Ulcerative Colitis: Shifting Sands

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Abstract
Ulcerative colitis (UC) is a chronic inflammatory bowel disease associated with considerable disease burden. We review some current misconceptions about UC in adults with the aim of optimizing care for patients. Although UC and Crohn’s disease (CD) are considered discrete diseases, distinctions between them are not always clear-cut and phenotypes may change over time. Patient management should take into account disease manifestations, disease severity and extent, and response to prior treatments. Although disease extent often defines severity, distal UC is not always less disabling than extensive disease as patients can progress to more extensive disease. In addition, severe proctitis can give rise to severe and debilitating symptoms, with a substantial impact on health-related quality of life. UC carries an increased risk of colorectal cancer (CRC) compared with CD; however, more recent data indicate a similar risk of CRC in CD with colonic involvement as with UC. Corticosteroids are widely used to induce remission in UC, and prolonged use of steroids in patients with UC is common, but corticosteroid-free maintenance of remission is an important therapeutic goal. Although biologic therapies provide a valuable treatment option in UC, they are not clinically effective in all patients and are also associated with secondary loss of response.

Key Points
Clarification of common misunderstandings regarding ulcerative colitis (UC) could help to optimize patient care.

Importantly, UC should not be regarded as completely different to Crohn’s disease as classification may be oversimplified, the disease genotypes often overlap, and both can be associated with an increased risk of developing colorectal cancer.

With regard to the treatment of UC, corticosteroids are not appropriate for maintenance therapy due to adverse effects and the importance of corticosteroid-free remission as a key target. In addition, healthcare providers should also be aware that biologics often fail to induce remission, and secondary non-responsiveness can develop.

1 Introduction
Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) limited to the colonic mucosa and submucosa, involving part or all of the colon, and characteristically resulting in symptoms such as urgency of defecation, tenesmus, bloody diarrhea, abdominal pain, and fatigue [1, 2]. Although the pathogenesis of UC is not completely understood, it is thought to result from an inappropriate immune response to gastrointestinal (GI) antigens and/or environmental triggers in genetically susceptible individuals [3–5]. UC has a negative impact on patients’ health-related quality of life (HRQoL) [6, 7]. Despite the considerable disease burden and progressive nature of this condition, healthcare providers responsible for the care of patients with UC often underestimate or misinterpret the impact of the disease [8].

The global prevalence of UC has been reported to range from 2.42 to 298.5/100,000, with the highest incidence reported in North America and Northern Europe [9]. UC is
This article seeks to highlight some common misunderstandings with regard to UC and the management of adult patients with UC, and to provide suggestions to optimize care for patients with this disease.

2 Current Misunderstandings

2.1 Crohn's Disease (CD) and Ulcerative Colitis (UC) are Completely Different Diseases

UC and Crohn's disease (CD), the most common forms of IBD, are generally considered to be discrete diseases [3]. Classification of IBD has been reported to be critical to ensure optimized clinical management [11]. Accurate classification has potential benefits in order to define disease prognosis, give appropriate patient counseling, and decide on the most appropriate form of therapy [12]. For example, surgical options differ between UC and CD, with total colectomy and ileal pouch–anal anastomosis (IPAA) considered an appropriate option in cases of medically refractory UC, but generally unsuitable for patients with CD [13]. However, the current classification into UC and CD is oversimplified and may not be appropriate.

Classification of UC and CD is generally based on endoscopic appearance, location and distribution of lesions, and histopathology. Inflammation in UC is limited to the colon and is usually continuous, whereas CD involves any part of the GI tract, presents with non-continuous lesions, and complications such as strictures, abscesses, and fistulas can occur [14]. Histologically, inflammatory changes in UC are limited to the mucosa and submucosa with cryptitis and crypt abscesses, whereas in CD there is transmural inflammation and submucosal thickening, with ulceration and granuloma formation in some patients [15].

Despite these differences, distinguishing UC and CD can be challenging, and it has been suggested that combinations of inflammatory, genetic and serologic markers [16] with colonoscopy [17] are used. Various imaging techniques are available in addition to colonoscopy, in the diagnosis and management of IBD, including abdominal ultrasound and magnetic resonance enterography [18]. Endoscopic ultrasound has also been proposed as a tool to differentiate these diseases [17].

Exceptions to classification criteria based on disease location are sometimes observed, such as discontinuous lesions [19] (including cecal patch [20] and rectal sparing [19, 21]) in UC. Rectal sparing and backwash ileitis are commonly seen in patients with primary sclerosing cholangitis and IBD [22]. Histologic features typical of UC may occur in resections from patients with CD, and vice versa [11]. Additionally, while perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) are considered a recognized marker for UC, this marker has limited value for individual diagnosis; 20% of patients with CD in one study [23], and 24% in another [24], expressed p-ANCA. Crohn’s colitis that is p-ANCA-positive may look very much like UC in the left colon but has a more typical appearance of CD in the right colon [25]. A small proportion of patients undergoing a proctocolectomy and IPAA for UC may subsequently develop CD [26, 27]; whether this is due to post-surgical development of CD, misdiagnosis of the original disease, or a true overlap between UC and CD is uncertain. Furthermore, in a recently published pilot study investigating zonulin (a biomarker of intestinal permeability), although significant differences in serum zonulin concentration were observed for patients with IBD compared with healthy controls, no differences were observed between patients with CD and UC [28].

Studies focused on the genotypes of patients with IBD have raised questions on the ‘classic’ classification into UC and CD: gene expression in colon mucosal pinch biopsies from patients with UC and CD is very similar [29], DNA from peripheral whole-blood samples of patients with UC and CD shares genetic variants related to impaired adaptive immune response [30], and genome-wide association studies have identified extensive overlap in the genetic susceptibility architecture between UC and CD [31]. A recent large genotype association study reported in The Lancet suggested that disease location—an intrinsic aspect of IBD—is at least partially genetically determined, and concluded that IBD is better considered as a continuum of disorders comprising three groups (ileal CD, colonic CD, and UC), rather than as either UC or CD [32]. In truth, more subtypes may belong to this spectrum, and clinical phenotyping may be too blunt to fully reflect the impact of underlying genetic causations.

There is a need for more research in this area to define the most homogeneous patient populations possible as this is paramount for the performance of randomized controlled trials (RCTs) and clinical care.

In summary, considering UC and CD to be completely different diseases is an oversimplification; there are exceptions to classification criteria based on the location and distribution of lesions and histopathology, and overlaps in the genetic variants are seen in the two diseases.

2.2 Distal Colitis is a Milder Form of UC

UC is generally classified based on the extent and severity of disease [33], using the Montreal classification system, with extent categorized as ulcerative proctitis, left-sided/distal
UC, or extensive UC/pancolitis, and severity categorized as clinical remission, mild, moderate, or severe. Severity of disease is defined as follows: (i) mild UC: four or fewer stools/day (with or without blood), absence of systemic symptoms, and normal inflammatory markers; (ii) moderate UC: four stools/day and minimum signs of systemic symptoms; and (iii) severe UC: six or more stools/day, pulse rate of ≥ 90 beats/min, temperature ≥ 37.5 °C, hemoglobin concentration < 105 g/L, and erythrocyte sedimentation rate ≥ 30 mm/h [2, 34]. Indeed, US, European, and UK clinical guidelines recommend treatment approaches based on the classification of UC by extent and severity [35–38].

However, consideration of other issues such as response to prior medication when choosing between treatment options is recommended in European UC guidelines [35], and it has been suggested that treatment refractoriness, in addition to the severity and location of UC, should also drive treatment decisions [2]. In developing a UC clinical decision support tool, one group of gastroenterologists recommended risk stratification, such as disease risk, taking into account factors beyond the extent and severity of disease [39].

In clinical trials involving patients with UC, approximately 60% of the patient population have refractory left-sided/distal UC [40–42]. However, approximately 20% of patients initially diagnosed with distal UC will develop more extensive disease over time [43–45], and this figure has been reported to exceed 50% over 25 years [46]. It has been reported that progression of colitis is associated with a significantly higher rate of extraintestinal manifestations and corticosteroid refractoriness than distal colitis [47]. There is some evidence that extension of initially distal disease carries an increased risk of colectomy in comparison with extensive UC at diagnosis [45], although this was not the finding in a recently reported study [44]. The fact that the extent of disease might change, and that initially limited disease might have a worse clinical outcome than extensive disease, calls into question the usefulness of the extent of disease to classify UC.

It is commonly assumed that distal UC is less severe than extensive colitis, and therefore might not warrant use of some treatments. This idea is complicated by the fact that patients with limited proctitis are often excluded from RCTs. However, at a symptomatic level, patients with distal UC may have equally or even more burdensome symptoms, and lower HRQoL, than patients with extensive disease as it is accepted that the most troublesome symptoms of urgency, tenesmus, and incontinence are related to rectal inflammation [48]. In addition to urgency and tenesmus, a proportion of patients with proctitis or left-sided colitis suffer from paradoxical constipation, while abdominal pain and bloody diarrhea are more prominent in pancolitis [14, 48].

In summary, distal colitis should not be assumed to be milder than extensive colitis as symptoms associated with distal disease may be more burdensome than those associated with extensive disease, and progression of initially distal disease has been reported to result in poor patient outcomes.

2.3 Malignancy is More of a Problem in UC than in CD

There is a recognized increased risk of colorectal cancer (CRC) in patients with IBD, with a reported annual increase of 0.5–1.0%, 8–10 years after diagnosis [49]. For both CD and UC, the risk of developing CRC increases with the duration and extent of disease, younger age at diagnosis, familial association, and primary sclerosing cholangitis [49]. The CRC risk in UC has been studied extensively and, in a meta-analysis, the overall prevalence has been estimated to be 3.7%, with a cumulative risk of 2% after 10 years, 8% after 20 years, and 18% after 30 years, reported in 2004 [50]. The use of surveillance colonoscopy for earlier detection of CRC is recommended for patients with left-sided and extensive UC [51]. However, the incidence of CRC in patients with UC has been reported to have decreased over time between 1971 and 2000 [52], and a meta-analysis including studies up to the end of 2013 also reported a decreasing risk over the previous six decades [53]. A more recent study reports the cumulative risk to be 1.4%, 2.0%, and 3.0% after 10, 20, and 30 years, respectively [54]. Improved colectomy policies and effective surveillance programs might have contributed to a decline in CRC risk in UC [55], as might the use of therapies that allow better control of inflammation, such as biologics [53, 56]. However, it is also likely that the magnitude of risk for CRC in UC has been overestimated in the past due to the use of aging cohorts and referral populations, in contrast to more recent population-based studies. Historic studies have reported a lower risk of CRC in CD than UC [57, 58]; however, recent data suggest that Crohn’s colitis carries a similar risk of CRC to UC [59, 60].

Colonoscopic surveillance programs for CRC in patients with UC were introduced more than 30 years ago [52], and surveillance of patients with IBD to detect dysplasia that might advance to CRC is recommended in relevant guidelines [61, 62]. Techniques used have evolved considerably over the last 30 years, with full-spectrum endoscopy [63] and chromoendoscopy [64] increasing the detection of dysplastic lesions. Recent surveillance guidelines recommend similar surveillance strategies for patients with UC and Crohn’s colitis [61, 62], reflecting the evolving view of the relative risk of CRC in different types of IBD.

In summary, recent analyses suggest that there is a similar risk of CRC in Crohn’s colitis and UC.
2.4 Corticosteroid Maintenance Treatment in UC is Acceptable

Therapeutic options for the long-term maintenance of remission in UC are currently somewhat limited. Aminosalicylates are effective treatments for UC [35], but no clinically relevant effects have been demonstrated in CD [65]. Although corticosteroids remain the first-line induction treatment of choice in moderate to severe UC, corticosteroid-free remission is an established therapeutic target, and short- and long-term adverse effects should preclude their use as maintenance treatment [66]. Thiopurines have been shown to be effective in achieving and maintaining corticosteroid-free remission in UC [67–69]. Corticosteroid-induced toxicities include moon face, cutaneous effects, adrenal suppression, hypertension, glucose intolerance, infectious complications, osteonecrosis, osteoporosis, psychiatric effects, and cataracts [70]. Reports of patients who are receiving oral corticosteroids being at high risk of colectomy if they experience a moderate flare [71] also argue against the use of corticosteroids as maintenance treatment in UC.

Despite the contraindications for prolonged corticosteroid use, an analysis of US claims data reported that 10–24% of patients with UC had, depending on index treatment, received corticosteroid treatment for more than 3 months of the 12-month study period [72]. Analysis of medical records in Olmsted County, MN, USA, also showed long-term corticosteroid use in patients with UC, with 12% of patients treated with corticosteroids for at least 6 months [73]. A recently published audit of British IBD clinics reported that approximately 15% of patients with IBD had received corticosteroids in excess of guidelines or had corticosteroid dependency, with excess exposure/dependency more common in moderate/severe UC than CD [74]. Use of tumor necrosis factor (TNF) antagonists and the existence of multidisciplinary IBD teams were both associated with lower levels of inappropriate long-term use of corticosteroids [75]. Finally, a recent large-scale survey of US gastroenterologists reported corticosteroid refractoriness and dependency as the most common drivers for initiating biologic therapies, with approximately 66% of respondents indicating this as a reason for prescribing a biologic [75].

It is critical that corticosteroids are not considered acceptable for the maintenance of remission in patients with UC. Well-documented corticosteroid-related toxicities, increased need for surgery due to disease flare while receiving corticosteroids, and the availability of agents with more favorable benefit:risk profiles all argue for the need to strive for corticosteroid-free remission in all patients.

In summary, the adverse effects of long-term use of corticosteroids should preclude their use for maintenance of remission, and corticosteroid-free remission must be a key therapeutic target.

2.5 Biologics Induce Remission in the Majority of Patients with UC

Currently, two biological classes are available for the treatment of UC: TNF antagonists (infliximab, adalimumab, and golimumab) and anti-integrin therapy (vedolizumab) [76]. The development of biologic therapies for the treatment of UC has added an important treatment option, particularly for moderate to severe disease that does not respond to other therapies [2, 76, 77]. Studies of patient preferences have also reported that patients with UC strongly prefer medical therapy to surgical intervention [78, 79]. However, one study reported a low level of use, with 6% of patients with UC in Western Europe, and 1% of those in Eastern Europe, receiving infliximab during the first year post-UC diagnosis [80].

However, biologics are not effective in achieving remission in a substantial proportion of patients. Of patients receiving infliximab, approximately 45% showed a clinical response and 35% clinical remission after 1 year of treatment [40], remission at 1 year was reported in 32% of patients responding to adalimumab induction therapy [81], remission was maintained after 1 year of golimumab treatment in approximately 25% of patients who responded initially [82], and up to 45% of patients responding to vedolizumab induction treatment were in remission after 1 year [83]. A recent systematic review reported that TNF antagonists reduced the odds of hospitalization by half, and surgery by 33–77% [84].

In addition to those patients who do not respond to initial biologic treatment, approximately 20–40% of patients lose response over time [85–87]. The development of antidrug antibodies is known to be a leading contributor to the loss of response to biologic therapies [88], and has been reported in 20% of patients receiving adalimumab for CD [89] and up to 60% of patients with IBD receiving infliximab [90]. A good deal of the secondary loss of response to TNF antagonists could be mitigated by therapeutic drug monitoring to allow dose optimization [91], as well as the use of concomitant immunomodulators, which suppress antidrug antibodies and can re-establish clinical efficacy in some patients [92]. Adverse drug reactions have been shown to be the second most common reason for patient discontinuation of biologic therapies, after primary non-response [93]. Pharmacogenetic studies may identify biomarkers that predict patient response to anti-TNF therapies [94].

Patients with UC could potentially benefit from novel small molecule therapies that do not induce antidrug antibody formation. A number of prospective treatments are also currently under investigation [95–97]. One class of drugs being considered is the Janus kinase inhibitors [98]; clinical efficacy and improvements in HRQoL in moderate to severe UC have been demonstrated with tofacitinib in phase II and III clinical trials [42, 99–102]. In a phase II trial in moderate to severe UC, the sphingosine-1-phosphate receptor agonist
ozanimod has also been reported to result in a slightly higher rate of clinical remission than placebo [103]. Another pathway as a potential focus for novel therapies includes interleukin (IL-)–mediated inflammatory response, targeted by the IL-23 and IL-12 antibody ustekinumab [95]. In addition, the use of fecal microbiota transplantation (FMT) has been suggested as a potential therapeutic strategy for patients with IBD; however, to date, only a small number of studies have investigated the efficacy of FMT in patients with IBD, and results have been inconclusive [104, 105]. Further studies in larger patient cohorts will therefore be required to assess the potential of FMT for IBD.

In summary, biologics fail to induce remission in a substantial proportion of UC patients, and secondary non–responsiveness develops in up to 40% of patients who respond initially.

3 Conclusions

The development of novel treatments for IBD, including small molecular therapies, continues and should widen the armamentarium of treatment options available to gastroenterologists. In addition to the expanded treatment options, improved surgical decision making and techniques and effective CRC surveillance programs have also contributed to the improvement of prognosis for patients with UC over the past 30 years or so. However, the persistence of a number of misconceptions among a subset of clinicians and healthcare professionals responsible for the management of patients with UC is resulting in suboptimal clinical care for some patients.

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