Natural History of Ulcerative Colitis in Children

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Introduction

Defining the natural history of a chronic disease is made difficult by the continuously changing landscape of available therapies, earlier recognition of disease by more sensitive diagnostic techniques, and changes in intrinsic biological behavior. The natural history of ulcerative colitis following therapy with aminosalicylates and corticosteroids from previous decades would be expected to differ from that following the current and increasingly widespread use of immunomodulators and biological therapy. The data presented in this chapter reflect what we know of natural history now and will likely be different than what we might describe 10 years from now. There are a number of aspects of ulcerative colitis whose natural history can be examined, including clinical indices, endoscopic measures, extraintestinal manifestations, and therapy changes. This chapter will focus on natural history elements pertaining to clinical remission, endoscopic remission, and colectomy. Discussion of drugs will mostly focus mainly on maintenance of remission. Lastly, possible methodology to predict response to therapy and alter natural history will be addressed.

Overview

Clinical reports from the 1970s describe a severe clinical course for children newly diagnosed with ulcerative colitis with chronic disease, recurrent hospitalizations, frequent colectomy, and not rare deaths [1, 2]. Cohorts examined since the beginning of widespread use of immunomodulators have presented data with more encouraging outcomes. A report in 1996 of 171 subjects seen at two large pediatric inflammatory bowel disease centers in the Northeastern United States found that 43% of patients had mild disease and 57% moderate to severe disease at presentation [3]. Forty-three percent had pancolitis. Over 80% had resolution of symptoms within 6 months of diagnosis, and during subsequent yearly follow-up intervals, 55% were symptom free, 38% had chronic intermittent symptoms, and 7% had continuous symptoms. Corticosteroid therapy was used in 27% of those with initially mild disease and 70% of those with moderate/severe disease by 1 year. Eleven percent of those with moderate/severe disease received additional immunomodulatory therapy (azathioprine/6-mercaptopurine or cyclosporine) during the first year. By 1 year following diagnosis, 1% of those with initial mild disease and 8% of those with moderate/severe disease had required colectomy; at 5 years the risk of colectomy was 9% and 26% in the two groups, respectively. A report from Denmark in 1997 describing 80 children with ulcerative colitis demonstrated a cumulative colectomy rate of 6% and 23% at 1 and 5 years, respectively [4]. A report of a regional incident cohort from Northern France in 2009 on 113 pediatric patients showed evolution from initial extensive disease in 37% at diagnosis to 60% by last follow-up and a cumulative colectomy rate of 20% by 5 years [5]. In a population-based cohort in Texas, 25% of patients had proctitis, 40% had left-sided disease, and 35% had extensive colitis at presentation [6]. At a mean of 4.4 years, 20% of patients with proctitis initially progressed to left-sided disease, while 80% progressed to extensive disease; of those with left-sided colitis, 40% had progressed to extensive colitis. Colectomy rates in this cohort were 4.1% at 1 year and 16% at 10 years of follow-up.

A few recent cohorts from Europe and North America have encompassed populations that were all diagnosed in the era of biologic agents. In a Slovenian IBD cohort with 39 UC

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patients, only 5% of the patients had proctitis at diagnosis, while 69% had extensive colitis or pancolitis [7]. A portion of this cohort had colonoscopy >2 years from diagnosis; none of whom had proctitis, while 82% had extensive pancolitis. In this cohort, only one patient proceeded to colectomy. A prospective, population-based cohort in Wisconsin found 66% of patients with pancolitis versus 34% with left-sided disease [8]. While the authors deemed the data on progression insufficient for analysis, they did report a colectomy rate of 13% in a mean follow-up of 4 years. A prospective population-based cohort from Denmark found 8% of patients initially presenting with proctitis and 65% with extensive colitis [9]. Again, the study did not analyze disease progression, but found a 1-year colectomy rate of 2.4%. A colectomy rate of 9% for children diagnosed with ulcerative colitis was reported in a regional center in the United Kingdom [10]. All children underwent colectomy after failing maximal medical therapy. A review of the published literature on population-based natural history studies of pediatric ulcerative colitis suggested an overall colectomy rate of about 20% at 10 years follow-up [11].

As mentioned previously the natural history of ulcerative colitis is largely a function of the efficacy of medications used to treat it. Large-scale blinded, placebo-controlled trials are generally lacking in the pediatric population.

Aminosalicylates

Data supporting the use of 5-aminosalicylate (5-ASA) compounds for the induction and maintenance therapy in adult ulcerative colitis (UC) are strong [12, 13]. There are also data in adults suggesting that higher-dose 5-ASA may be more effective in inducing remission (4.8 g mesalamine vs. 2.4 g mesalamine), but this added efficacy seemed limited to patients with moderate disease and was not observed in those with mild disease [14].

In 1993, a small blinded pediatric study compared sulfasalazine (30 mg/kg/day) versus olsalazine (60 mg/kg/day [15]. Neither agent is in common use currently. A more recent study assessed the safety and efficacy of high- and low-dose oral delayed-release mesalamine in children with mild to moderately active ulcerative colitis [16]. Patients with a pediatric ulcerative colitis activity index (PUCAI) score of 10–55 received a weight-dependent low or high dose of delayed-release mesalamine. The primary outcome was achieving a PUCAI score of <10 at 6 weeks. No difference was found in the two dosing groups with each achieving a little over 50% remission. A limitation of this study was the wide range of dosing given even within each of the two dosing groups. Data on the use of aminosalicylates in a large, prospective North American observational cohort of 213 patients has been reported [17]. Children who received either an aminosalicylate alone or aminosalicylate plus corticosteroid were followed; however, children who required additional therapy such as infliximab, calcineurin inhibitors, or surgery in the first 30 days were excluded from outcome analysis. The mean dose of 5-ASA used in the treated population was 52 mg/kg/day. The use of 5-ASA with or without CS in the first 30 days was associated with corticosteroid-free inactive disease at 1 year with no need for additional rescue therapy in approximately 40% of patients. Adherence was not monitored, and recent data show alarming rates of non-adherence into oral medications in children with IBD [18]. The effect of better adherence on long-term outcomes of children with newly diagnosed ulcerative colitis is an area currently being studied.

The use of rectal mesalamine therapy (suppositories, enemas) is often encouraged in those with largely limited distal disease or proctitis, but many children and adolescents prefer oral therapy instead.

Corticosteroids

Corticosteroids remain the mainstay of induction therapy for moderate to severe ulcerative colitis, and therefore understanding the course of disease following these medications is critical to understanding natural history. Traditional corticosteroid therapy has usually meant prednisone for moderate to severe disease though more recently budesonide MMX has been used for mild to moderate disease [19].

The outcome of corticosteroid therapy for adults with UC in a population-based study in Olmsted County, Minnesota, was published in 2001 [20]. In this study of 185 patients diagnosed with UC over a 23-year period, only 63 (34%) received corticosteroids. Fifty-four percent of subjects receiving corticosteroids had a complete clinical response by 30 days, 30% a partial response, and 16% no response. By 1 year, 49% had a prolonged response, 22% were termed corticosteroid-dependent, and 29% had undergone colectomy. Immunomodulators were used in very few of these patients. Corticosteroid use is more widespread in the treatment of pediatric ulcerative colitis compared with adults, with a rate of 79% reported in an observational registry [21]. This difference may be at least partially explained by the generally extensive and severe presentation of ulcerative colitis at diagnosis. In this registry report, 60% of children with ulcerative colitis treated with corticosteroids within 30 days of diagnosis were noted to have inactive disease activity at 3 months with mild disease in 27% and continued to moderate/severe activity in 11%. At 1 year, 31/62 (50%) of the corticosteroid-treated patients were considered corticosteroid-responsive and 28 (45%) corticosteroid-dependent. A total of four patients receiving corticosteroids (5%) required colectomy in the first year. Immunomodulators

were used in 61% of all corticosteroid-treated patients. Optimal dosing regimens for corticosteroids have not been established though there appears to be little advantage to exceeding the equivalent of 40–60 mg/day in adults. The mechanisms underlying corticosteroid resistance are beyond the scope of this discussion and have been reviewed elsewhere [22]. In a study of 128 children hospitalized with ulcerative colitis and treated with intravenous corticosteroids, nonresponse to therapy was associated with overexpression of several genes involved in inflammatory pathways [23]. In vitro studies have identified expression of certain microRNAs as potential mediators of glucocorticoid resistance [24], but clinical studies have not been published that support this relationship.

Immunomodulators

The use of immunomodulators has become standard of care in corticosteroid-dependent ulcerative colitis in children and adults, though as discussed below, the emergence of newer biologic agents may be changing this paradigm. A review of seven blinded, controlled trials of azathioprine in ulcerative colitis highlighted the methodological issues with many early studies of adults which left unanswered the question of whether this drug was useful in maintaining remission [25]. A review of the 30-year experience with azathioprine in a large cohort of adult patients in Oxford, England, suggested significant utility of azathioprine in maintaining remission [26]. Almost two-thirds of patients maintained remission for up to 5 years and median time to relapse upon stopping the drug with 18 months. The addition of the 5-aminosalicylate olsalazine to azathioprine did not improve the maintenance of remission rate compared to azathioprine alone in steroid-dependent adults with ulcerative colitis. A recent meta-analysis supported the role of thiopurines in maintaining remission in adult ulcerative colitis [27].

Pediatric data are more limited. One report detailed their use in 133 children from an inception registry cohort in North America [28]. Of these, 65 (49%) had CS-free inactive UC without rescue therapy at 1 year from thiopurine start. CS-free inactive disease at 1 year after initiating thiopurine was not affected by starting thiopurine ≤3 months versus >3 months from diagnosis, gender, age, or concomitant treatment with 5-aminosalicylates. Kaplan-Meier analysis showed that the likelihood of remaining free of rescue therapy (surgery, calcineurin inhibitors, or biologic therapy) in the thiopurine-treated patients was 73% at 1 year. A French cohort reported a 54% success rate treating patients with azathioprine, with success defined as few to no symptoms and no corticosteroid rescue therapy, at a minimum of 2 years' follow-up [5]. A large population-based study from Greece of children and young adults suggested that the use of thiopurines in ulcerative colitis therapy had not benefit in lowering the risk of colectomy [29].

The use of methotrexate as an immunomodulator for the treatment of ulcerative colitis remains controversial, and until recently little data were available. A recent randomized double-blind placebo-controlled study from Europe compared 25 mg of parenteral methotrexate weekly with placebo in adults with corticosteroid-dependent ulcerative colitis [30]. Steroid-free remission at week 16 was achieved by 19/60 patients given methotrexate (31.7%) and 10/51 patients given placebo (19.6%) – a difference of 12.1% (95% confidence interval [CI], −4.0% to 28.1%; $P = .15$). The proportions of patients in steroid-free clinical remission at week 16 were 41.7% in the methotrexate group and 23.5% in the placebo group, for a difference of 18.1% (95% CI, 1.1%–35.2%; $P = .04$). The proportions of patients with steroid-free endoscopic healing at week 16 were 35% in the methotrexate group and 25.5% in the placebo group-a difference of 9.5% (95% CI, −7.5% to 26.5%; $P = .28$). A Cochrane review meta-analysis of the literature prior to this report concluded there were insufficient data in the literature to support or refute a role for methotrexate in the management of ulcerative colitis in adults [31]. The use of methotrexate for the treatment of inflammatory bowel disease in general has recently been reviewed [32].

Though calcineurin inhibitors are widely accepted as effective therapy for inducing remission in severe ulcerative colitis [33–35], their use as maintenance therapy is uncommon. In children there are limited data on the use of these agents, and while short-term response averages about 80%, the majority of treated children still require colectomy within 2–3 years of their use [36, 37]. Additionally, because of their nephrotoxicity, increased susceptibility to infection, and other side effects, the use of calcineurin inhibitors is generally limited to several months as a bridge to other immunomodulators, infliximab, or surgery.

Biologics

There are ample data demonstrating the efficacy of anti-TNFα therapy in the treatment of adult [38] and pediatric ulcerative colitis [39]. In 2005, two randomized, double-blind, placebo-controlled studies, ACT 1 and ACT 2, were published in a single paper [38] evaluating the efficacy of infliximab for induction and maintenance in 728 adults with active ulcerative colitis (Mayo score 6–12). Clinical response at 8 weeks (decrease in Mayo score by 3 points) was observed in approximately 65% of subjects receiving a three-dose induction of infliximab (either 5 mg/kg/dose or 10 mg/kg/dose) compared to approximately 33% of placebo patients. Clinical remission at week 8 (Mayo score of 2 or lower, no

item more than one) was observed in approximately 33% of infliximab-treated patients versus 10% in the placebo group. Mucosal healing at week 8 was seen in approximately 60% of infliximab-treated patients versus 30% of placebo treated patients. Week 54 data were available for 364 ACT 1 patients; 42% of infliximab-treated patients were in remission compared to 20% of those treated with placebo. Clinical remission without corticosteroids was seen in 9% of placebo-treated patients, 26% of those receiving 5 mg/kg maintenance doses of infliximab every 8 weeks, and 16% of those receiving 10 mg/kg doses. At the start of ACT 1 and ACT 2, approximately 30% of patients were felt to have corticosteroid refractory disease, 50–60% were taking corticosteroids at the time infliximab was initiated, 70% were receiving 5-aminosalicylate preparations, and 40–50% were taking immunomodulators. Average disease duration was approximately 6 years.

Subsequent observations since the ACT trials were published have greatly impacted the use of infliximab in the treatment of ulcerative colitis. It has been demonstrated that low serum trough levels of infliximab as well as the development of antibodies to infliximab negatively affect response and durability [40]. Rapid clearance of drug is noted in those patients with extensive disease and high C-reactive protein levels, likely through multiple mechanisms including the concept of a "large antigen sink" of TNF, hypoalbuminemia, and loss in the stool [40–43].

In a formal clinical trial of 60 children and adolescents with active ulcerative colitis despite treatment with corticosteroids, immunomodulators, and 5-aminosalicylates, a response as defined by a drop in Mayo score was seen at 8 weeks in 73% of patients following a three-dose induction of 5 mg/kg at 0, 2, and 6 weeks [39]. Clinical remission by Mayo score was seen in 40% at 8 weeks. At 54 weeks, in those patients treated with this induction regimen followed by maintenance therapy every 8 weeks, remission was noted in 38% of subjects. Similar to the experience in adults, a direct relationship was found between serum infliximab levels and a positive therapeutic response [44]. In a prospective observational registry, data on 51 children with ulcerative colitis treated with infliximab (65% corticosteroid refractory, 35% corticosteroid-dependent, 63% receiving immunomodulators) were available [45]. Inactive disease at 3 months following initiation of therapy was noted in 36% (26% also corticosteroid-free). At 12 months inactive disease was noted in 49% (38% corticosteroid-free).

There are no controlled pediatric data on the use of adalimumab to treat ulcerative colitis. In a controlled, randomized, placebo-controlled study of adult patients with moderate to severely active disease despite conventional therapy, adalimumab was associated with clinical remission in 16.5% of treated patients at 8 weeks compared to 9.3% treated with placebo; at 52 weeks the corresponding remission rates were 17.3% and 8.5% [46]. Golimumab, another humanized IgG1 antibody to TNFα, has been shown to be more effective than placebo in inducing and maintaining remission [47, 48]. While direct comparison between infliximab, adalimumab, and golimumab is difficult because of differences in treatment design, a recent meta-analysis of data in adults suggested that infliximab was most likely of the three to prevent colectomy [49]. A lesson learned from all of these trials as well as real-world experience is the importance of achieving therapeutic drug levels no matter what agent is used [50].

Anti-integrin therapy has now shown efficacy in the treatment of adults with ulcerative colitis though there are no published data in children [51]. Response rates at week 6 were 47.1% and 25.5% among patients in the vedolizumab group and placebo group, respectively ($P < 0.001$). At week 52, 41.8% of patients who continued to receive vedolizumab every 8 weeks and 44.8% of patients who continued to receive vedolizumab every 4 weeks were in clinical remission, compared with 15.9% of patients who switched to placebo ($P < 0.001$). The frequency of adverse events was similar in the vedolizumab and placebo groups. Many patients in this study had previously been treated with anti-TNFα therapy.

It is quite likely that in the future both adult and pediatric patients with ulcerative colitis may cycle through several biologic agents, achieve clinical response or remission, have a good quality of life, and avoid colectomy.

Can We Predict the Course of Disease?

The wide range in phenotypic expression of pediatric ulcerative colitis and its response to therapy has heretofore made prediction of disease course difficult. Clinical factors examined have included features such as severity of disease (i.e., fulminant features requiring hospitalization), endoscopic appearance, laboratory markers, and early response to therapy [52–54]. Clinical severity, the need for hospitalization at diagnosis, and the need for rapid rescue with calcineurin inhibitors or anti-TNF agents remain the greatest risk factors for early colectomy. There are data in adults with ulcerative colitis suggesting that mucosal healing after a first course of corticosteroids for newly diagnosed ulcerative colitis is highly predictive of future course [55]. One hundred fifty-seven patients were followed for up to 5 years following their first course of corticosteroids. The group that displayed both clinical and endoscopic remission by 3 months had significantly lower rates of relapse, hospitalizations, and the need for immunosuppression than partial responders or non-responders. Moreover, the colectomy rate during follow-up was 3.3% in those with complete mucosal healing compared to 18% in partial responders and 17% in those without mucosal healing.

Attempts have also been made to try to correlate disease course with genetic profiles. An association between severe and extensive disease and the major histocompatibility complex (MHC) genes DRB1*0103 and DRB1*15 has been identified [56–58]. A structural polymorphism in the IKBL (inhibitor of κB-like) gene, located in the central region of the MHC locus, has also been associated with severe disease [59]. A genome-wide association study (GWAS) compared 324 adults with ulcerative colitis who required colectomy for refractory disease with 537 ulcerative colitis patients who did not [60]. A risk score determined from a combination of 46 single-nucleotide polymorphisms (SNPs) associated with the medically refractory group accounted for a little less than 50% of the variance for the colectomy risk. The sensitivity and specificity of the risk score were over 90%. Microarray of RNA isolated from colonic biopsy tissue has identified genes that may predict the response to infliximab in adults [61].

This panel of five genes (osteoprotegerin (OPG), stanniocalcin-1, prostaglandin-endoperoxide synthase 2 (COX2), interleukin 13 receptor alpha2, and interleukin 11) discriminated responders from non-responders with 95% sensitivity and 85% specificity. Another study of mucosal gene expression found a positive correlation between high IL-17 and IFN-γ expression and response to infliximab [62]. Variants of the IL-23R gene that increase susceptibility to UC seem to improve response to infliximab [63]. One study used a pharmacogenetics GWAS to evaluate infliximab non-response in a combined ulcerative colitis and Crohn disease group, finding BRWD1, TACR1, FAM19A4, and PHACTR3 to predict non-response [64].

In pediatric patients elevated fecal levels of OPG are associated with failure to respond to intravenous corticosteroids in children with severe ulcerative colitis [65]. Patients with colonic tissue that expresses high levels of the integrin αE gene (ITGAE) were shown to have improved response to a novel anti-integrin antibody, etrolizumab [66]. Emerging areas of research into biologic molecules (e.g., metabolomics, proteomics, epigenomics) have the potential to clarify disease phenotypes, behavior, and responsiveness to medications [67–69].

Summary

The optimal therapy for ulcerative colitis quickly induces and then effectively maintains remission with healing of the colonic mucosa and presents minimal toxicity to the patient. While 5-aminosalicylates are effective in inducing and maintaining remission in some patients, their efficacy in both aspects of therapy is limited for those with more severe disease. Nonetheless, 5-aminosalicylates should be the cornerstone of therapy if possible. Immunomodulators and anti-TNFα therapy are effective in many patients not maintained in remission on 5-aminosalicylates, but remission is noted in less than half of patients treated with these agents, and disease flares are still common. Evidence suggests that the short-term impact of biologic agents on disease course is positive, though it is not clear that disease course is altered for those who present with fulminant disease. This group continues to exhibit a greater degree of treatment unresponsiveness and has an unacceptably high rate of colectomy. Long-term observations will be required to better understand the changing natural history of ulcerative colitis in children with the emergence of new therapies. Current research holds the promise of development of risk assessment (e.g., gene expression, microbiome, genetics) promptly following diagnosis that will facilitate treatment design, decreasing the likelihood of treatment failure and complications of ineffective treatments.

References

1. Goel KM, Shanks RA. Long-term prognosis of children with ulcerative colitis. Arch Dis Child. 1973;48(5):337–42.
2. Michener WM, Farmer RG, Mortimer EA. Long-term prognosis of ulcerative colitis with onset in childhood or adolescence. J Clin Gastroenterol. 1979;1(4):301–5.
3. Hyams JS et al. Clinical outcome of ulcerative colitis in children. J Pediatr. 1996;129(1):81–8.
4. Langholz E et al. Inflammatory bowel diseases with onset in childhood. Clinical features, morbidity, and mortality in a regional cohort. Scand J Gastroenterol. 1997;32(2):139–47.
5. Gower-Rousseau C et al. The natural history of pediatric ulcerative colitis: a population-based cohort study. Am J Gastroenterol. 2009;104(8):2080–8.
6. Malaty HM et al. The natural history of ulcerative colitis in a pediatric population: a follow-up population-based cohort study. Clin Exp Gastroenterol. 2013;6:77–83.
7. Urlep D et al. Incidence and phenotypic characteristics of pediatric IBD in northeastern Slovenia, 2002-2010. J Pediatr Gastroenterol Nutr. 2014;58(3):325–32.
8. Adamiak T et al. Incidence, clinical characteristics, and natural history of pediatric IBD in Wisconsin: a population-based epidemiological study. Inflamm Bowel Dis. 2013;19(6):1218–23.
9. Jakobsen C et al. Pediatric inflammatory bowel disease: increasing incidence, decreasing surgery rate, and compromised nutritional status: a prospective population-based cohort study 2007-2009. Inflamm Bowel Dis. 2011;17(12):2541–50.
10. Ashton JJ et al. Colectomy in pediatric ulcerative colitis: a single center experience of indications, outcomes, and complications. J Pediatr Surg. 2016;51:277–81.
11. Fumery M et al. Review article: the natural history of paediatric-onset ulcerative colitis in population-based studies. Aliment Pharmacol Ther. 2016;3:346–55.
12. Sutherland L, Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2006;(2):CD000543.
13. Sutherland L, Macdonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2006;(2):CD000544.
14. Hanauer SB et al. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative

colitis: the ASCEND II trial. Am J Gastroenterol. 2005;100(11):2478–85.
15. Ferry GD et al. Olsalazine versus sulfasalazine in mild to moderate childhood ulcerative colitis: results of the Pediatric Gastroenterology Collaborative Research Group Clinical Trial. J Pediatr Gastroenterol Nutr. 1993;17(1):32–8.
16. Winter HS et al. High- and low-dose oral delayed-release mesalamine in children with mild-to-moderately active ulcerative colitis. J Pediatr Gastroenterol Nutr. 2014;59(6):767–72.
17. Zeisler B et al. Outcome following aminosalicylate therapy in children newly diagnosed as having ulcerative colitis. J Pediatr Gastroenterol Nutr. 2013;56(1):12–8.
18. LeLeiko NS et al. Rates and predictors of oral medication adherence in pediatric patients with IBD. Inflamm Bowel Dis. 2013;19(4):832–9.
19. Lichtenstein GR. Budesonide multi-matrix for the treatment of patients with ulcerative colitis. Dig Dis Sci. 2016;61:358–7.
20. Faubion Jr WA et al. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. Gastroenterology. 2001;121(2):255–60.
21. Hyams J et al. The natural history of corticosteroid therapy for ulcerative colitis in children. Clin Gastroenterol Hepatol. 2006;4(9):1118–23.
22. De Iudicibus S et al. Molecular mechanism of glucocorticoid resistance in inflammatory bowel disease. World J Gastroenterol. 2011;17(9):1095–108.
23. Kabakchiev B, et al. Gene expression changes associated with resistance to intravenous corticosteroid therapy in children with severe ulcerative colitis. PLoS One. 2010;5(9):1–8.
24. De Iudicibus S et al. MicroRNAs as tools to predict glucocorticoid response in inflammatory bowel diseases. World J Gastroenterol. 2013;19(44):7947–54.
25. Sands BE. Immunosuppressive drugs in ulcerative colitis: twisting facts to suit theories? Gut. 2006;55(4):437–41.
26. Fraser AG, Orchard TR, Jewell DP. The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. Gut. 2002;50(4):485–9.
27. Khan KJ et al. Efficacy of immunosuppressive therapy for inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol. 2011;106(4):630–42.
28. Hyams JS et al. Outcome following thiopurine use in children with ulcerative colitis: a prospective multicenter registry study. Am J Gastroenterol. 2011;106(5):981–7.
29. Chhaya V et al. The impact of timing and duration of thiopurine treatment on colectomy in ulcerative colitis: a national population-based study of incident cases between 1989–2009. Aliment Pharmacol Ther. 2015;41(1):87–98.
30. Carbonnel F et al. Methotrexate is not superior to placebo in inducing steroid-free remission, but induces steroid-free clinical remission in a larger proportion of patients with ulcerative colitis. Gastroenterology. 2016;150:380–8.
31. Wang Y, et al. Methotrexate for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2015;8:CD007560.
32. Herfarth HH et al. Use of methotrexate in the treatment of inflammatory bowel diseases. Inflamm Bowel Dis. 2016;22(1):224–33.
33. Shibolet O, et al. Cyclosporine A for induction of remission in severe ulcerative colitis. Cochrane Database Syst Rev. 2005;(1):CD004277.
34. Navas-Lopez VM et al. Oral tacrolimus for pediatric steroid-resistant ulcerative colitis. J Crohns Colitis. 2014;8(1):64–9.
35. Kawakami K et al. Effects of oral tacrolimus as a rapid induction therapy in ulcerative colitis. World J Gastroenterol. 2015;21(6):1880–6.
36. Turner D et al. Consensus for managing acute severe ulcerative colitis in children: a systematic review and joint statement from ECCO, ESPGHAN, and the Porto IBD Working Group of ESPGHAN. Am J Gastroenterol. 2011;106(4):574–88.
37. Watson S et al. Outcomes and adverse events in children and young adults undergoing tacrolimus therapy for steroid-refractory colitis. Inflamm Bowel Dis. 2011;17(1):22–9.
38. Rutgeerts P et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353(23):2462–76.
39. Hyams J et al. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol. 2012;10(4):391–9. e1
40. Brandse JF et al. Pharmacokinetic features and presence of antidrug antibodies associate with response to infliximab induction therapy in patients with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol. 2016;14:251–8.
41. Hoekman DR et al. The association of infliximab trough levels with disease activity in pediatric inflammatory bowel disease. Scand J Gastroenterol. 2015;50(9):1110–7.
42. Brandse JF et al. Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. Gastroenterology. 2015;149(2):350–5. e2
43. Ordas I, Feagan BG, Sandborn WJ. Therapeutic drug monitoring of tumor necrosis factor antagonists in inflammatory bowel disease. Clin Gastroenterol Hepatol. 2012;10(10):1079–87. ; quiz e85-6
44. Adedokun OJ et al. Pharmacokinetics of infliximab in children with moderate-to-severe ulcerative colitis: results from a randomized, multicenter, open-label, phase 3 study. Inflamm Bowel Dis. 2013;19(13):2753–62.
45. Hyams JS et al. Outcome following infliximab therapy in children with ulcerative colitis. Am J Gastroenterol. 2010;105(6):1430–6.
46. Sandborn WJ et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012;142(2):257–65. e1-3
47. Sandborn WJ et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146(1):85–95. ; quiz e14-5
48. Sandborn WJ et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146(1):96–109. e1
49. Lopez A et al. Efficacy of tumour necrosis factor antagonists on remission, colectomy and hospitalisations in ulcerative colitis: meta-analysis of placebo-controlled trials. Dig Liver Dis. 2015;47(5):356–64.
50. Ungar B et al. Optimizing anti-TNFalpha therapy: serum levels of infliximab and adalimumab associate with mucosal healing in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2015;14:550–7.
51. Feagan BG et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369(8):699–710.
52. Turner D et al. Endoscopic and clinical variables that predict sustained remission in children with ulcerative colitis treated with infliximab. Clin Gastroenterol Hepatol. 2013;11(11):1460–5.
53. Schechter A et al. Early endoscopic, laboratory and clinical predictors of poor disease course in paediatric ulcerative colitis. Gut. 2015;64(4):580–8.
54. Kumar S et al. Severe ulcerative colitis: prospective study of parameters determining outcome. J Gastroenterol Hepatol. 2004;19(11):1247–52.
55. Ardizzone S et al. Mucosal healing predicts late outcomes after the first course of corticosteroids for newly diagnosed ulcerative colitis. Clin Gastroenterol Hepatol. 2011;9(6):483–9. e3
56. Bouma G et al. Genetic markers in clinically well defined patients with ulcerative colitis (UC). Clin Exp Immunol. 1999;115(2):294–300.

57. Trachtenberg EA et al. HLA class II haplotype associations with inflammatory bowel disease in Jewish (Ashkenazi) and non-Jewish caucasian populations. Hum Immunol. 2000;61(3):326–33.
58. Ahmad T et al. The contribution of human leucocyte antigen complex genes to disease phenotype in ulcerative colitis. Tissue Antigens. 2003;62(6):527–35.
59. de la Concha EG et al. Susceptibility to severe ulcerative colitis is associated with polymorphism in the central MHC gene IKBL. Gastroenterology. 2000;119(6):1491–5.
60. Haritunians T et al. Genetic predictors of medically refractory ulcerative colitis. Inflamm Bowel Dis. 2010;16(11):1830–40.
61. Arijs I et al. Mucosal gene signatures to predict response to infliximab in patients with ulcerative colitis. Gut. 2009;58(12): 1612–9.
62. Rismo R et al. Mucosal cytokine gene expression profiles as biomarkers of response to infliximab in ulcerative colitis. Scand J Gastroenterol. 2012;47(5):538–47.
63. Jurgens M et al. Disease activity, ANCA, and IL23R genotype status determine early response to infliximab in patients with ulcerative colitis. Am J Gastroenterol. 2010;105(8):1811–9.
64. Dubinsky MC et al. Genome wide association (GWA) predictors of anti-TNFalpha therapeutic responsiveness in pediatric inflammatory bowel disease. Inflamm Bowel Dis. 2010;16(8): 1357–66.
65. Sylvester FA et al. Fecal osteoprotegerin may guide the introduction of second-line therapy in hospitalized children with ulcerative colitis. Inflamm Bowel Dis. 2011;17(8):1726–30.
66. Tew GW et al. Association between response to etrolizumab and expression of integrin alphaE and granzyme A in colon biopsies of patients with ulcerative colitis. Gastroenterology. 2016;150: 477–87.
67. Fukuda K, Fujita Y. Determination of the discriminant score of intestinal microbiota as a biomarker of disease activity in patients with ulcerative colitis. BMC Gastroenterol. 2014;14:49.
68. Rantalainen M et al. Integrative transcriptomic and metabonomic molecular profiling of colonic mucosal biopsies indicates a unique molecular phenotype for ulcerative colitis. J Proteome Res. 2015;14(1):479–90.
69. Hasler R et al. A functional methylome map of ulcerative colitis. Genome Res. 2012;22(11):2130–7.