatment in the United Arab Emirates (UAE) [7].

2. Results

We identified three biological classes (anti-tumor necrosis factors (anti-TNFs), anti-integrins, and anti-interleukins) and one small-molecule therapy class (Janus kinase (JAK) inhibitor) licensed for UC treatment. We found three anti-TNFs (infliximab, adalimumab, and golimumab), one anti-integrin (vedolizumab), one anti-interleukin (ustekinumab), and two JAK inhibitors (tofacitinib, upadacitinib). Various clinical trials have investigated the safety and efficacy of these drugs in UC management (Table 1). Biosimilars have been compared to their original biologics (Table 2), and several pipeline biologics were identified (Table 3).

Table 1. Key clinical trials investigating biological and small-molecule therapies currently licensed for UC.

Trial (Study Weeks)	Intervention	No. of Patients	% Remission * (p vs. Placebo)	% Adverse Events **	% Infections **	Most Common Adverse Event (%)
ACT1 2005 [8] (30)	Placebo	121	14.9	85.1	38.8	UC exacerbation (33.1)
	Infliximab 5 mg/kg	121	38.8 ($p < 0.001$)	87.6	43.8	UC exacerbation (19.0)
	Infliximab 10 mg/kg	122	32.0 ($p < 0.002$)	91.0	49.2	UC exacerbation (21.3)
ACT2 2005 [8] (54)	Placebo	123	5.7	73.2	23.6	UC exacerbation (16.3)
	Infliximab 5 mg/kg	121	33.9 ($p < 0.001$)	81.8	27.3	Headache (15.7)
	Infliximab 10 mg/kg	120	27.5 ($p < 0.001$)	80.0	28.3	Headache (21.7)
Sands et al., 2001 [9] (12)	Placebo	3	0	100	-	UC exacerbation (66.7)
	Infliximab 5 mg/kg	3	66.7 #	100	-	Cellulitis (33.3)
	Infliximab 10 mg/kg	3	33.3 #	100	-	Headache (66.7)
	Infliximab 20 mg/kg	2	50 #	100	-	Pruritus (50.0)
Probert et al., 2003 [10] (6)	Placebo	40	30	5 (SAE)	-	Sepsis/colectomy
	Infliximab 5 mg/kg	41	39 ($p = 0.76$)	0 (SAE)	-	-
Järnerot et al., 2005 [11] (12)	Placebo	21	37.5	61.9	4.7	Sepsis (8.3)
	Infliximab 5 mg/kg	24	100 #	54.1	8.3	Arthralgia (14.3)
ULTRA1 2011 [12] (8)	Placebo	130	9.2	48.4	15.7	ISR (3.1)
	Adalimumab 160/80/40 mg	130	18.5 ($p = 0.031$)	50.2	14.3	ISR (5.8)

Table 1. *Cont.*

Trial (Study Weeks)	Intervention	No. of Patients	% Remission * (p vs. Placebo)	% Adverse Events **	% Infections **	Most Common Adverse Event (%)
ULTRA2 2012 [13] (52)	Placebo	246	8.5	83.8	39.6	ISR (3.8)
	Adalimumab 160/80/40 mg	248	17.3 (p = 0.004)	82.9	45.1	ISR (12.1)
ULTRA3 2014 [14] (208)	Open-label, Adalimumab 40 mg weekly/fortnightly	588	24.7	17.7 (E/100)	344.6 (E/100)	UC exacerbation (25.2 E/100)
Suzuki et al., 2017 [15] (196)	Open-label, Adalimumab 40 mg or 80 mg fortnightly	126	19.2	431.5 (E/100)	137.5 (E/100)	UC exacerbation (11.7 E/100)
InspirADA 2017 [16] (26)	Open-label, adalimumab 160/80/40 mg	463	48	74.3	29.6	ISR (9.9)
PURSUIT-SC 2014 [17] (6)	Placebo	331	6.4	38.2	12.1	Headache (5.2)
	Golimumab 200/100 mg	331	17.8 (p = 0.0437)	37.5	11.8	Nasopharyngitis (3.3)
	Golimumab 400/200 mg	331	17.9 (p = 0.0008)	38.9	12.3	Headache (4.5)
PURSUIT-M 2014 [18] (54)	Placebo	156	15.6	66	28.2	UC exacerbation (18.6)
	Golimumab 50 mg	151	23.2 (p = 0.122)	72.7	39.0	UC exacerbation (17.5)
	Golimumab 100 mg	151	27.8 (p = 0.004)	73.4	39.0	UC exacerbation (15.6)
PURSUIT-J 2017 [19] (52)	Placebo	31	6.5	71	35.5	Nasopharyngitis (22.6)
	Golimumab 100 mg	32	50 #	96.9	65.6	Nasopharyngitis (53.1)
PROgECT 2018 [20] (50)	Open-label golimumab 200 mg/100 mg	103	13.1	67	24.3	UC exacerbation
GEMINI-I Induction 2013 [21] (6)	Placebo	149	5.4	46	15	UC exacerbation (5) and headache (5)
	Double-blind vedolizumab 300 mg	225	16.9 (p = 0.001)	40	14	Headache (7)
	Open-label Vedolizumab 300 mg	521	-	47	14	Headache (8)
GEMINI-1 Maintenance 2013 [21] (52)	Placebo	126	15.9	84	71	Nasopharyngitis (12)
	Vedolizumab 300 mg every 4 weeks	125	44.8 (p < 0.001)	81	71	Nasopharyngitis (14)
	Vedolizumab 300 mg every 8 weeks	122	41.8 (p < 0.001)	82	71	Nasopharyngitis (16)
VARSITY 2019 [22] (52)	Vedolizumab	383	31.3	62.7	23.4	UC exacerbation (11.5)
	Adalimumab	386	22.5 (p = 0.006) ^	69.2	34.6	UC exacerbation (16.3)
OCTAVE Induction 1 2017 [23] (8)	Placebo	598	8.2	59.8	15.6	Nasopharyngitis (7.4)
	Tofacitinib 10 mg	-	18.5 (p = 0.007)	56.5	23.3	Headache (7.8)
OCTAVE Induction 2 2017 [23] (8)	Placebo	541	3.6	52.7	15.2	Headache (8.0)
	Tofacitinib 10 mg	-	16.6 (p < 0.001)	54.1	18.2	Headache (7.7)

Table 1. *Cont.*

Trial (Study Weeks)	Intervention	No. of Patients	% Remission * (p vs. Placebo)	% Adverse Events **	% Infections **	Most Common Adverse Event (%)
OCTAVE Sustain 2017 [23] (52)	Placebo	593	11.1	75.3	24.2	UC exacerbation (35.9)
	Tofacitinib 5 mg	-	34.3 ($p < 0.001$)	72.2	35.9	UC exacerbation (18.2)
	Tofacitinib 10 mg	-	40.6 ($p < 0.001$)	79.6	39.8	UC exacerbation (14.8)
UNIFI Induction 2019 [24] (8)	Placebo	319	5.3	48	15.4	UC exacerbation (5.6)
	Ustekinumab 130 mg	320	15.6 ($p < 0.001$)	41.4	15.9	Headache (6.9)
	Ustekinumab 6 mg/kg	322	15.5 ($p < 0.001$)	50.6	15.9	Headache (4.1)
UNIFI Maintenance 2019 [24] (52)	Placebo	175	24	78.9	46.3	UC exacerbation (28.6)
	Ustekinumab 90 mg every 12 weeks	172	38.4 ($p = 0.002$)	69.2	33.7	Nasopharyngitis (18)
	Ustekinumab 90 mg every 8 weeks	176	43.8 ($p < 0.001$)	77.3	48.9	Nasopharyngitis (14.8)
U-ACCOMPLISH Induction [25] 2022 (8)	Placebo	177	4.1	39.5	4	Headache (5.1)
	Upadacitinib 45 mg	345	33.5 ($p < 0.0001$)	52.9	9	Acne (7)
U-ACHIEVE Induction [25] 2022 (8)	Placebo	155	5	62	5.2	UC exacerbation (13.5)
	Upadacitinib 45 mg	319	26.1 ($p < 0.0001$)	56.4	6.9	Neutropenia (5) Creatinine kinase elevation (5)
U-ACHIEVE Maintenance [25] 2022 (52)	Placebo	149	12	76	18	UC exacerbation (30)
	Upadacitinib 15 mg	148	30.7 ($p < 0.0001$)	78	25	UC exacerbation (13)
	Upadacitinib 30 mg	154	39 ($p < 0.0001$)	79	27	Nasopharyngitis (14)

Abbreviations: ISR, injection-site reactions; UC, ulcerative colitis. Indications for trials were moderate-to-severe UC except for the following: Sands et al. [9] (severe UC), Probert et al. [10] (steroid-resistant UC). * Remission was assessed based on the Mayo score except for the following: Sands et al. [9] (Truelove and Witts score), Probert et al. [10] (ulcerative colitis symptom score), Järnerot et al. [11] (Seo index), InspirADA [16] (simple clinical colitis activity index), U-ACCOMPLISH, U-ACHIEVE induction and maintenance [25] (adapted Mayo: Mayo score excluding physician global assessment). ** Adverse events and infections are expressed in percentages except when stated otherwise: Events per 100 patient years (E/100). Probert et al. [10] published values for serious adverse events (SAE) rather than total adverse events. # p value vs. placebo not provided in the study. ^ p value given for the comparison between Adalimumab and Vedolizumab.

Table 2. Summary of clinical trials comparing biosimilars to their respective biologic agents.

Biologic	Biosimilar	Investigators	Design	Cohort	Outcome
Infliximab	Inflectra	Jørgensen et al., 2017 [26]	Phase IV, randomized, double-blind study	Adult patients on stable treatment with Infliximab >6 months	Rate of remission at 52 weeks higher for inflectra compared to infliximab (93% vs. 88%). Frequency of adverse events was similar
		Kaniewska et al., 2017 [27]	Phase III, open-label study	Acute severe UC	Similar rates of remission compared to infliximab (42% vs. 32%). No significant differences in safety
	Remicade	Shin et al., 2015 [28]	Phase I, randomized, single-blind study	Healthy subjects	Pharmacokinetic equivalence was demonstrated
	Imraldi	Shin et al., 2015 [29]	Phase I study	Healthy subjects	Pharmacokinetic bioequivalence
	Hyrimoz	Jaun-Lembach et al., 2017 [30]	Phase I study	N/A	Highly similar structure, purity, and biological activity

Table 3. Summary of biologic drugs currently in the pipeline for UC.

Drug Name	Mechanism of Action	Trial Identifier	Current Status
Adrilumab	α4β7 integrin antagonist	NCT01694485	Phase II study
Etrolizumab	α4β7 integrin antagonist	NCT02118584	Phase III study
Risankizumab	α4β7 integrin antagonist	NCT03398148	Phase II/III study
Mirikizumab	IL-23 inhibitor	NCT03518086	Phase III study
Spesolimab	IL-36 inhibitor	NCT03482635	Phase II/III study
Ontamalimab	MAdCAM-1 antagonist	NCT03290781	Phase III study
PF-00547659	MAdCAM-1 antagonist	NCT01620255	Phase II study
Bertililumab	Chemokine CCL11 inhibitor	NCT01671956	Phase II study
Neihulizumab	PSGL-1/CD162 antagonist	NCT03298022	Phase II study
KHK4083	OX40 receptor antagonist	NCT02647866	Phase II study

3. Methods

The British Society of Gastroenterology (BSG) [5] and European Crohn's and Colitis Organisation (ECCO) [6] guidelines were used to generate keywords (Table 4). We conducted a literature search of these keywords using the PubMed, Embase, and MEDLINE databases to identify relevant journal articles. Papers looking at biological and small-molecule treatments for UC in adult populations were included. Pediatric, pregnancy, and cost-effectiveness studies were excluded. Here, we provide a comprehensive literature review of the indications, efficacy, and safety of biologics and their biosimilars in UC treatment.

Table 4. Keywords used in the literature search of the databases.

'inflammatory bowel disease', 'IBD', 'ulcerative colitis', 'biologics', 'biosimilars', 'tumour necrosis factor', 'integrin', 'interleukin', 'Janus kinase', 'Adalimumab', 'Infliximab', 'Golimumab', 'Vedolizumab', 'Ustekinumab', 'Upadacitinib', 'Tofacitinib'

We searched online, including the UAE Ministry of Health website, to clarify which medicines were licensed in the UAE.

4. Discussion

4.1. Anti-Tumor Necrosis Factors

Infliximab, adalimumab, and golimumab are monoclonal anti-TNF antibodies that neutralize TNF-alpha, a proinflammatory cytokine that is oversecreted in the lamina propria of IBD patients [31]. Anti-TNF agents are indicated for treating moderate-to-severe, active UC when first-line therapies are contraindicated, not tolerated, or fail to cause a response [5]. The majority of the clinical trials used the Mayo score to assess their outcomes (Tables 5 and 6) [32].

Table 5. Components of the full Mayo score [32].

Parameter	Clinical Evaluation (One Option)	Score
1. Stool frequency (per day)	Normal number of stools	0
	1–2 stools more than normal	1
	3–4 stools more than normal	2
	≥5 stools more than normal	3

Table 5. *Cont.*

Parameter	Clinical Evaluation (One Option)	Score
2. Rectal bleeding	No blood seen	0
	Streaks of blood with stool less than half the time	1
	Obvious blood with stool most of the time	2
	Blood alone passes	3
3. Endoscopic findings	Normal mucosa or inactive disease	0
	Mild disease (erythema, decreased vascular pattern, mild friability)	1
	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)	2
	Severe disease (spontaneous bleeding, ulceration)	3
4. Physician's global assessment *	Normal	0
	Mild disease	1
	Moderate disease	2
	Severe disease	3

* Global assessment includes daily record of abdominal discomfort, general sense of well-being, and other observations such as physical findings or performance status.

Table 6. Interpretation of the calculated Mayo score [32].

Score	Interpretation
0–2	Remission (if one subscore = 2 and the other three = 0, this is classified as mild activity)
3–5	Mild activity
6–10	Moderate activity
>10	Severe activity

4.2. Infliximab (Remicade®)

4.2.1. Efficacy

Multiple studies have investigated the efficacy of infliximab for UC treatment. In the ACT1 and ACT2 trials [8], patients with a prior inadequate response to corticosteroids were treated with infliximab at a dose of 5 mg/kg, 10 mg/kg, or a placebo, and were followed until week 54 (ACT1) or week 30 (ACT2). In both trials, the proportion of patients achieving the primary endpoint, a clinical response (≥3-point decrease in Mayo score), was 1.7–2 times greater for infliximab compared to the placebo ($p < 0.001$ for all comparisons). The secondary endpoint, incidence of colectomy, was significantly lower in the infliximab patients compared to those who received the placebo (10% vs. 17%, $p < 0.007$). These findings are corroborated by Järnerot et al. [11], who found that a lower proportion of the patients receiving infliximab required a colectomy compared to the patients receiving the placebo (29% vs. 67%, $p < 0.017$). Sands et al. [9] assessed infliximab's efficacy via a clinical response at week 2 and the risk of colectomy, concluding that infliximab successfully treated UC. Of the patients receiving infliximab, 50% achieved a clinical response compared to 0% in the placebo group. A greater number of patients required colectomies in the placebo group. This study was not adequately powered, as only 11 participants were included; therefore, the reliability of results is questionable. Probert et al. [10] further refutes the evidence in Sands' study [9], finding no significant difference in the remission rates between the infliximab and placebo groups. However, Probert used stricter efficacy measures than Sands, reducing the comparability between these studies. Their study also only gave two doses of infliximab to induce remission, rather than the more standard three doses, and it had only small numbers of patients within the trial.

4.2.2. Safety

Infliximab is associated with an increased risk of serious infections. Tuberculosis risk in patients receiving infliximab is 2.86-fold greater than in patients receiving a placebo ($p = 0.03$) [33]. In ACT1 and ACT2 [8], a similar proportion of patients experienced adverse reactions in the placebo and infliximab groups. In ACT1, the incidence of serious infections was higher in patients receiving 10 mg/kg infliximab compared to those receiving the placebo (6.6% vs. 4.1%). In ACT2, a greater proportion of patients experienced adverse events when receiving 5 mg/kg (1.7%) and 10 mg/kg (2.5%) infliximab compared to those receiving the placebo (0.8%). One patient taking infliximab developed tuberculosis. Sands [9], Probert [10], and Järnerot [11] all report similar incidences of adverse effects between their placebo and infliximab-treated groups. The most common adverse events reported by Sands [9] were pruritus and urinary tract infections. Serious adverse effects in the Probert study [10] occurred in the placebo group only.

4.3. Adalimumab (Humira®)

4.3.1. Efficacy

Several studies have demonstrated adalimumab's efficacy for induction and maintenance therapy in moderate-to-severe UC patients with inadequate responses to conventional therapies. In ULTRA1 [12], a greater proportion of anti-TNF-naïve patients treated with subcutaneous adalimumab at a dose of 160 mg at week 0, 0.80 mg at week 2, and 40 mg at weeks 4 and 6 achieved the primary outcome measure, remission at 8 weeks, compared to patients receiving the placebo (18.5% vs. 9.2%, $p = 0.031$). There was no significant difference in the clinical response between the treatment and placebo groups.

ULTRA2 [13] was a 52-week maintenance study. Following induction, 40 mg of adalimumab was given weekly to non-responders and fortnightly to responders. A greater proportion of the adalimumab patients achieved the primary outcome of remission at 8 weeks (16.5% vs. 9.3%, $p = 0.019$) and 52 weeks (17.3% vs. 8.5%, $p = 0.004$) compared to the group receiving the placebo. In the anti-TNF-experienced patients, remission rates at 52 weeks were greater for adalimumab compared to the placebo (10.2% vs. 3%, $p = 0.039$), but no significant difference in remission was seen between the groups at 8 weeks. A clinical response at 52 weeks was achieved in a greater percentage of the adalimumab patients compared to those receiving the placebo (30.2% vs. 18.3%, $p = 0.002$).

ULTRA3 [14] was an open-label extension of 588 of the adalimumab-responsive patients from ULTRA1/2. After 4 years on adalimumab, 24.7% of the patients were in remission. Of those entering the extension study in remission, 63.6% remained in remission at 4 years. In total, 59.9% of the patients maintained mucosal healing from week 32 to week 144. A Japanese open-label extension [15] found that 40 mg fortnightly caused 23.3% and 15.8% of the patients to achieve clinical remission at weeks 52 and 196, respectively. Steroid-free remission increased from 10.2% at week 32 to 40.5% at week 196. The open-label InspirADA study [16] investigated a regimen of 160 mg at week 0, 0.80 mg at week 2, and 40 mg fortnightly from week 4 to week 24. At week 8, the proportion of the patients achieving a clinical response and remission were 79% and 49%, respectively. By week 26, these decreased to 49% and 29%, respectively.

4.3.2. Safety

The adalimumab treatment was well tolerated, with a comparable safety profile to the placebo. ULTRA2 [13] observed a higher incidence of infection and serious adverse events, leading to discontinuation in the placebo group. The most common adverse events included infection, nasopharyngitis, injection-site reactions (ISRs), and UC exacerbation. The adalimumab treatment was associated with an increased risk of developing ISRs (12.1% vs. 3.8%) and infections (45.1% vs. 39.9%) compared to the placebo. InspirADA [16] identified a 39.3% increase in adverse events and a 4% increase in serious adverse events, possibly related to adalimumab. The malignancy rates were under 1% and comparable to the placebo group.

4.4. Golimumab (Simponi®)

4.4.1. Efficacy

The PURSUIT trials [17–19,34] included moderate-to-severe UC patients with an inadequate response to conventional therapies, as well as steroid-dependent patients. PURSUIT-SC [17] investigated the efficacy of subcutaneous golimumab for induction and maintenance therapy. A similar study, PURSUIT-IV [34], stopped enrolment following the observation of the limited efficacy of the intravenous therapy compared to PURSUIT-SC findings. Phase III of PURSUIT-SC [17] investigated two induction regimens: 200 mg at week 0 and 100 mg at week 2, and 400 mg at week 0 and 200 mg at week 2. At 6 weeks, the proportion of the patients achieving the primary outcome of a clinical response was greater in the golimumab groups at doses of 200/100 mg (51.0%) and 400/200 mg (54.9%) compared to the placebo group (30.3%) ($p < 0.0001$ for both comparisons). Remission rates were greater in the golimumab groups compared to the placebo group (18% vs. 6.4%, $p < 0.0001$). The percentages of the patients achieving mucosal healing were significantly greater in the golimumab groups at doses of 200/100 mg (42.3%) and 400/200 mg (45.1%) compared to the placebo group (28.7%) ($p = 0.0014$ and $p < 0.0001$, respectively).

PURSUIT-M [18] studied 464 of the responders from the PURSUIT induction trials using maintenance therapy of 100 mg or 50 mg every four weeks. The primary outcome of a clinical response was achieved in a greater proportion of the golimumab patients at doses of 100 mg (49.7%) and 50 mg (47%) compared to the placebo group (31.2%) ($p < 0.001$ and $p = 0.01$, respectively). Mucosal healing was achieved in a greater proportion of the golimumab patients at week 30 (42.4%) and week 52 (41.7%) compared to the placebo group (26.6%) ($p = 0.002$ for both comparisons).

PURSUIT-J [19] was a Japanese study on induction therapy, with a dosage of 200 mg at week 0, 100 mg at week 2, and maintenance of 100 mg every four weeks for to 52 weeks. A clinical response was achieved in 43.8% of the patients during the induction phase. Among the responders, more of the golimumab patients maintained this response to 54 weeks (56.3% vs. 19.4%) and were in remission at weeks 30/54 (50% vs. 6.5%) compared to the patients in the placebo group. Of those completing the induction phase in remission, more of the golimumab patients maintained a remission state compared to those in the placebo group (64.3% vs. 15.4%). More of the golimumab patients achieved steroid-free remission compared to those in the placebo group (55.6% vs. 11.1%), as was mucosal healing at weeks 30/54 (59.4% vs. 16.1%). This study was limited by the lack of statistical power to detect differences between the treated and placebo groups; therefore, these comparisons were purely descriptive.

The open-label PROgECT study [20] achieved a clinical response rate of 48.5% at week 30. A sustained response from week 6 to week 30 was achieved in 30.3% of the patients. Additionally, 22% achieved remission by week 30, with 5.1% in sustained remission, and 28.3% had mucosal healing at week 30.

4.4.2. Safety

Golimumab's safety profile was similar to other anti-TNF-drugs. The common adverse events reported in PURSUIT [17–19,34] and PROgECT [20] included nasopharyngitis, UC exacerbation, and headaches. PURSUIT-M [18] observed benign or malignant neoplasms in 2.1% and 0.6% of the golimumab and placebo patients, respectively. The infection rates were generally higher for the golimumab group; however, no statistical analyses were undertaken to compare the safety between the groups.

PURSUIT-SC [17] showed similar rates of adverse events between the 200/100 mg, 400/200 mg, and placebo groups (37.5%, 38.9%, and 38.2%, respectively). Serious adverse events were reported in 3% of the golimumab and 6.1% of the placebo patients. In PURSUIT-M [18], the number of patients reporting at least one treatment-emergent adverse event for the 50 mg, 100 mg, and placebo groups were 72.7%, 73.4%, and 66%, respectively. Infections were reported in 39.0% of the golimumab and 28.2% of the placebo patients. PURSUIT-J [19] and PROgECT [20] reported infections in 65.5% and 24.3% of the patients, respectively.

4.5. Anti-Integrin

4.5.1. Vedolizumab (Entyvio®)

Vedolizumab is a humanized recombinant monoclonal antibody targeting $\alpha_4\beta_7$-integrin. Vedolizumab prevents gut-homing T helper lymphocytes interacting with the intestinal vascular endothelium, inhibiting lymphocyte trafficking to the gut and causing gut-selective anti-inflammatory activity [35]. Intravenous vedolizumab is indicated for induction and maintenance therapy in moderate-to-severe UC patients with intolerance or inadequate responses to conventional or anti-TNF therapies [5].

4.5.2. Efficacy

GEMINI-I [21] evaluated vedolizumab's efficacy for clinical response induction (Mayo score reduction of $\geq$3 and $\geq$30% from baseline, accompanied by rectal bleeding subscore reduction $\geq$1 or absolute rectal bleeding subscore $\leq$1) at 6 weeks and maintenance of clinical remission (Mayo score $\leq$2, with no individual subscore >1) at 52 weeks. The induction phase treatment arms received 300 mg of vedolizumab at week 0 and week 2. The clinical response rates in the vedolizumab group were significantly greater than in the placebo group (47.1% vs. 25.5%, $p < 0.001$). For the maintenance phase, subjects demonstrating a clinical response at week 6 were re-randomized to receive 300 mg of vedolizumab every 4 weeks, 8 weeks, or a placebo until week 50. Subjects with no clinical response at week 6 continued vedolizumab treatment every 4 weeks during the maintenance phase. The clinical remission rates were significantly greater in the 4-week (41.8%) and 8-week (44.8%) treatment arms compared to the placebo group (15.9%) ($p < 0.001$ for both comparisons).

VARSITY [22] compared the efficacy and safety of vedolizumab to adalimumab treatment over 52 weeks. The subjects were assigned to receive either 300 mg vedolizumab infusions plus placebo injections or an induction and maintenance regime of subcutaneous adalimumab injections plus placebo infusions. The primary outcome was clinical remission (Mayo score $\leq$2, with no individual subscore >1). The secondary outcomes were mucosal healing (Mayo score endoscopic subscore $\leq$1) and corticosteroid-free remission (participants using oral corticosteroids at baseline who discontinued corticosteroids and were still in clinical remission). At week 52, a significantly greater proportion of the vedolizumab patients achieved clinical remission (31.3% vs. 22.5%, $p = 0.006$) and mucosal healing (39.7% vs. 27.7%, $p < 0.001$) compared to the adalimumab patients. Corticosteroid-free remission, however, was lower in the vedolizumab patients compared to the adalimumab patients (12.6% vs. 21.8%).

4.5.3. Safety

Vedolizumab's most common adverse effects are headaches, UC exacerbation, and nasopharyngitis. VARSITY [22] found that vedolizumab caused fewer exposure-adjusted infections (23.4% vs. 34.6%) and serious infections (1.6% vs. 2.2%) compared to adalimumab, possibly due to its gut-targeted method of action. Although there are no reported cases, there is a small risk of progressive multifocal leukoencephalopathy (PML), a rare, incurable brain infection caused by human polyomavirus-2 reactivation. PML has been reported in natalizumab patients, and it has a similar mechanism of action to vedolizumab. A few cases of hepatotoxicity have been reported. This association has not been adequately studied; however, similar reports were made for patients receiving natalizumab [36].

4.6. Anti-Interleukin

4.6.1. Ustekinumab (Stelara®)

Ustekinumab is a monoclonal antibody which binds to the p40 subunits of IL-2 and IL-23, inhibiting their ability to activate CD4+ and natural killer cells [37]. Fewer pro-inflammatory cytokines are released as a result, leading to its recommendation in chronic inflammatory conditions such as psoriatic arthritis, Crohn's disease, and moderate-to-severe UC [38].

4.6.2. Efficacy

The UNIFI trial [24] evaluated the efficacy of ustekinumab for induction and maintenance therapy in moderate-to-severe UC patients. The primary endpoint of clinical remission (total Mayo score ≤2, with no individual score >1) at week 8 was achieved in a significantly higher percentage of patients treated with an intravenous ustekinumab dose of 130 mg (15.6%) or 6 mg/kg (15.5%) compared to patients receiving the placebo (5.3%) ($p < 0.001$ for both comparisons). The percentages of patients reaching all major secondary endpoints (endoscopic improvement, clinical response, and histo-endoscopic mucosal healing) were significantly greater with any dose of ustekinumab compared to those receiving the placebo ($p < 0.001$ for all comparisons). Of the patients who had a clinical response to ustekinumab and were re-randomized to treatment, a significantly higher percentage had clinical remission at week 44 when treated with 90 mg of subcutaneous ustekinumab every 8 weeks (43.8%) or 12 weeks (38.4%) compared to the placebo group (24.0%) ($p < 0.001$ and $p = 0.002$, respectively).

4.6.3. Safety

Through week 44 of maintenance therapy, the incidence of at least one adverse event in the groups receiving 90 mg ustekinumab for 8 weeks, 12 weeks, and the placebo were 77.3%, 69.2%, and 78.9%, respectively, with the most common adverse event being nasopharyngitis. The percentages of patients experiencing at least one serious adverse event were 8.5%, 7.6%, and 9.7%, respectively, with the most common serious adverse event being a UC flare-up. There could have been possible publication bias, as Janssen Research and Development, the owner of Stelara® rights worldwide, played a major role in contributing to the design, analysis, and interpretation of data, writing of the manuscript, and funding of this trial. Following the positive results from UNIFI [24], ustekinumab was recently licensed by the Food and Drug Administration [38] and European Medicines Agency [39]. A phase IV, open-label clinical trial (NCT03885713) comparing ustekinumab to infliximab, adalimumab, golimumab, and vedolizumab is currently ongoing.

4.7. Janus Kinase Inhibitors

Tofacitinib and upadacitinib are synthetic, small-molecule JAK inhibitors [40]. Although not a biologic, tofacitinib is indicated in the UAE [6] for the same stage of UC as anti-TNFs and vedolizumab, with the same level of recommendation, while upadacitinib is recommended by NICE for moderate-to-severe active UC [41], though not yet the UAE [6]. Similarly, filgotionib is not yet licensed in the UAE.

Unlike biologics, which are mainly selective for a single cytokine or integrin, tofacitinib acts on a multitude of cytokines by targeting the JAK-1 and JAK-3 pathways, blocking the inflammatory cascade. This suppresses T- and B-cell activity, reducing chronic gastrointestinal inflammation. As tofacitinib is not a biologic, it is not antigenic and therefore does not trigger an immune response [42]. In contrast, upadacitinib has a higher degree of selectivity for JAK-1. Both agents are given orally and are approved for the treatment of moderate-to-severe UC when conventional or biological agents cause an inadequate response or cannot be tolerated [5].

4.7.1. Tofacitinib (Xeljanz®)

Tofacitinib is a small-molecule JAK inhibitor, working on cytokines targeting the JAK-1 and JAK-3 pathways, to suppress T and B cell activity [40]. It is used in UC, rheumatoid arthritis and psoriatic arthritis.

4.7.2. Efficacy

The OCTAVE Induction 1, Induction 2, and OCTAVE Sustain trials [23] assessed the efficacy of tofacitinib in moderate-to-severe UC patients. In the Induction trials, the primary endpoint of clinical remission (total Mayo score of ≤2, with no subscore >1, and a rectal bleeding subscore of 0) at 8 weeks was assessed in patients taking 10 mg tofacitinib twice

daily and those taking a placebo. The percentage of the patients achieving clinical remission was greater for the tofacitinib group compared to the placebo group in both Induction 1 (18.5% vs. 8.2%, $p = 0.007$) and Induction 2 (16.6% vs. 3.6%, $p < 0.001$). Mucosal healing was achieved in a greater proportion of the tofacitinib patients compared to the placebo group in both Induction 1 (31.3% vs. 15.6%, $p < 0.001$) and Induction 2 (28.4% vs. 11.6%, $p < 0.001$). The patients demonstrating a clinical response in the Induction trials were re-randomized to receive maintenance therapy in OCTAVE Sustain. Significantly higher remission rates were seen at 52 weeks in the patients treated with tofacitinib at doses of 5 mg (34.3%) and 10 mg (40.6%) compared to those receiving the placebo (11.1%) ($p < 0.001$ for both comparisons). The secondary endpoint of mucosal healing at 52 weeks was also achieved in a significantly higher percentage of the patients treated with 5 mg (37.4%) and 10 mg (45.7%) compared to the placebo group (13.1%) ($p < 0.001$ for both comparisons).

4.7.3. Safety

In OCTAVE Sustain [23], the proportion of patients reporting at least one serious adverse event in the 5 mg, 10 mg, and placebo groups were 72.2%, 79.6%, and 75.3%, respectively. The most common adverse events were nasopharyngitis, arthralgia, and headaches. Serious adverse events were reported in 5.1%, 5.6%, and 6.6% of the patients, respectively. Tofacitinib has been associated with an increased risk of infections, including herpes zoster, in the treatment of rheumatoid arthritis [43] and psoriasis [44]. The OCTAVE trials [23] reported higher infection rates in the patients receiving tofacitinib compared to those receiving the placebo. In the maintenance trial, serious infection rates in the tofacitinib group were higher than in the placebo group but similar between the treatment arms. The number of herpes zoster cases was higher in the 10 mg group compared to the 5 mg and placebo groups. However, most cases affected one or two adjacent dermatomes, and none resulted in discontinuation. A current ongoing open-label extension trial, OCTAVE Open (NCT01470612), hopes to evaluate tofacitinib's long-term UC safety profile.

4.7.4. Upadacitinib (Rinvoq®)

Upadacitinib, like tofacitinib, is a small-molecule JAK inhibitor, though more selective for the JAK-1 pathway.

4.7.5. Efficacy

The U-ACCOMPLISH and U-ACHIEVE trials [25] assessed the response in patients with moderately to severely active UC, stratified by an adapted Mayo score of 5–9 (Mayo score minus the physician global assessment). There was a required washout period of 8 weeks for anti-TNF therapy and vedolizumab and 12 weeks for ustekinumab. Patients with previous biological failure were included in the trials, though those with three or more previous failures were limited to <30% of the participants. The primary endpoint was clinical remission at 8 weeks, defined as an adapted mayo score of $\leq$2, with a stool frequency of $\leq$1, rectal bleeding = 0, and an endoscopic subscore of $\leq$1 without friability. There were many secondary endpoints, including endoscopic improvement and remission, decreases in the adapted Mayo score not fulfilling the criteria above, mucosal and histological healing, and corticosteroid-free remission.

Clinical remission was achieved for 26% and 33% of the patients on upadacitinib in the U-ACHIEVE and U-ACCOMPLISH studies, compared to 5% and 4% for the placebo group, respectively, with a p value of < 0.0001. All the secondary endpoints were also achieved at a statistically significant ($p < 0.0001$) higher rate for those on upadacitinib than for the placebo group.

For maintenance of remission, the patients were randomized equally to into a placebo group and a group receiving upadacitinib doses of 15 mg and 30 mg. The patients who achieved a clinical response in the two induction trials at either 8 or 16 weeks were eligible. Of the patients receiving the placebo, 12% were still in remission after 52 weeks, compared to 42% and 52% of those on 15 mg and 30 mg of upadaticinib, respectively ($p < 0.0001$).

Again, for every secondary endpoint, including steroid-free remission, endoscopic remission, and a lack of symptoms such as bowel urgency and abdominal pain, those on upadacitinib performed better than those receiving the placebo, with a trend towards better outcomes for those on 30 mg compared to those on 15 mg. For instance, 59% of those on 15 mg maintained steroid-free remission at 52 weeks, compared to 70% on 30 mg.

4.7.6. Safety

For the two induction trials (U-ACHIEVE and U-ACCOMPLISH) [25], the safety profile was slightly discordant, though both demonstrated that upadaticinib has an AE profile similar to the placebo.

The rates of AEs were at 56% in U-ACHIEVE, compared to 62% for the placebo, with a treatment difference of −5.5 (95% CI −14.9 to 3.9). The rates of serious AEs were also higher in the placebo group, at 6% compared to 3% for upadacitinib. This trend continued for events leading to discontinuation, with 9% and 2%, respectively. There was, however, a higher rate of AEs in the upadacitinib group in the U-ACCOMPLISH study compared to the placebo group, at 53% and 40%, respectively, with a treatment difference of 13.4 (95% CI 4.4 to 22.3). The rates of serious AEs, however, were 3% for upadacitinib and 5% for the placebo.

The most common adverse events reported in the placebo group were UC exacerbation and headaches, while for upadacitinib, they were acne, neutropenia, and creatine kinase elevation. Higher rates of infection were reported in the upadacitinib group, at 6.9% and 9%, than in the placebo group, at 5.2% and 4%. Serious infections, however, were minimal, at 2% and 1% for the upadacitinib group in both trials. There were three instances of opportunistic infections and three instances of herpes zoster in the upadacitinib group, with no instances reported in the placebo group.

The rates of AEs in the U-ACHIEVE maintenance study were similar, at 76%, 78%, and 79% for the placebo, 15 mg upadacitinib, and 30 mg upadacitinib groups, respectively. The most common AEs were UC exacerbation in the placebo and 15 mg upadacitinib groups, at 30% and 13%, respectively, as well as nasopharyngitis (14%) in the 30 mg Upadacitinib group. While the infection rates were higher for the upadacitinib 15 mg and 30 mg groups compared to the placebo group, at 25%, 27%, and 18%, respectively, the rate of serious infection was higher in the placebo group, at 4% compared to 3% for both upadacitinib doses. Of the patients on both doses of upadacitinib, 4% developed a herpes zoster infection, compared to none of the patients receiving the placebo. No deaths were reported in any of the trials that assessed induction or maintenance.

4.8. Biosimilars

With patent expiration for infliximab (Remicade®) and adalimumab (Humira®), there has been an increase in approved biosimilars (Table 2). Biosimilars are biological products with no meaningful differences in clinical efficacy or safety compared to the patented biologic. The safety and efficacy of infliximab biosimilars were assessed in comparison to Remicade®. Studies conducted by Jørgensen et al. [26] and Kaniewska et al. [27] demonstrated equivalent efficacy and safety between Inflectra® and Remicade®. Shin et al. [29] also compared the pharmacokinetic properties of Renflexis® and Remicade®, showing no significant differences between Renflexis® and Remicade®. Imraldi [29], Hyrimoz [30], and Hulio [45] are Humira® biosimilars, with studies comparing biosimilars to Humira® showing comparable efficacy and safety.

Currently, there are limited studies comparing biologics, with no studies directly comparing all UC biologics or small-molecule treatments. One trial, VARSITY [22], compared two biologic classes, while the others compared the drugs to placebos. VARSITY [22] found that vedolizumab had a higher remission rate, with fewer infections and serious infections than adalimumab. Tofacitinib and other pipeline JAK inhibitors (Table 3) are particularly exciting, as they lack immunogenicity. In all the studies—apart from Probert et al. [10]—of infliximab, the treatment drug showed higher clinical remission rates compared to the

placebo. The infection rates were higher than in the placebo group in all the trials except for the ULTRA1 [13], PURSUIT-SC [17], GEMINI-1 [21], and UNIFI [24] maintenance studies. As statistical tests were not performed, it is difficult to draw definitive conclusions regarding remission and infection rates. UC exacerbation was the most common adverse effect in the majority of the studies, followed by headaches (Table 1). The reported cases of malignancy were not considered to be related; however, the majority of the studies lasted only 52 weeks, with the longest study period being 4 years. With numerous biologics currently in clinical trials (Table 3), the arsenal of UC therapies continues to expand, leading to more efficacious and safer drugs.

4.9. Considerations

This paper provides a comprehensive, in-depth review of biological and small-molecule UC therapies, as well as an overview of biosimilars and pipeline biologics. Our review is limited, as it was not systematic. Conducting a rigorous systematic review is a lengthy process, during which findings can be overtaken by more recent results. Many systematic reviews reference the same trials; therefore, RCTs were preferred, as they are considered the best primary source of evidence [28]. Furthermore, the methods used to define remission and response were heterogeneous between the trials, making comparisons between the drugs difficult. Additionally, whilst different dosing regimens were investigated, no firm conclusions on optimal doses were made. The majority of the RCTs included in this review were comparative against a placebo. Although this is an important baseline comparison, emphasis on the therapeutic value to standard non-biologic therapies or commonly used biologics such as infliximab and adalimumab would be of greater value.

5. Conclusions

We have summarized the currently licensed treatments for UC in the United Arab Emirates, including their most common adverse events, with reference to biosimilar drugs. This can serve as a comprehensive guide for clinicians working in the UAE, providing a resource for information regarding currently licensed drugs, as well as the evidence base behind them and the percentage of patients achieving remission.

When choosing the agent for patients, potential adverse events are an important factor. In Table 1, it is clear to see that two of the most common adverse events seen in both the treatment and placebo arms were exacerbations of ulcerative colitis and nasopharyngitis. In terms of the exacerbations of ulcerative colitis, this is, unfortunately, a result of the fact that all the biologic medications we have still have a high rate of failure and lack of efficacy. This makes the proliferation of these new agents so timely, as there are many different options with different mechanisms of action available if one fails. Nasopharyngitis as another common adverse event is a function of the fact that all biologic medications suppress the immune system, increasing the risk of infections overall.

Direct comparisons between agents, as well as formulating a therapeutics ladder, is unfortunately made difficult by the relative paucity of direct comparative studies between different agents, as well as the heterogeneity of the criteria set for the induction and maintenance of remission across the trials. We have also included some studies which compare different biologics with each other, though these are difficult to compare to studies comparing one agent with a placebo. Decisions regarding the appropriate agent, therefore, should be based on multiple factors, including age, co-morbidities, price, and patient and clinician preference.

The use of biological therapies is becoming increasingly common in UC management. New treatment classes such as anti-integrins, anti-interleukins, and JAK inhibitors have added to the paradigm of disease management. Future trials comparing drug classes and assessing combination therapies are necessary, in addition to the identification of biomarkers that may predict responses to each biological therapy.

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