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REVIEW



## Epidemiology, disease burden, and treatment challenges of ulcerative colitis in Africa and the Middle East

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### ABSTRACT

**Introduction:** Ulcerative colitis is an idiopathic, chronic, inflammatory bowel disorder characterized by an unpredictable course of alternating cycles of relapse and remission. Traditionally viewed as a disease of Western countries, the prevalence of ulcerative colitis is reported to be increasing in the developing world. In these regions, there is the potential to further explore the etiology of the disease, mainly through genetic studies. With this in mind, we consider available data relating to the epidemiology, clinical manifestations, and disease course of ulcerative colitis in Africa and the Middle East. Current treatment approaches in these countries are also reviewed and discussed in the context of new, small molecule, orally administered therapies.

**Areas covered:** Available data on the epidemiology, clinical manifestations, and risk factors of ulcerative colitis in Africa and the Middle East are reviewed using a PubMed database search.

**Expert commentary:** Epidemiologic studies from African and Middle Eastern countries suggest disease trends similar to the West, and an important health and economic burden. The management of ulcerative colitis within these developing countries is challenging, with the need to improve early diagnosis, access to healthcare, and patient education, along with facilitation of access to treatment options and improvement of medication adherence.

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## 1. Introduction

Inflammatory bowel disease (IBD) is a complex group of diseases including ulcerative colitis (UC) and Crohn's disease (CD). Despite sharing some characteristics, these conditions can be distinguished by differences in genetic predisposition, risk factors, and clinical endoscopic and histologic features [1]. UC is an idiopathic, chronic, incurable inflammatory disorder of the colon, characterized by alternating periods of relapsing and remitting mucosal inflammation that can have significant impact on quality of life (QoL) [1]. There is no single unifying cause of UC, but the pathogenesis likely relates to changes in the colonic environment of a genetically susceptible person, resulting in bowel inflammation [2]. Structural damage to the intestinal epithelial barrier allows luminal gut microbiota to elicit an inflammatory response, characterized by the activation of immune cells and cytokine production [3], contributing to the pathogenesis of UC by mediating the chronic cycle of inflammation and disrupting mucosal homeostasis [4]. If untreated, patients are at risk of requiring a colectomy or developing colorectal cancer (CRC) [5,6].

While traditionally viewed as prevalent, mainly in Western countries, the incidence pattern of UC has changed over the

last two decades, with incidence continuing to rise in the West, and rising incidence in previously low incidence areas such as Asia and the Middle East [7]. Incidence rates vary considerably, ranging from 0.97–57.9 per 100,000 in Europe, 8.8–23.14 per 100,000 in North America, and 0.15–6.5 per 100,000 in Asia and the Middle East [7].

The increasing incidence of UC in previously low incidence areas has important implications for those responsible for healthcare policy planning, with a need for specific services and education while balancing the health needs and social burdens of the countries. The development of appropriate treatment strategies will be informed by accumulating data on clinical characteristics of patient populations in Africa and the Middle East, including epidemiology and clinical manifestations.

This review summarizes the current knowledge of the epidemiology, clinical manifestations, and risk factors of UC in African and Middle Eastern countries. Literature searches were conducted via the U.S. National Library of Medicine's PubMed (<https://www.ncbi.nlm.nih.gov/pubmed>) database, incorporating all studies published on or before 31 January 2018, based on the following search terms: ulcerative colitis, inflammatory bowel disease, natural history of IBD, colorectal cancer, Africa,

sub-Saharan Africa, Algeria, Bahrain, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Middle East, Morocco, Oman, Qatar, Saudi Arabia, South Africa, Syria, Tunisia, United Arab Emirates, and Yemen. Between search terms, 'and' was applied appropriately. Identified references were manually reviewed for relevance and limited to those written in English. Articles reporting UC in countries outside of Africa and the Middle East, and those exclusively detailing other forms of IBD (including CD), were excluded. References in all relevant studies and reviews were examined to identify additional articles. In total, there were five articles documenting UC in Africa and 29 in the Middle East. To guide appropriate interpretation of data within the identified references, the authors drew on their knowledge of the wider literature to provide context.

## 2. Epidemiology of UC

The comparison of incidence and prevalence rates of UC across multiple studies is challenging. Our literature search identified differences in detection rates and diagnostic criteria between studies, and access to diagnostic procedures such as endoscopy varied over time and between countries/centers. Prospective, population-based studies are preferable in descriptive epidemiology, compared with studies using secondary data that depend upon hospital or public health registry systems; however, these studies are expensive, time consuming, and consequently rare, especially in lower-income countries. It is therefore essential to consider whether differences between regions are attributable to real differences in environmental factors, lifestyle, and genetic susceptibility, or if they are simply due to methodological differences. In the absence of databases or registries to track disease progression, UC data from Africa and the Middle East are lacking [8] and, consequently, available data are generally derived from hospital-based studies, providing limited accounts of epidemiology.

### 2.1. Epidemiology of UC in Africa

Our literature search did not identify any large patient data series from any country in Africa. Those data available are sporadic reports documenting a number of cases over a period of time: thirty-two cases of UC reported in Senegal over 7 years, 20 cases reported in Burkina Faso over 11 years [9], and 8 cases reported from three hospitals in Southern Nigeria over 3 years [10]. In the absence of population-based data, the incidence of UC appears to be low in Africa. Our literature search identified two references documenting a comparison of IBD cases over time. A review of IBD clinical presentation from 1997 to 2011 in Accra, Ghana, reported the diagnosis of 28 new patients with IBD in 2004–2011, compared with 17 in 1997–2004, representing a 65% rise in incidence [11]. An epidemiologic study conducted in a Tunisian hospital over 15 years noted an increase in the frequency of IBD cases over time, with 21 cases diagnosed during 1991–1993 compared with 43 in 2003–2005 [12].

### 2.2. Epidemiology of UC in the Middle East

As shown in Table 1, in the Middle East, the reported incidence of UC varies from 1.35 per 100,000 in Oman [13] to 4.98 per 100,000 in Iran [14], with the prevalence varying from 35.52 per 100,000 in Iran [15] to 106.2 per 100,000 in Lebanon [16]. These rates are lower than those reported for Northern Europe and North America, where incidence varies from 1.7 to 57.9 per 100,000, and prevalence from 90.8 to 505 per 100,000 [7].

The majority of reports describing the clinical epidemiology and natural course of UC in the Middle East are derived from secondary data within a specific country/region; these studies are summarized in Table 1.

Over the last two decades, some Middle Eastern countries have reported a rise in cases of IBD, including a 3.6-fold rise in Iran [15].

The evolution of IBD in the developing world has been described as following a pattern of initial low IBD incidence, followed by an increase in UC incidence while CD incidence remains low, and finally an increase in CD incidence that slowly approaches the levels of UC incidence [6]. Abdulla et al. [20] reported a cohort of patients with IBD attending a medical center in Bahrain that followed this general pattern, with annual incidence trends in Bahrain during the study period of 1984–2014 suggesting that both UC and CD incidence were increasing at a similar rate [20]. Increases in IBD incidence have also been reported in other Middle Eastern countries, including Lebanon, where gradual increases in IBD rates were reported from a study at a single health center, with an increase in new diagnoses from 1.8% of patients in 2001 to 2.7% in 2004 [16]. Similarly, a cross-sectional study of patients with IBD referred during 2002–2012 in Gilan province, Iran, detailed an increase in overall IBD incidence from 2.98 per 100,000 in 2009 to 6.2 per 100,000 in 2012 [21]. In addition, Esmat et al. [8] noted a marked increase in UC diagnoses over a 15-year period (1995–2009) in Cairo, Egypt, with 17 cases recorded in 1995–1999 and 76 recorded in 2005–2009.

Contrary to other reports from the region, two studies from Saudi Arabia have reported greater numbers of CD cases than UC cases [22,23]. In a retrospective review of patients with IBD attending a gastroenterology-orientated clinic over 17 years, the annual rate of UC remained steady throughout the study period, but was accompanied by a sharp increase in CD rate, particularly over the later study years. Overall, there was a greater number of patients with CD ( $n = 455$ ) than UC ( $n = 238$ ) [23]. In a second retrospective review of patients with IBD attending a tertiary care center over 38 years, patients with CD ( $n = 197$ ) outnumbered those with UC ( $n = 115$ ), and the number of patients diagnosed with IBD increased each year [22]. It is unclear if the referral bias of these two studies was responsible for the increase in CD cases over UC cases, as these two tertiary referral centers received only complicated IBD cases.

## 3. Diagnosis and clinical features of UC

UC typically presents with hematochezia, diarrhea, urgency and tenesmus [24]. These classical symptoms were described

Table 1. Summary of UC epidemiology studies conducted in Middle Eastern countries.

Country	Study period	Study design	Study population	Epidemiologic data	Reference
Bahrain	1984–2014	Retrospective	<ul style="list-style-type: none"> <li>Medical complex</li> </ul>	<ul style="list-style-type: none"> <li>UC prevalence: 17.27/10<sup>5</sup></li> <li>Increase in diagnosis: two cases in 1984–2001 to eight cases in 2002–2014</li> </ul>	Abdulla et al. [20]
Egypt	1995–2009	Case series	<ul style="list-style-type: none"> <li>Tertiary care referral center</li> </ul>	<ul style="list-style-type: none"> <li>Increase in UC diagnosis: 17 cases in 1995–1999 to 76 cases in 2005–2009</li> </ul>	Esmat et al. [8]
Iran	1987–2012	Systematic review	<ul style="list-style-type: none"> <li>11 case series</li> <li>Two case-control studies</li> </ul>	<ul style="list-style-type: none"> <li>Incidence: 3.04–3.25/10<sup>5</sup></li> <li>Prevalence: 15/10<sup>5</sup></li> </ul>	Shayesteh et al. [17]
	1990–2012	Systematic review	<ul style="list-style-type: none"> <li>Outpatient data</li> <li>16 case series</li> <li>Two population-based studies</li> <li>Two review articles</li> </ul>	<ul style="list-style-type: none"> <li>Incidence: 2.70/10<sup>5</sup></li> <li>Prevalence: 35.52/10<sup>5</sup></li> <li>Significant increase (<i>p</i> &lt; 0.05) in the incidence of UC over the study period</li> </ul>	Malekzadeh et al. [15]
	2001–2013	Retrospective	<ul style="list-style-type: none"> <li>Hospital based</li> <li>Inpatients</li> <li>Outpatients</li> </ul>	<ul style="list-style-type: none"> <li>Increase in UC cases in later study years</li> </ul>	Balajii et al. [18]
Egypt	2002–2012	Retrospective, cross-sectional	<ul style="list-style-type: none"> <li>Private and government hospital referrals</li> </ul>	<ul style="list-style-type: none"> <li>UC incidence increase: 2.82/10<sup>5</sup> in 2009 to 5.32/10<sup>5</sup> in 2012</li> </ul>	Mansour-Ghanaei et al. [21]
	2005–2007	Cross-sectional	<ul style="list-style-type: none"> <li>Hospital referrals</li> </ul>	<ul style="list-style-type: none"> <li>UC to CD ratio: &gt; 10:1</li> </ul>	Shirazi et al. [30]
	2011–2012	Cross-sectional, medical record review	<ul style="list-style-type: none"> <li>Newly diagnosed patients with UC</li> <li>12 gastrointestinal endoscopy clinics</li> </ul>	<ul style="list-style-type: none"> <li>Incidence: 4.98/10<sup>5</sup></li> </ul>	Zahedi et al. [14]
	2014–2015	Cross-sectional, census	<ul style="list-style-type: none"> <li>Subspecialty gastrointestinal clinic</li> </ul>	<ul style="list-style-type: none"> <li>70.7% urban residents</li> </ul>	Ghanadi et al. [25]
Kuwait	2005–2006	Cross-sectional, medical record review	<ul style="list-style-type: none"> <li>Tertiary care centers</li> </ul>	<ul style="list-style-type: none"> <li>Three age peaks in UC presentation: 11–15 years, 26–35 years, and 51–55 years</li> </ul>	Siddique et al. [26]
	1985–1999	Retrospective	<ul style="list-style-type: none"> <li>Gastrointestinal clinic referrals</li> </ul>	<ul style="list-style-type: none"> <li>Incidence: 2.8/10<sup>5</sup></li> <li>Prevalence: 41.7/10<sup>5</sup></li> </ul>	Al-Shamali et al. [70]
	1998–2008	Retrospective	<ul style="list-style-type: none"> <li>Pediatric gastrointestinal clinic</li> </ul>	<ul style="list-style-type: none"> <li>Incidence: 0.6/10<sup>5</sup></li> <li>31% family history</li> </ul>	Al-Qabandi et al. [19]
Lebanon	2000–2004	Retrospective	<ul style="list-style-type: none"> <li>Health maintenance organization medical records</li> <li>IBD registry data review</li> </ul>	<ul style="list-style-type: none"> <li>Incidence: 4.1/10<sup>5</sup></li> <li>Prevalence: 106.2/10<sup>5</sup></li> <li>Increase in IBD cases: 32 cases in 2001 to 67 cases in 2004</li> <li>IBD has a moderately severe impact on QoL</li> </ul>	Abdul-Baki et al. [16]
Oman	1987–1994	Prospective	<ul style="list-style-type: none"> <li>Hospital based</li> </ul>	<ul style="list-style-type: none"> <li>Incidence: 1.35/10<sup>5</sup></li> <li>Incidence stable over study period</li> </ul>	Radhakrishnan et al. [13]
Saudi Arabia	1970–2008	Retrospective	<ul style="list-style-type: none"> <li>Single tertiary care hospital</li> </ul>	<ul style="list-style-type: none"> <li>Increasing trend in the number of new cases</li> </ul>	Fadda et al. [22]
	1993–2009	Retrospective	<ul style="list-style-type: none"> <li>Outpatients</li> </ul>	<ul style="list-style-type: none"> <li>UC in a steady state: 10.2 cases/year in 1993–2004 and 13.3 cases/year in 2005–2009</li> </ul>	Al-Mofarreh et al. [23]
	2003–2012	Retrospective, descriptive	<ul style="list-style-type: none"> <li>Pediatric patients with UC</li> <li>15 medical centers</li> </ul>	<ul style="list-style-type: none"> <li>Presenting features in a pediatric population of Saudi Arabia, similar to other populations</li> </ul>	AlSaleem et al. [27]
	2009–2013	Cross-sectional, prospective	<ul style="list-style-type: none"> <li>Four tertiary care centers</li> </ul>	<ul style="list-style-type: none"> <li>Majority (68.4%) of patients were 17–40 years of age</li> <li>Male preponderance</li> </ul>	Alharbi et al. [35]

CD: Crohn's disease; IBD: inflammatory bowel disease; QoL: quality of life; UC: ulcerative colitis.

in the patient populations of all reports identified by the literature search that included data on the presenting features of UC [8,13,22,23,25–27].

Among the literature, there was a paucity of data reporting the time from first symptom to diagnosis. Two case series describing six cases from Nigeria reported that diagnosis took between 2 and 7 years [9,28]. This diagnostic delay is longer than the time period reported from the Swiss IBD study cohort that reported a median time period of 4 months from symptom onset to diagnosis [29]. The delay in diagnosis of these cases in Nigeria may potentially indicate that UC is underdiagnosed in the African population.

Data from three reports in the Middle East indicated long periods from first symptom to diagnosis: 13.2 months in Oman [13], and 14 months [30] and 18.9 months in Iran [25]. In contrast, 92% of patients in Saudi Arabia received a diagnosis within 6 months, of whom 77% were diagnosed within 1 month [23]. Earlier diagnosis in this Saudi Arabian study could be attributed to increased awareness of UC, improved diagnostic facilities, and greater access to gastroenterologists. In countries with more delayed diagnosis, this could be due to a lack of disease awareness, difficulties in diagnosing UC, and the presence of infectious colitis in the region.

### 3.1. Classification of disease extent and severity

Diagnosis of UC is based on clinical symptoms confirmed by findings from endoscopic and histologic examinations [1]. Inflammation starts in the rectum and extends proximally, with differing degrees of involvement of the colon [1]. Assessment of disease extent at diagnosis provides vital knowledge of the anatomic extent of mucosal inflammation – essential for the selection of appropriate treatment – and has prognostic implications for short- and long-term follow-up [1]. Patients with UC are classified by extent of disease: ulcerative proctitis is limited to the rectum (distal to the rectosigmoid junction), ulcerative proctosigmoiditis affects the rectum and sigmoid colon, left-sided UC extends from the colorectum distal to the splenic flexure, and extensive UC (pancolitis) affects the length of the colon proximal to the splenic flexure [31]. The Montreal classification simplifies classification of

**Table 2.** Montreal classification of extent and severity of UC [32].

Extent	Anatomy
E1: Ulcerative proctitis	Limited to the rectum
E2: Left-sided colitis (distal)	Limited to the portion of the colorectum distal to the splenic flexure
E3: Extensive colitis (pancolitis)	Extends proximally to the splenic flexure
Severity	Definition
S0: Clinical remission	Asymptomatic
S1: Mild	≤ 4 stools/day (with or without blood), absence of systemic illness, and normal inflammatory markers
S2: Moderate	> 4 stools/day, but minimal signs of systemic toxicity
S3: Severe	≥ 6 bloody stools/day, pulse ≥ 90 beats/min, temperature ≥ 37.5°C, hemoglobin < 105 g/L, and erythrocyte sedimentation rate ≥ 30 mm in the first h

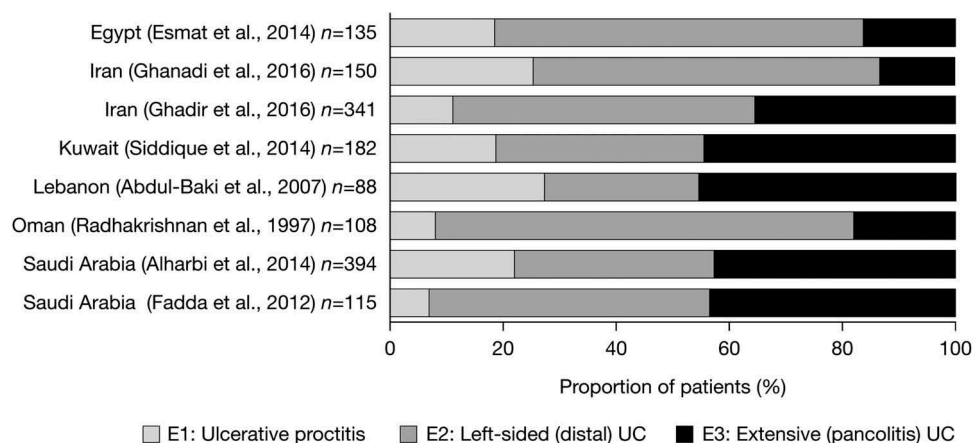
UC: ulcerative colitis.

extent of UC into three subgroups: ulcerative proctitis (E1), left-sided colitis (E2), and extensive colitis (E3) (Table 2), and divides disease severity into four subgroups, based on the number of daily stools and the presence or absence of systemic signs of inflammation (Table 2) [32].

### 3.2. Disease extent and severity in the Middle East

While the literature search did not identify any data on the extent of UC in patients in Africa, such data were reported for eight of the 18 studies conducted in the Middle East. Figure 1 shows the variations in UC extent reported in these studies.

Overall, ulcerative proctitis accounted for a lower proportion of UC cases in Middle Eastern countries (6.9–27.3%) than has been reported in Western-based populations (30–60%) [33]. A similar observation has been reported for South Asian patients: in a study conducted in London, ulcerative proctitis accounted for a significantly lower proportion of UC cases among South Asian patients (9.9%) than among North European patients (26.1%;  $p < 0.0001$ ) [34]. Conversely, in the same study, extensive colitis accounted for a significantly greater proportion of UC cases among South Asian patients (63.0%) than among North European patients (42.5%;  $p < 0.0001$ ) [34]. Broader ranges have been reported from



**Figure 1.** Middle Eastern study cohorts: proportion of patients with UC in each subgroup of disease extent. UC: ulcerative colitis.

hospital-based studies in Asia, in which ulcerative proctitis accounted for 8.5–38.4% (compared with 30–60% of cases in Western-based population studies) and extensive colitis accounted for 21.3–42.4% of cases (compared with 18–35% of cases in Western-based population studies [33]). In the Middle East, the most common site of colon involvement was the left colon, which accounted for 13.9–74.0% of cases (compared with 16–40% of cases in Western-based population studies [33]).

A high proportion of patients within Kuwait, Lebanon and Saudi Arabia were classified as having extensive colitis [16,22,26,35]. The high rate of extensive colitis in studies reporting on patients from Kuwait and Saudi Arabia might be because of referral and acceptance bias, with the centers involved in these studies accepting the most refractory and difficult-to-treat patients. Furthermore, differences in colon site involvement may be due to worldwide differences in disease pathogenesis or colonoscopy practices, and failure to assess the full length of colon involvement. The anatomic extent of mucosal inflammation is one of the most important factors determining disease course: patients with more severe disease tend to have inflammation involving more of the colon than those with less severe disease [1].

Similarly, the literature search did not identify any data on the severity of UC in patients in Africa (such data were reported for seven of the 18 Middle Eastern studies) with data suggesting that the majority of patients had UC of mild/moderate severity (Figure 2). Compared with the findings of the other six studies, Ghanadi et al. [25] reported a higher percentage of patients in Iran with severe disease (26.6%), which may reflect the cohort of this study conducted in a subspecialty gastroenterology clinic. Other limitations may have included the small cohort ( $n = 150$ ) and the short, 14-month study period.

The symptoms of UC have the potential to interfere with social activities, interpersonal relationships, and employment, alongside the psychological impact of such a chronic disease. Patients from Lebanon reported a moderately severe impact on QoL, as measured by the IBD QoL questionnaire [16]. Investigation of the psychological status of

Iranian patients with UC and the relationship between QoL and disease activity showed half of the patients to have at least one psychological disturbance, the severity of which was strongly associated with disease activity [36]. In addition, anxiety was independently associated with active disease status [36].

### 3.3. Age and gender

The age of UC onset has been described as bimodal in most Western populations, with the first peak occurring between the ages of 20 and 39 years, and the second between 70 and 79 years [37]. In the Middle East, mean age at onset in the adult studies varied from 27.3 (standard deviation [SD]: 11.7) [8] to 40 years [21], with the study cohorts' mean ages ranging from 28.4 [22] to 46.73 (SD: 15.79) years [21] (Table 3). None of the studies reported a second peak later in life. From these studies, we can conclude that the age at which UC occurs is unimodal, with the peak age of initial disease occurring at a slightly higher age than observed in Western studies.

Published data have indicated either that gender has no apparent influence on the incidence of UC, or that incidence is slightly higher in men [6,38]. Of the studies reviewed here, there is a roughly equal gender split (Table 3).

## 4. Risk factors

### 4.1. Lifestyle risk factors for UC

The increase in the incidence of UC in countries where the condition was previously uncommon has been attributed to the westernization of lifestyles [39]. The adoption of a Western diet (highly refined grains, saturated fats, overrefined sugars, and animal protein) is thought to predispose people to UC, most likely by changing the gut microbiota [40]. A case-controlled study from Iran concluded that patients with the most pro-inflammatory diet were at greatest risk of developing UC [41]. Other changes in lifestyle and improvements in socio-economic indices have also been associated with an increase

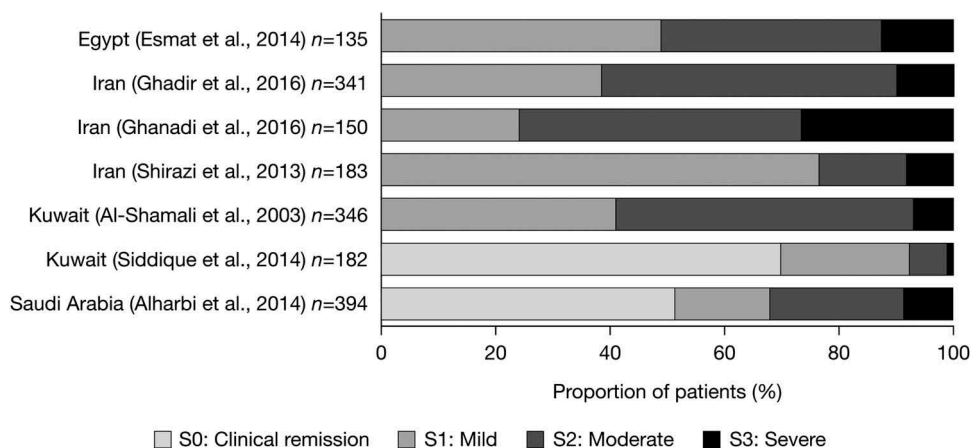


Figure 2. Middle Eastern study cohorts: proportion of patients with UC in each subgroup of disease severity. UC: ulcerative colitis.

Table 3. Middle Eastern study cohorts: demographic and clinical characteristics of patients with UC.

Country	Patients, n	Study period	Age (years), mean (SD)	Age at onset (years), mean (SD)	Female, %	Family history of UC, %	No history of smoking, %	Reference
Bahrain	123	1984–2014	-	28.35	47.2	-	92.7	Abdulla et al. [20]
Egypt	135	1995–2009	-	27.3 (11.7)	53.3	1.5	89.6	Esmat et al. [8]
Iran	183	2005–2007	37.24 (14.97)	31.54 (14.23)	48	10.9 <sup>d</sup>	73	Shirazi et al. [30]
	756	2002–2012	46.73 (15.79)	40	52.1	12.6	88.5	Mansour-Ghanaei et al. [21]
Kuwait	150	2014–2015	33.7 (12.5)	29.4 (12.1)	56	7.8	93.3	Ghanadi et al. [25]
	153	2014–2015	31.02 (12.34)	-	51.9	25.6 <sup>c</sup>	81.2 <sup>c</sup>	Zobeiri et al. [69]
Kuwait	1914	2001–2013	33.87 (13.35)	-	53	14.2	93.4	Balaji et al. [18]
	346	1985–1999	45	-	48	-	-	Al-Shamali et al. [70]
Lebanon	36	1998–2008	-	10.0	69	31 <sup>e</sup>	-	Al-Qabandi et al. [19]
	182	2005–2006	36.5 <sup>a</sup>	28.5 <sup>a</sup>	50	14.3	85.2	Siddique et al. [26]
Oman	88	2000–2004	35.5 (14.1)	-	38.6	26.1	75	Abdul-Baki et al. [16]
	108	1987–1994	36	-	52	-	86.1	Radhakrishnan et al. [13]
Saudi Arabia	115	1970–2008	28.4 <sup>c</sup> (10.8)	25.5 (10.6)	54.8	11.1	81.2	Fadda et al. [22]
	238	1993–2009	34 <sup>a</sup>	-	39.9	-	-	Al-Mofarreh et al. [23]
Saudi Arabia	188	2003–2012	-	9.08 (4.58) <sup>b</sup>	48.4	9	-	AlSaleem et al. [27]
	394	2009–2013	30.1	30.2 (0.6)	49	7	92.2	Alharbi et al. [35]

<sup>a</sup>Median age.<sup>b</sup>Pediatric study.<sup>c</sup>Value related to IBD.<sup>d</sup>Positive first-degree relative.<sup>e</sup>Percentage of relatives with IBD.

CD: Crohn's disease; IBD: inflammatory bowel disease; SD: standard deviation; UC: ulcerative colitis.

in UC incidence, such as improvements in healthy drinking water, waste disposal, better access to gas and electricity, better communications, and higher literacy rates [15].

Controversy exists surrounding the association of smoking and UC. A meta-analysis evaluating the relationship between smoking and IBD concluded smoking to be an important environmental factor in IBD, with differing effects in UC and CD. The authors found evidence of an association between current smoking and CD (odds ratio [OR]: 1.76; 95% confidence interval [CI] 1.40; 2.22) and former smoking and UC (OR: 1.79; 95% CI 1.37; 2.34). Current smoking was shown to be associated with a lower incidence of UC when compared with controls (OR: 0.58; 95% CI 0.45; 0.75) [42]. The etiology of IBD is thought to involve interaction of genetic and environmental factors. The influence of smoking in genetically predisposed patients with IBD has been analyzed in family studies; these show a high concordance between smoking habits and IBD phenotype within a family, with UC typically developing in nonsmokers and CD in smokers [43]. The majority of patients with UC in the Middle Eastern studies had no previous history of smoking (Table 3), although, in Iran, patients who smoked were less likely to have extensive disease than nonsmokers [26].

#### 4.2. Genetic risk factors

First-degree relatives of patients with UC, as compared with the general population, have a 10-fold increase in the risk of developing UC [44]. Reports on familial propensity among studies from the Middle East varied from 1.5 to 26.1% (Table 3).

Consanguineous marriage (the union between individuals who share at least one ancestor) is common within Africa and the Middle East [45], and consanguinity has been suggested to be associated with UC. However, within a Saudi Arabian cohort of children with UC, 32.6% had positive consanguinity, lower than the 56% prevalence in the general population [27]. Another study also reported no association, with similar rates of consanguinity in children with UC (61.5%) and control children (70.5%) [46].

Genome-wide association studies have revolutionized the complex field of polygenic diseases, leading to the identification of 163 distinct genetic risk loci for IBD, of which 23 have been found to be associated with a susceptibility to UC [47].

The single human multidrug resistance 1 (MDR1) nucleotide polymorphism C3435T is associated with intestinal P-glycoprotein expression, and has been found to occur at a higher frequency in patients with UC. In an Iranian study, this polymorphism was found at a significantly higher frequency in patients with UC than in healthy controls ( $p < 0.001$ ) [48].

Mohammadi et al. [49] investigated the association of human leukocyte antigen (HLA) class II genes with UC in the population of Kerman, Iran. A protective role of HLA-DRB1\*04 against UC was identified – a finding that agrees with a meta-analysis of 15 studies in Japanese and Northern European populations [50]. An interesting result of Mohammadi et al. was the association of the HLA-DRB1\*13 in patients with UC

and the significant association with disease severity ( $p = 0.01$ ). In this population of patients with UC, inheritance of this type of HLA-DRB1 resulted in less severe disease [49].

Other relevant genes of interest in IBD are those in the HLA class III region, including those encoding tumor necrosis factor alpha (TNF $\alpha$ ). The frequency of two polymorphisms in the promoter region of the TNF $\alpha$  gene (alleles 857 and 863) was found to be higher in Iranian patients with UC than in healthy controls, although the difference was not significant ( $p = 1.00$  and  $p = 0.66$ , respectively) [51].

#### 4.3. Risk factors for serious outcomes

The disease course of UC can be difficult to predict. However, a number of clinical parameters are thought to be predictors for the development of severe UC. Among patients with UC in Bahrain, younger age correlated positively with need for surgical intervention, anemia and gastrointestinal complications [20]. In addition, a significant ( $p < 0.05$ ) relationship has been reported between younger age at diagnosis and the presence of extensive colitis in the Arab population [26]. It is possible that those with a strong genetic background and multiple environmental risk factors present with UC earlier in life.

The manifestations of UC may not be restricted to the colon and rectum. Some patients with UC may also have extra-intestinal manifestations (EIM) [52], the presence of which has been associated with greater extent of disease [53]. However, among Egyptian patients with UC, there was no correlation between EIM presence and UC severity [8].

Patients with UC have an increased risk of developing CRC, compared with the general population [5]; however, this risk is modifiable with treatment. Across studies identified by the literature search, there were no CRC cases reported from Oman (although study follow-up was  $< 7$  years) [13], one case reported in Egypt [8], and several cases reported in two Saudi Arabian studies. CRC affected nine patients (2.9%) of the IBD cohort described by Fadda et al. [22] and, in a separate study, 11 patients with UC (2.8%) underwent surgery due to detection of dysplasia and cancer [35].

In patients with UC, a family history of CRC has been associated with an increased risk of developing CRC [54]. In the study conducted by Alharbi et al., 0.9% of patients with UC reported a first-degree relative with CRC [35]. Two studies from Lebanon reported on the correlation between CRC and UC: the first reported two patients with long-standing UC (1%) who later developed CRC [16], the second showed no correlation when the incidence of CRC was compared in patients with or without IBD ( $p = 0.871$ ) [55].

### 5. Treatment of UC

Traditionally, treatment goals focused on achieving rapid resolution of symptoms and achievement of remission; however, the optimal endpoints have evolved to include maintenance of steroid-free remission, prevention of hospital admission and surgery, mucosal healing, improved QoL, and avoidance of disability [1,56]. Treatment success is reliant upon, and requires consideration of, multiple factors, such as induction versus maintenance, dose, and drug adherence [1,57]. Despite advances in UC management in Europe and North America, the use of these tools is still limited in

**Table 4.** Advantages and disadvantages of current therapies for moderate-to-severe UC.

Drug/route of administration	Advantages	Disadvantages
<b>Corticosteroids</b> Oral and intravenous	<ul style="list-style-type: none"> <li>• Oral</li> <li>• Potent at inducing remission</li> </ul>	<ul style="list-style-type: none"> <li>• Only suitable for induction [61]</li> <li>• Not suitable for long-term maintenance therapy, due to associated side effects [59]: <ul style="list-style-type: none"> <li>• Short term: mood disturbances, fluid retention, and weight gain</li> <li>• Long-term: thinning of skin, poor wound healing, cataracts, osteoporosis, adrenal insufficiency, and increased risk of infections</li> </ul> </li> <li>• Potential for corticosteroid dependence or refractoriness [59]</li> </ul>
<b>Immunosuppressants</b> <b>Azathioprine/6-mercaptopurine</b> Oral	<ul style="list-style-type: none"> <li>• Oral</li> </ul>	<ul style="list-style-type: none"> <li>• Slow therapeutic response, and not therefore suitable for induction [61]</li> <li>• Safety concerns include pancreatitis, opportunistic infections, myelosuppression, hepatotoxicity, and lymphoma [59,71]</li> <li>• Thiopurine methyltransferase activity screening required [71]</li> </ul>
<b>Antitumor necrosis factor</b> <b>Infliximab</b> Intravenous <b>Adalimumab</b> Subcutaneous <b>Golimumab</b> Subcutaneous	<ul style="list-style-type: none"> <li>• Infliximab rapid induction</li> <li>• Subcutaneous administration: adalimumab and golimumab</li> </ul>	<ul style="list-style-type: none"> <li>• Loss of response over time</li> <li>• Safety concerns: risk of infection of intracellular pathogens (e.g. tuberculosis) and malignancies [59,61]</li> <li>• Immunogenic</li> <li>• Intravenous infusion (infliximab) requires administration in healthcare setting</li> <li>• Potential for injection/infusion site reaction [61]</li> <li>• Additional burden of monitoring [61]</li> </ul>
<b>Anti-integrin agents</b> <b>Vedolizumab</b> Intravenous	<ul style="list-style-type: none"> <li>• Reduced systemic side effects</li> <li>• Steroid-free remission</li> </ul>	<ul style="list-style-type: none"> <li>• Intravenous infusion requires administration in healthcare setting</li> <li>• Potential for infusion site reaction [61]</li> <li>• Nasopharyngeal infection risk [61]</li> <li>• Immunogenic [62]</li> </ul>

UC: ulcerative colitis.

many parts of the world, including the Middle East and most parts of Africa, due to their high cost, limited evidence base, and dependence on clinical experience [58].

Conventional therapies for UC include agents that target the inflammatory cascade either locally in the gut (e.g. aminosalicylates [ASAs]) or systemically (corticosteroids and immunosuppressants [e.g. thiopurines, azathioprine, and 6-mercaptopurine]) [59]. ASAs are the standard therapy for inducing and maintaining remission in patients with mild-to-moderate UC [60], but in the event of achieving an inadequate response with ASAs, corticosteroids are the alternative treatment option for inducing remission [59]. However, corticosteroids provide only limited, short-term benefit for the treatment of UC, and long-term use for maintenance therapy is not appropriate due to their association with adverse events (AEs) and lack of mucosal healing (Table 4) [59].

Improved understanding of the biologic pathways involved in the pathogenesis of IBD has led to the development of several new biologic medications. TNF $\alpha$  plays a central role in the perpetuation of chronic inflammation [63]. Anti-TNF $\alpha$  agents adalimumab and infliximab have been shown to induce clinical and endoscopic remission in patients with UC, diminishing exacerbations and surgery rates [64,65]. However, these agents have limitations (Table 4).

The Saudi Arabian position statement for the use of biologic agents recommends adalimumab, infliximab, or golimumab for patients with moderate-to-severe active UC, corticosteroid-dependent disease, or a history of failure to respond to conventional therapy [66]. All six studies from the Middle East identified by the literature search reported similar treatment patterns, with the majority of patients receiving ASAs or corticosteroids (alone or in combination) (Table 5).

Alharbi et al. (2014) reported 85.2% of the Saudi Arabian cohort to be responsive to corticosteroids, while 7.0% were corticosteroid dependent, and 6.2% did not respond to corticosteroid treatment [35]. These data are similar to those reported in a UK study in which 82% of patients had a complete or partial response to steroids and 18% had no response [67]. In Iran, Kuwait and Saudi Arabia, immunomodulators were used the least, and in all studies few patients received anti-TNF $\alpha$  drugs. Regional guidelines have been developed to aid physicians on the appropriate use of anti-TNF $\alpha$  drugs in Saudi Arabia. However, data presented here show low usage, despite these therapies being shown to improve patient outcomes [66]. The low usage of anti-TNF $\alpha$  therapies may be due to substantial associated costs with these drugs, or limited access. Moreover, their use often requires the presence of certain health resources for administration, including infusion centers and trained healthcare professionals [68].

Patients with severe UC may require hospital admission for treatment, usually with intravenous corticosteroids due to worsening symptoms [1]. Hospitalization rates were reported for four studies in the Middle East, and were generally considered to be high (Iran: 34.6% [69]; Kuwait: 44.5% [26]; Saudi Arabia: 47% [22]; and Kuwait: 71% [70]).

### 5.1. Surgery for UC

Surgery to remove the burden of an inflamed colon is a treatment option if a patient with UC becomes refractory to treatment and the usual approach is a restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) [71]. Surgery may have a positive or negative impact on QoL,

**Table 5.** Middle Eastern study cohorts: treatments received by patients with UC.

Country	Treatment						Reference
	Aminosalicylates, %	Corticosteroids, %	Immunomodulators (azathioprine or 6-mercaptopurine), %	Anti-TNF $\alpha$ , %	Hospitalization, %	Surgery, %	
Bahrain	93.0	60.0	68.0	-	-	-	Abdulla et al. [20]
Iran	76.0	33.0	27.0	-	-	2.70	Shirazi et al. [30]
Kuwait	100.0	73.6	37.9	4.9	44.5	3.8	Siddique et al. [26]
	100.0	59.0 <sup>a</sup>	11.1	-	71.0	-	Al-Shamali et al. [70]
Saudi Arabia	62.0	62.5	17.5	8.3	-	5.8	Alharbi et al. [35]
	86.0	69.0	33.0	4.0	47.0	20.0	Fadda et al. [22]

<sup>a</sup>Oral corticosteroids.

TNF $\alpha$ : tumor necrosis factor alpha; UC: ulcerative colitis.

and these surgical procedures have risks of complications, such as pouchitis (reported in 30% of patients who have undergone IPAA), and reduced fertility in female patients [71]. Patients undergoing colectomy have a mortality rate of 2–5%, which may be higher in patients who undergo emergency colectomy [72]. Rates of UC-related surgery varied between 2.7 and 20% among the Middle Eastern studies identified by the literature search (Table 5). Total colectomy rates in Egypt were 2.9%, lower than rates reported in Western studies (24–34% after 10 years) [8].

### 5.2. Economic burden of the treatment of UC

The chronic and recurrent nature of UC means that patients often require either continuous or intermittent treatment throughout their lives. Hence, the treatment of UC requires considerable healthcare resources, due in part to the likelihood of hospitalization and surgery [73]. When combined with the indirect costs related to lost work productivity and daily activity impairment, the overall costs of UC pose a significant economic burden to society. A systematic review of the medical costs associated with UC in North America and Europe concluded UC to be a costly disease, with a direct medical cost of \$9754–17,353 per patient per year [73]. The costs of treating UC in developing countries are largely unknown. However, a study in Serbia estimated the costs of UC treatment. Direct costs were estimated to be 1183.97 EUR, and indirect costs 178.39 EUR (per patient per year), with hospitalization being the greatest component of the direct costs [74]. These costs reported from Serbia are lower than those of developed countries, due to under-utilization of expensive biological therapy and low level of control of health service costs by the state [74].

Biologics such as infliximab and adalimumab are considered costly and may have a significant economic burden on individuals, especially for patients who reside in countries where health insurance is not available. Access to medical treatments varies between countries, and patients from lower-income countries may have less access to biologics due to financial and administrative restrictions, as was found across Europe in patients with rheumatoid arthritis (RA) [75].

Compared with conventional therapies, in the majority of UC clinical situations, biologics have been shown not to provide value for money at their current costs, particularly when administered to maintain remission [76]. Consideration of the cost-effectiveness of UC treatment is important, and

models require adjustment to country-specific conditions [77]. The World Health Organization recommendation for cost-effectiveness deems interventions to be cost-effective if the incremental cost-effectiveness ratio value is less than three times gross domestic production per capita. Economic evaluation of the treatment of patients with moderate-to-severe UC in Iran with infliximab was found not to be cost-effective [78].

The chronic nature of UC leads to a substantial impact on a patient's QoL, interfering with their social activities, relationships, and employment. Biologics have the potential to improve the QoL of patients with UC [79], and should be considered when evaluating the cost-effectiveness of treatments.

The availability of biosimilar agents for UC will hopefully alleviate some of the costs associated with UC treatment [76].

### 5.3. Medication adherence

In addition to long-term treatment, patients with UC often require a medical regimen involving multiple drugs, which can influence QoL [57]. The mode of delivery, frequency of treatment, compatibility with daily life, effectiveness, and adverse effects of current treatments may play important roles in patient preference and adherence [80]. Nonadherence in UC is associated with an increase in disease activity and relapse [81]. Multiple factors are implicated in nonadherence to medication, including age, sex, employment status, duration of disease, number of medications, and number of required daily doses [57]. The nonadherence rate in a cohort of patients with IBD from Iran was 33.3% [82], with intentional nonadherence reported in 27.6% of patients. The main reasons for patients' decisions to stop medication were symptom improvement (42.7%) and dislike of the number of drugs prescribed (36.9%) [82].

Patients with UC find many aspects of current treatments to be inconvenient or burdensome, including the application of rectal medications, the need to refrigerate biologics, and large pill burden [83]. In a survey of patients with UC ( $n = 22$ ) and physicians ( $n = 20$ ), both groups identified oral administration as a highly relevant factor contributing to patient comfort and medication adherence [80]. A recent study from Lebanon evaluating physicians' beliefs about medication adherence in immune-mediated inflammatory diseases, including IBD, identified four key areas associated with improving adherence: 360-degree education (patient-nurse-

physician), improved patient-physician communication, patient perception/concerns, and market access solutions [84].

#### 5.4. Emerging therapies

There is an unmet need for the development of easily administered, targeted therapies for UC. With this in mind, several orally administered, low molecular weight, small molecule therapies are under investigation, including: ozanimod (a sphingosine-1-phosphate receptor [S1P-R] subtypes 1 and 5 modulator) [85] and the Janus kinase (JAK) inhibitors filgotinib [86] and tofacitinib [87,88]. These small molecule therapies act by interfering with intracellular signaling and may have many advantages compared with biologics, such as reduced production costs [89] and a lower likelihood of immunogenicity [90]. Their oral administration and rapid absorption may also be advantageous, and could improve patient acceptance, particularly given the discomfort associated with the application of parenteral substances [91].

Ozanimod is an agonist of the S1P-R subtypes 1 and 5. S1P-Rs are located on the surface of lymphocytes and are an essential part of the signaling pathways trafficking these cells out of lymph nodes [91]. S1P is generated via the phosphorylation of sphingosine, and this reaction is catalyzed by sphingosine kinases (SphKs) that can be further distinguished as the homologous kinases SphK1 and SphK2 [91]. Patients with UC have an increased expression of SphK1 and associated higher levels of S1P compared with healthy individuals [91]. The interaction of ozanimod with S1P-R subtypes 1 and 5 leads to the internalization of the receptor, preventing egress of lymphocytes from the lymph nodes, such that fewer lymphocytes can migrate into the gut [91]. Ozanimod has been assessed in adults with moderate-to-severe UC, in a randomized, placebo-controlled, double blind Phase 2 study. Treatment with ozanimod 1 mg once daily resulted in slightly higher rates of clinical remission at Week 8 than placebo (16% vs. 6%,  $p = 0.048$ ) [85].

JAK-dependent intracellular signaling pathways are involved in the pathophysiology of many chronic inflammatory diseases, including IBD. Filgotinib is a specific inhibitor of JAK1 and inhibits the signaling pathways associated with interleukin (IL)-2, IL-6, and interferon- $\gamma$  [91,92]. In a Phase 2 study, filgotinib was demonstrated to improve clinical activity in patients with CD compared with placebo [86].

Tofacitinib is an oral, small molecule JAK inhibitor for the treatment of UC. Tofacitinib preferentially targets the JAK1 and JAK3 isoforms, blocking the downstream effects of proinflammatory cytokines including IL-2, IL-4, IL-6, IL-12, IL-15, IL-21, and interferon- $\gamma$  [92,93]. In Phase 3 studies, induction treatment with tofacitinib 10 mg twice daily (BID) was associated with a significant clinical response compared with placebo. In the OCTAVE Induction 1 trial (NCT01465763), remission at Week 8 occurred in 18.5% of tofacitinib-treated patients compared with 8.2% of placebo-treated patients ( $p = 0.007$ ). In the OCTAVE Induction 2 trial (NCT01458951), remission occurred in 16.6% versus 3.6% ( $p < 0.001$ ) [88]. In patients who had a clinical response in the OCTAVE Induction 1 and 2 studies, efficacy of tofacitinib as maintenance therapy was demonstrated in the OCTAVE Sustain trial (NCT01458574), with 40.6% of tofacitinib-

treated patients in remission at Week 52 compared with 11.1% of placebo-treated patients ( $p < 0.001$ ) [88]. In addition, rates of sustained corticosteroid-free remission with tofacitinib were superior to placebo: 47.3% of tofacitinib-treated patients compared with 5.1% of placebo-treated patients ( $p < 0.001$ ) [88]. Furthermore, the QoL of those who received tofacitinib was significantly improved compared with placebo [88,94]. In these Phase 3 studies, the rapid onset of efficacy of tofacitinib treatment was observed, with significant symptomatic improvements observed as early as Day 3 [95]. For patients who lost initial clinical response to tofacitinib 10 mg BID induction therapy while on tofacitinib 5 mg BID maintenance therapy, dose escalation back to 10 mg BID recaptured clinical response [96], and in patients with a prior response to tofacitinib, retreatment following a period of treatment interruption was efficacious [97]. Patients who failed to achieve clinical response to tofacitinib in induction studies and subsequently received an additional 8 weeks of treatment achieved clinical response [98].

The safety profile of tofacitinib has been well established in RA trials [99]. In the OCTAVE trials, AEs including serious AEs (SAEs) did not differ between the treatment and placebo groups [88]. In OCTAVE Induction 1, AEs occurred in 56.5% of patients in the tofacitinib 10 mg BID group and 59.8% in the placebo group; corresponding percentages in OCTAVE Induction 2 were 54.1% and 52.7% [88]. In OCTAVE Induction 1, SAEs occurred in 3.4% of patients in the tofacitinib 10 mg BID group and 4.1% in the placebo group; corresponding percentages in OCTAVE Induction 2 were 4.2% and 8.0% [88]. Similarly in OCTAVE Sustain, AEs occurred in 72.2% of patients in the tofacitinib 5 mg BID group, 79.6% in the tofacitinib 10 mg BID group, and 75.3% in the placebo group [88]; corresponding percentages of SAEs were 5.1%, 5.6%, and 6.6% [88]. Across the tofacitinib UC program, an analysis of all patients ( $n = 1157$ ) who received  $\geq 1$  dose of tofacitinib (5 mg BID or 10 mg BID) with a total exposure to tofacitinib of 1613 patient-years and up to 4.4 years of treatment showed an incidence rate (IR; patients with events per 100 patient-years of exposure) of 4.1 for herpes zoster (HZ), 2.0 for serious infections, 1.3 for opportunistic infections (OIs), 0.7 for non-melanoma skin cancer (NMSC), 0.5 for malignancy (excluding NMSC), 0.2 for major adverse cardiac events, and 0.2 for death [100].

In summary, tofacitinib improved clinical activity and the endoscopic situation in patients with UC, and conferred benefits as both an induction and maintenance treatment. Overall, the occurrences of AEs and SAEs were similar in the tofacitinib treatment groups and placebo group. The safety profile for tofacitinib in patients with UC generally appeared similar to that previously reported in RA (including increased risk of HZ) [99,100].

#### 5.5. Special considerations for the use of emerging therapies in Africa and the Middle East

As expected with immunosuppressive drugs, there is an increased risk of infection with ozanimod, filgotinib, and tofacitinib. Patients with UC who received ozanimod for 8 weeks had a reduced absolute lymphocyte count compared with normal ranges, consistent with the mechanism of drug action and suggesting a potential increased risk of infection [85].

Within Phase 1, Phase 2, Phase 3, and long-term extension studies of tofacitinib in patients with RA, the overall crude IR of OIs was 0.5 (95% CI 0.4; 0.6) per 100 patient-years [99]. For tuberculosis (TB) and non-TB, IRs were 0.2 (95% CI 0.1; 0.3) and 0.3 (95% CI 0.2; 0.4), respectively [99]. TB rates reflected geographical background TB prevalence [99]. In Phase 3 trials, all OIs occurred in patients treated with tofacitinib, and the IRs were higher in those who received tofacitinib 10 mg BID (0.93 [95% CI 0.55; 1.58]) compared with tofacitinib 5 mg BID (0.20 [95% CI 0.07; 0.64]) [101].

Mouse models have shown that tofacitinib administration leads to increased bacterial replication, indicating a risk of TB reactivation [102]. TB is endemic in many developing countries, and the majority of TB-infected individuals will develop latent TB infection, which will reactivate in about 10% of these patients, leading to active TB [103,104]. In patients with RA, tofacitinib has been associated with an increased risk of mycobacterial infections [105]. In a mouse model, tofacitinib was found to accelerate bacterial clearance when co-administered with canonical TB chemotherapy [106]. The findings of this study strengthen the concept that strategies promoting awakening of dormant TB are favorable for patients with TB, when applied concomitantly with chemotherapy. Screening for TB, and initiation of treatment for latent TB infection, are therefore recommended prior to initiation of tofacitinib treatment [101]. Long-term safety analysis of AEs, in patients with RA (6194 patients with a total 19,406 patient-years' tofacitinib exposure and median tofacitinib exposure of 3.4 patient-years) and tofacitinib exposure through 8.5 years (data cut-off 31 March 2015) showed that TB rates reflected the background TB prevalence, with most cases (28/36) occurring in regions endemic for TB [99]. Data from an ongoing open-label Phase 3 trial of tofacitinib in UC (OCTAVE Open, NCT01470612) will be crucial in providing further information regarding the risk of OIs.

In the Phase 3 trials of tofacitinib in patients with UC, a higher rate of infections occurred with tofacitinib than with placebo, including HZ (five tofacitinib-treated patients, compared with one placebo-treated patient) [88]. A review of clinical trial data from the tofacitinib global development program for the treatment of RA concluded that age, glucocorticoid use, tofacitinib dose, and enrollment within Asia were independent risk factors for HZ [107]. Nevertheless, HZ infection in most patients was nonserious, limited to a single dermatome and all were manageable with standard antiviral treatment [107].

### 5.6. Limitations and opportunities in Africa and the Middle East

As highlighted within this review, evidence regarding the burden of UC within Africa and the Middle East is limited, and the incidence is expected to increase over the next decade. Anti-TNF $\alpha$  drugs have been available within countries in this region; however, data on their actual use are lacking. In the era of emerging therapies for the treatment of UC, long-term safety data on the use of these agents in patients from Africa and the Middle East with UC, via the establishment of local and regional registries, will aid in the assessment and

evaluation of various parameters such as safety, efficacy, cost-effectiveness, drug survival, QoL, and long-term use in patients with UC. National or local guidelines for the treatment of UC are lacking, with recommendations for the use of anti-TNF $\alpha$  drugs only available in Saudi Arabia [66], with clinicians relying on US or European recommendations to inform treatment decisions, which do not consider local medical, legal, religious, or practical considerations relevant for Africa and the Middle East. As new therapies become available, there is an urgent need for guidelines for their use specific to the locality, as well as for disease registries, patient associations, and support groups. Adding to these challenges is the different healthcare systems and laws concerning the drug registration of individual countries.

## 6. Conclusion

While prevalence is still much lower than in North America and Europe, rates of UC appear to be increasing in the Middle East and Africa. Key risk factors for the African and Middle Eastern populations include diet, family history, and genetic factors. The economic burden of UC is substantial and will undoubtedly continue to rise in African and Middle Eastern countries as the number of diagnosed cases of UC increases. The development and maintenance of a central registry of patients with UC in these regions may help to facilitate the comprehensive treatment of those affected. The goals of treatment for active UC include the induction and maintenance of remission. Orally administered, low molecular weight, small molecule therapies may be less likely to be immunogenic than biologics, may not require therapeutic drug monitoring, and may provide an alternative treatment option for UC. However, there may be treatment adherence issues when comparing oral therapies with intravenous therapies and also different safety profiles between drug classes, for example the increased risk of HZ with tofacitinib.

## 7. Expert commentary

UC is a chronic, potentially disabling condition characterized by chronic relapsing inflammation and progressive damage to the colon. Recent population-based studies suggest a more favorable clinical course, with colectomy rates of 7.5–10% at 10 years. However, the unmet therapeutic need still exists, with approximately half of patients with moderate-to-severe UC failing to achieve a sustained clinical remission with current treatment options, impacting on patients' QoL. The prevalence of UC is increasing steadily worldwide, including in Africa and the Middle East. Epidemiologic studies from these countries largely suggest similar disease trends to the West and UC is an important health and economic burden.

Despite significant developments in the treatment of UC, many patients are resistant to current biologic therapies, and a significant number lose response over time, resulting in limited therapeutic options. A deeper understanding of the immunopathology of UC, and an accelerated translational and clinical research program, have helped identify a number of potential targets for drug development. Most notable are orally administered small molecules such as agonists of the S1P receptor subtypes, or JAK

inhibitors that target cytokine signaling. Ozanimod – an S1P receptor modulator – has been shown to induce response, remission, and mucosal healing in patients with moderate-to-severe UC, proving that targeting mediators downstream of the sphingolipids inflammation cascade is a potential novel target in the treatment of UC. Similarly, tofacitinib – a JAK inhibitor – was shown in Phase 2 and 3 trials to be effective at inducing remission and maintenance of a response leading to mucosal healing in moderate-to-severe UC, and therefore supporting the JAK/signal transducer and activator of transcription pathway as a target that, if suppressed, will decrease inflammation. Another area of interest is fecal microbial transplant, which has led to some promising data from recent intervention trials.

The widely variable rates of response seen with all agents underscore the complex nature of UC, highlighting the future need for precision and personalized medicine based on molecular, immunologic, and genetic research in UC. However, an important and emerging treatment paradigm has been to treat early with safe and sufficiently potent drug regimens, using tight control, and to a designated target (namely mucosal healing) – a strategy that has been shown to lead to improved outcomes in UC. The use of biochemical markers such as C-reactive protein and surrogate markers of mucosal inflammation such as fecal calprotectin in the monitoring of disease and response to therapy has become standard in clinical trials, and is increasingly accepted in clinical practice. Particular challenges in the management of UC in Africa and the Middle East include the need to improve early diagnosis and linkage to specialized healthcare, optimize patient education and disease awareness, facilitate access to treatment options, and enhance adherence.

## 8. Five-year view

The study and science of IBD has changed dramatically over the last two decades. The introduction of anti-TNF biologics has resulted in improved clinical outcomes in patients with severe and moderate-to-severe disease, but the current treatment paradigm continues to depend on systemic immunosuppression (steroids and immunomodulators) and surgical intervention in a significant number of patients, underscoring a significant unmet need. A number of genetic and immunologic abnormalities have unraveled, including aberrant intestinal mucosal defence function, abnormal intestinal permeability, deregulated bacterial antigen processing by macrophages and presentation to T cells, cellular immune regulation and signaling, cytokine production, and leukocyte trafficking. Understanding these molecular mechanisms and effector pathways presents an opportunity for the development of new and improved targeted therapies with high rates of clinical, endoscopic, and histologic remission. Most experts agree, however, that the holy grail in IBD lies in the move toward personalized precision medicine, where clinical, biochemical, morphologic, and genetic parameters and data are used to identify the pathway of inflammation in each individual with UC, leading to provision of targeted, safe, and highly effective therapy.

## Key issues

- The incidence and prevalence of UC is increasing worldwide, including in Africa and the Middle East.
- UC distribution and severity in the Middle East are largely similar to the West. The absence of a distinct second peak in older patients is a peculiar difference.
- Prompt diagnosis of UC and access to care and proper medical therapy are important challenges in the developing world. Medication adherence is another important hurdle that requires near-perfect alignment between physicians and patients, as regards treatment goals and challenges.
- Orally administered small molecules for moderate-to-severe UC constitute a long-awaited treatment development that promises to change the management landscape.

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