

# Medical Therapy for Ulcerative Colitis 2004

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There continue to be evolutionary changes in the management of ulcerative colitis despite the fact that, aside from a variety of aminosalicylate formulations, no new therapies have been approved over the past few decades. Nevertheless, debates continue regarding the optimization of treatment with aminosalicylates and the short- and long-term benefits of immunomodulation in ulcerative colitis. This article focuses on the most recent clinical studies pertaining to the management of ulcerative colitis and explores both the advances and controversies pertaining to aminosalicylate therapy, corticosteroids, cyclosporine, and the purine antimetabolites. Novel therapeutic approaches—including preliminary experience with biological therapies directed at tumor necrosis factor and other cytokines, adhesion molecules, growth factors, and probiotics—will be reviewed. Recent data regarding potential chemoprevention in long-standing ulcerative colitis and management of postoperative complications and pouchitis will also be discussed.

Despite recent advances in the understanding of the genetics, immune and inflammatory mechanisms, and potential environmental triggers that contribute to ulcerative colitis, an exact etiopathogenesis remains elusive. In parallel to the basic underpinning of disease evolution and perpetuation and in contrast to the confirmed utility of biological (anti-tumor necrosis factor [TNF]) therapy for Crohn's disease, advances in medical therapy for ulcerative colitis continue to be evolutionary rather than revolutionary. Nevertheless, a number of advances have either improved the efficacy or reduced the toxicity related to acute (inductive) and chronic (maintenance) therapy. At the same time, a number of controversies have come to light regarding the optimization of therapy with aminosalicylates, corticosteroids, immunomodulators, novel biologics, and probiotics. This review will focus on the most recent advances and current controversies in therapy for ulcerative colitis.

## Aminosalicylates

The aminosalicylates remain the mainstays of therapy for induction of remission in mild to moderately active ulcerative colitis<sup>1</sup> and to prevent relapse of quiescent disease.<sup>2</sup> The expansion of mesalamine formulations

and delivery systems has exposed several gaps in the evidence base for the treatment of ulcerative colitis that require further elucidation. These include substantiating differences in pharmacokinetic profiles and systemic "load" of different formulations, discrimination between formulations for differing extents of disease, and clarification of the dose response for active and maintenance therapy.

The development of the azo-bond formulation, balsalazide,<sup>3</sup> by using aminobenzoyl- $\beta$ -alanine, an inert carrier devoid of the sulfa moiety, has created controversies regarding the pharmacokinetics and competitive advantages of different aminosalicylates for the treatment of ulcerative colitis. Recent trials have shown that balsalazide is comparable in efficacy to sulfasalazine and is better tolerated when equimolar concentrations of mesalamine are administered to patients with active ulcerative colitis.<sup>4,5</sup> However, recent comparative trials with mesalamine have been more controversial in their interpretation.<sup>6-8</sup> Unfortunately, lack of standardized evaluations of disease activity, differing definitions of improvement or remission, and exuberant reliance on secondary end points impair optimal interpretation of these trials.<sup>7,9,10</sup> In a trial reported by Green et al.,<sup>11</sup> balsalazide 6.75 g/day was compared with a European pH-release mesalamine formulation of Asacol (Proctor and Gamble, Cincinnati, OH) 2.4 g/day in patients with active ulcerative colitis over 12 weeks. The authors reported a faster onset of action (not the primary end point) and improved tolerance in this study population, which included patients with moderate or even severe disease. Post hoc analysis also suggested that patients with left-sided disease might have responded better to balsalazide. Two additional trials have been performed comparing balsalazide 6.75 g/day with mesalamine 2.4 g/day. Both trials showed similar efficacy according to the primary end point of symptomatic remission at 8 weeks.<sup>12,13</sup>

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*Abbreviations used in this paper:* EBV, Epstein-Barr virus; EGF, epidermal growth factor; IFN, interferon; IL, interleukin; IL-2R, IL-2 receptor; TNF, tumor necrosis factor.

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Secondary or post hoc analyses suggested a faster onset of action and improved responses for patients with left-sided disease. Although the authors suggested that there was less systemic absorption of mesalamine from balsalazide and considered pharmacokinetics as a rationale for (possible) improved efficacy in left-sided colitis, a recent meta-analysis of pharmacokinetic studies with all the mesalamine compounds showed greater similarities in systemic availability and renal excretion than differences between any of the agents.<sup>14</sup>

Direct comparison studies are necessary to determine whether patients with left-sided disease respond better to an azo-bond compound than to alternative delivery systems of mesalamine.<sup>7,9</sup> Even in the trials described previously, there was a lack of consistency in primary endpoint evaluations, with "remissions" defined as "no or mild symptoms, a sigmoidoscopy score of 0 or 1, and no use of rectal steroids"<sup>11</sup>; "normal stool frequency, no blood in stool for 48 hours, physician's global assessment of "quiescent," and a sigmoidoscopy score of normal or mild,"<sup>12</sup>; and "a patient functional assessment rating of normal or mild and absence of rectal bleeding."<sup>13</sup> In a recent critical systematic review focusing on evidence-based interpretation of the use of mesalamine in ulcerative colitis, the authors emphasized the requisite for well-defined primary end points, cautious interpretation of secondary end points when primary end points are not achieved, prespecification of statistical corrections for multiple secondary end points, and post hoc or posttrial analyses.<sup>10</sup>

In clinical trials with oral mesalamine compounds, both pH-dependent and time-release, patients with pancolitis and left-sided colitis responded similarly.<sup>15-17</sup> However, a potential mechanism for azo-bond drug efficacy in left-sided disease is the increased small-bowel secretion that has been shown with olsalazine<sup>18</sup> and, most recently, with sulfasalazine and balsalazide (E. Chang, personal communication, March 2004). This may also limit the upward dosing of azo-compounds in active disease because of increased loosening of stools, as has been shown with olsalazine at doses greater than 2 g/day (similar to balsalazide at 6 g/day). In any event, the issue of optimal therapy for left-sided disease with varied formulations of oral aminosalicylates is made less relevant by the well-defined superiority of topical (rectal) mesalamine in distal colitis.<sup>19</sup>

Another recent controversy regarding mesalamine pertains to the dose response for active and quiescent disease. While most clinicians in the U.S. have advocated a dose response up to 4.8 g/day in active disease, these recommendations have been based on trials with formu-

lations of Pentasa<sup>15</sup> (Shire Pharmaceuticals, Cincinnati, OH) and Asacol.<sup>16</sup> However, a recent European trial failed to show superiority of a new oral mesalamine formulation at doses greater than 3 g/day.<sup>20</sup> Controlled maintenance trials, to date, have not evaluated doses greater than 1.6 g of mesalamine daily to prevent relapse.<sup>21</sup> Nevertheless, many clinicians believe that there will be a dose response at greater than 1.6 g of mesalamine to maintain remissions for patients with ulcerative colitis,<sup>22</sup> particularly for patients who have required higher doses to achieve remission. Controlled trials to assess this postulate would be helpful to complete the evidence base for maintenance therapy with aminosalicylates in ulcerative colitis.<sup>2</sup>

Finally, no medication is likely to be effective if the patient is not adherent (compliant). Kane et al.<sup>24</sup> have followed up on their previous studies<sup>23</sup> to determine the effect of compliance on the clinical outcomes of maintenance therapy with mesalamine. They showed that patients who were nonadherent (more often unmarried men or patients taking numerous concomitant medications) had a 5-fold risk of relapsing compared with patients who took at least 80% of their prescribed dose. These findings have been supported by others, who have shown that nonadherence (present in approximately 40% of patients receiving maintenance therapy) is worse with more frequent dosing (3 times daily) or in patients with depression<sup>25</sup> and that an educational program with self-directed therapy during chronic therapy can improve outcomes, as defined by physician visits and hospitalizations.<sup>26</sup>

## Corticosteroids

Although corticosteroids remain the primary therapy for moderate to severe ulcerative colitis or for patients who have failed initial therapy with an aminosalicylate,<sup>22</sup> there have been few recent developments regarding glucocorticoid therapy in this setting. The biological effects of corticosteroids are pluripotent and include both immunologic and anti-inflammatory properties, including the inhibitory effects on nuclear factor- $\kappa$ B and activating protein-1 regulation of proinflammatory cytokines<sup>27,28</sup> and the downstream effects on leukocyte function and eicosanoid production.<sup>29</sup> Recent efforts have also been undertaken to identify why some patients with ulcerative colitis are less responsive or lose their response to corticosteroids.<sup>30,31</sup> Higher levels of glucocorticoid receptors<sup>32</sup> and glucocorticoid receptor messenger RNA<sup>33</sup> have been identified in patients with steroid-refractory ulcerative colitis. It has also been suggested that up-regulated production of pro-inflammatory

cytokines leads to an accumulation of the  $\beta$  isoform of the glucocorticoid receptor, which inhibits the function of the  $\alpha$  receptor isoform, which leads to proinflammatory cytokine transcription after binding to glucocorticoid hormones and translocating to the nucleus.<sup>34</sup> Increased expression of the  $\beta$  receptor on circulating lymphocytes has been associated with resistance to steroid therapy in ulcerative colitis.<sup>35</sup> Despite the long-term knowledge of corticosteroid effects, much remains to be learned regarding the mechanisms of action and prediction of the response to steroids in ulcerative colitis.

It is reassuring to recognize that outside of tertiary centers, only approximately one third of patients require systemic steroid therapy.<sup>36</sup> In a survey of the Olmsted county population, 54% of patients treated with systemic steroids went into complete remission, and only 16% of patients did not respond. However, after 1 year, only half of the patients remained in remission, and nearly one third of patients who required steroids progressed to the need for colectomy. These data are consistent with prior meta-analyses of therapeutic outcomes in ulcerative colitis that reported long-term remissions in only approximately 50% of patients who received parenteral steroids for severe ulcerative colitis.<sup>37</sup> It remains to be determined whether high-dose pulse dexamethasone therapy will improve on conventional parenteral steroid regimens.<sup>38</sup> Recent experience has also emphasized that patients who have required steroid therapy also have a relatively poor prognosis for maintenance therapy with standard-dose mesalamine.<sup>39</sup>

Pharmacological development of novel glucocorticoids has been more difficult in ulcerative colitis, compared with Crohn's disease, because of variations in colonic pH, transit time, and bacterial metabolism.<sup>40</sup> Trials of enteric-coated budesonide have not been effective in the setting of distal colitis,<sup>41</sup> although a recent trial of combination therapy with beclomethasone dipropionate 5 mg/day in conjunction with mesalamine did show an additive benefit, albeit with evidence of inhibition of the hypothalamic-pituitary-adrenal axis.<sup>42</sup> Topical corticosteroid therapy has been relegated to a secondary role in distal ulcerative colitis because numerous trials have shown superiority of rectal mesalamine compared with either conventional or nonsystemic steroids.<sup>19,43</sup> Combination therapy with topical mesalamine and a corticosteroid may provide additive benefits.<sup>43</sup>

### Immunomodulators

The efficacy of cyclosporine in severe ulcerative colitis has been validated since the pioneering trials by Lichtiger and Present<sup>44</sup> and Lichtiger et al.<sup>45</sup> Parenteral

cyclosporine in conjunction with steroids has been consistently effective in the approximately 40% of patients with severe ulcerative colitis who have failed corticosteroid therapy.<sup>46</sup> Over the past several years, trials have also shown that parenteral cyclosporine is effective alone, without steroids.<sup>47,48</sup> In the group of patients randomized to cyclosporine and maintained on azathioprine, the 1-year prognosis was superior to that of the steroid-treated group maintained on aminosalicylates (78% vs. 37% remissions), and this, again, calls into question the prognosis of patients maintained on aminosalicylates after steroid therapy.<sup>47</sup> The Leuven group confirmed that 2 mg/kg dosing, compared with 4 mg/kg, was equally effective and safe in a randomized, controlled trial<sup>49</sup> that has been substantiated in clinical practice.<sup>48,50,51</sup> Although most cyclosporine therapy for ulcerative colitis has been administered parenterally, for severe disease, microemulsion formulations<sup>52,53</sup> or tacrolimus<sup>54,55</sup> may eventually become useful as an adjunctive therapy for steroid-refractory ulcerative colitis. Currently, although intravenous cyclosporine has become an acceptable therapy for severe, steroid-refractory ulcerative colitis, the oral agents have not been widely accepted because of their potential toxicity and requisite evaluation in a controlled setting.<sup>46</sup> Meanwhile, it is reassuring that several series have not identified increased postoperative complications in patients who have failed cyclosporine and required colectomy.<sup>56,57</sup>

There have been few new data regarding the utility of purine antimetabolites, azathioprine, and 6-mercaptopurine for ulcerative colitis. It is also intriguing that, despite their general acceptance for steroid-dependent ulcerative colitis,<sup>58,59</sup> there remain limited evidence-based data to support the overall efficacy or to delineate a dose response in ulcerative colitis. The clinical trials from the 1970s provided equivocal results regarding the efficacy of azathioprine in ulcerative colitis, although steroid-sparing effects were suggested.<sup>60-62</sup> The most convincing controlled trial to date evaluated the maintenance benefits of azathioprine for patients who had required azathioprine to achieve remission.<sup>63</sup> The 12-month relapse rate was 36% for patients maintained on azathioprine, compared with 59% for patients randomized to placebo. In the latter trial, most patients had maintained aminosalicylate therapy, although a recent case series calls into question whether the addition of aminosalicylates is necessary.<sup>64</sup> Uncontrolled experience has suggested a benefit from azathioprine or 6-mercaptopurine for ulcerative colitis.<sup>59,65-68</sup> An area of consistency has been the general acceptance that a purine antimetabolite is useful to prolong remissions after in-

duction with cyclosporine.<sup>69,70</sup> The benefits for refractory left-sided disease may not be as paramount as with more extensive disease,<sup>71</sup> and it is, again, reassuring that immunomodulatory therapy with the purine analogues has not affected surgical outcomes or morbidity for patients who fail therapy.<sup>72</sup>

Optimal dosing for the purine metabolites has not been established for ulcerative colitis, nor has the question of therapeutic monitoring in this setting been evaluated.<sup>73–75</sup> Recently, a novel potential mechanism of action for azathioprine—induction of apoptosis of CD4<sup>+</sup> T cells—has been proposed and warrants further investigation.<sup>76</sup>

### Biological Agents

The remarkable effect that infliximab has had on the treatment of Crohn's disease has not yet been extrapolated to ulcerative colitis. To date, there are no biological agents approved for ulcerative colitis in the United States or abroad.

Infliximab has been evaluated in a few open-label and controlled clinical trials in ulcerative colitis, and, compared with the results in Crohn's disease, the outcomes could best be described as ambiguous. In the first reported pilot trial, 4 of 8 patients with severe, steroid-refractory ulcerative colitis randomly assigned to receive a single dose of infliximab at 5, 10, or 20 mg/kg responded by week 2, versus none of the 3 placebo-treated patients.<sup>77</sup> Subsequently, in an open-label series, Chey et al.<sup>78</sup> reported a response in all 8 patients with refractory ulcerative colitis who received a single 5 mg/kg infusion of infliximab, and, in a subsequent report, the authors described the achievement of clinical remission and maintenance for more than 4 months in 14 of 16 patients (88%).<sup>79</sup> In another positive open-label observation, 4 of 6 patients with severe, steroid-refractory ulcerative colitis were reported in a long-term remission (median follow-up, 5.5 months) after a single 5 mg/kg infliximab infusion.<sup>80</sup> Similarly, Kohn et al.<sup>81</sup> treated 13 patients with severe, steroid-refractory ulcerative colitis with a single infusion of infliximab 5 mg/kg, and of 10 with a clinical response, 9 patients were reported to have maintained clinical remission off corticosteroids at a mean of 10 months. In a separate uncontrolled experience from several separate practices, 27 patients with medically refractory active ulcerative colitis received either a single infusion or multiple infusions of infliximab. Of these, 44% were reported to have achieved remission and 22% partial response.<sup>82</sup> Half of the responders experienced a relapse, 95% of whom responded to repeat infusions.

However, in contrast to previous reports, steroid-refractory patients were less likely to respond to infliximab.

In contrast to these aforementioned positive and mostly uncontrolled studies, Actis et al.<sup>83</sup> reported an initial response rate in 4 of 8 patients who received a single dose of infliximab, but a sustained response rate was maintained in only 2 patients after 7 months with combinations of azathioprine and repeated infliximab dosing. In another open-label study, although infliximab was able to induce a rapid response in 30 patients with ulcerative or "indeterminate" colitis refractory to conventional treatment, long-term results were less favorable, with frequent relapses, and one third of patients required a colectomy by 1 year.<sup>84</sup> Finally, in the only published randomized, placebo-controlled trial, Probert et al.<sup>85</sup> did not identify a difference in remission rates at 6 weeks in moderately severe steroid-resistant ulcerative colitis treated with 2 doses of infliximab 5 mg/kg or placebo at 0 and 2 weeks (39% vs. 30%;  $P = 0.76$ ). Although this study was inadequately powered and a true clinical difference may have been missed (type II error), the disparity among published reports needs to be clarified and the efficacy of infliximab needs to be assessed with properly conducted placebo-controlled trials. Results of ongoing phase III trials will provide long-awaited answers.

CDP571, an immunoglobulin G4 humanized monoclonal antibody, has also been evaluated in a pilot study that enrolled 15 patients with mild to moderate ulcerative colitis.<sup>86</sup> Although there was a modest but significant reduction in clinical activity by 1 week after a single infusion, the effects were short lived and failed to remain significant at 2 weeks.

Although some rationale remains for the treatment of ulcerative colitis with anti-TNF therapy—based on increased levels of TNF- $\alpha$  in the colonic mucosa<sup>87</sup>; increased production of TNF- $\alpha$  by lamina propria mononuclear cells<sup>88</sup>; high concentrations of TNF- $\alpha$  in stools, rectal dialysates, and urine<sup>89,90</sup>; and beneficial effects of CDP571 in cotton-top tamarins<sup>91</sup>—it remains to be determined whether these strategies will have similar effects on the human disease.

RDP58, a novel anti-inflammatory decapeptide, blocks TNF production at a posttranscriptional level and also inhibits the production of interferon (IFN)- $\gamma$ , interleukin (IL)-2, and IL-12.<sup>92,93</sup> RDP58 has been effective in murine and primate models of colitis, and in a phase II study, 127 patients with mild to moderate active ulcerative colitis were randomized to receive placebo or an oral solution of RDP58 at 100, 200, or 300 mg daily for 4 weeks.<sup>94</sup> Clinical remission was reported in 72%, 70%, 29%, and 40% of patients in the 300, 200, and

100 mg groups and placebo, respectively (combined  $P = 0.0006$ ), and histological scores also improved in the 200 and 300 mg groups ( $P = 0.008$ ) compared with placebo. RDP58 seems to be safe and may become an attractive approach because of its oral delivery and low bioavailability.

Anti-leukocyte adhesion therapies are a novel approach to prevent egress of inflammatory cells into the tissues of patients with inflammatory bowel disease. To date, preliminary trials have been reported regarding monoclonal antibodies to the  $\alpha_4$  integrin (natalizumab)<sup>95</sup> and  $\alpha_4\beta_7$  integrin (MLN-02)<sup>96</sup> for ulcerative colitis and an antisense compound inhibiting production of intercellular adhesion molecule-1 (ISIS 2302) for pouchitis.<sup>97</sup> The results are too preliminary to make ultimate predictions regarding ultimate efficacy or risk/benefit ratio.

### Anti-Interleukin-2 Therapies

The pathogenic role of IL-2 in ulcerative colitis is inferred from the established efficacy of cyclosporine in severe ulcerative colitis, which inhibits IL-2 synthesis through inhibition of the calcineurin pathway. Recent approaches to the treatment of transplant rejection have targeted the IL-2 receptor (IL-2R) with the monoclonal antibodies daclizumab and basiliximab. Daclizumab, a recombinant humanized immunoglobulin G1 monoclonal antibody to IL-2R $\alpha$  (CD25), binds with high affinity. In an open-label, single-center pilot study, 2 infusions of daclizumab 1 mg/kg 4 weeks apart in 10 patients with refractory ulcerative colitis resulted in significant decreases in clinical activity scores after week 2 with a parallel decrease in C-reactive protein and significantly reduced CD25<sup>+</sup> cells in mucosal biopsy samples.<sup>98</sup> Eight of 10 patients achieved a clinical response, of which 5 were in remission after 8 weeks. However, all patients in clinical remission did not achieve mucosal healing, as assessed by endoscopic and histological scores. Basiliximab, a chimeric monoclonal antibody to IL-2R, has also been evaluated in a pilot open-label study in ulcerative colitis.<sup>99</sup> After a single dose of intravenous basiliximab 40 mg, 9 of 10 patients with steroid-resistant disease achieved a clinical remission by 8 weeks, with significant improvement in the clinical activity score as early as 1 week. Although 8 of the 9 responders relapsed after a median of 9 weeks, remissions were easily reestablished by increasing the steroid dose, adding azathioprine, or both. These trials suggest that, in addition to immunosuppressive actions, anti-IL-2R antibodies may have steroid-sensitizing properties that could lead to improved efficacy when administered in combination with steroids. Unfortunately, retreatment with basiliximab is compromised by reports of hypersensitivity with repeated infu-

sions secondary to the development of human antichimeric antibodies. Ultimately, a role for "bridging" therapy for steroid-resistant patients to a maintenance immunomodulator may need to be compared with the efficacy and safety of cyclosporine in future trials.

### Anti-CD3 Therapy

Visilizumab (HuM291), a humanized antibody with a mutated immunoglobulin G2 Fc region directed at the CD3 $\epsilon$  chain of the T-cell receptor complex, has been shown to selectively induce apoptosis in activated T cells.<sup>100</sup> Preliminary results of an ongoing phase I dose-escalation study recently described 7 patients with severe steroid-refractory ulcerative colitis who received 2 daily infusions of visilizumab 15  $\mu$ g/kg.<sup>101</sup> Data presented for 5 patients described clinical and endoscopic remissions for all 5 patients that persisted for several months as steroids were tapered. Side effects included a transient decrease in T-lymphocyte counts and cytokine-release symptoms, although no infectious complications were seen in this small pilot study. Two patients had transient low-level Epstein-Barr virus (EBV) titers not associated with clinical symptoms. In trials with visilizumab for graft-versus-host disease, EBV reactivation and post-transplantation lymphoproliferative disease have been encountered that necessitated close monitoring of EBV DNA. Preemptive treatment with rituximab, based on increasing DNA titers, seems to prevent the complication of posttransplantation lymphoproliferative disease after visilizumab in patients with graft-versus-host disease.<sup>102</sup>

The role of IFNs has been evaluated in ulcerative colitis, initially in 7 patients with chronic active hepatitis and quiescent colitis.<sup>103</sup> The absence of worsening symptoms led to a 6-month trial with subcutaneous IFN- $\alpha$ -2a (3–9 MIU thrice weekly) in 28 inpatients who had a rapid response (within 2 weeks) and an eventual 82% remission rate within 6 months.<sup>104</sup> In a randomized study comparing 12 weeks of subcutaneous IFN- $\alpha$ -2a with 30 days of prednisolone enemas in 32 patients with mild to moderate left-sided colitis, IFN- $\alpha$ -2a treatment was as effective as steroid enemas,<sup>105</sup> and, most recently, the efficacy of pegylated IFN- $\alpha$ -2b was recently evaluated in 60 patients with ulcerative colitis randomized to placebo, 0.5  $\mu$ g/kg, or 1  $\mu$ g/kg of subcutaneous pegylated IFN- $\alpha$ -2b once weekly for 12 weeks.<sup>106</sup> Clinical remission at week 12 was highest in the pegylated IFN 0.5  $\mu$ g/kg group (58%) compared with placebo (40%), although the pegylated IFN 1  $\mu$ g/kg was less well tolerated: 8 of 21 patients dropped out of the study because of adverse events.

IFN- $\beta$ -1a has also been evaluated in a several trials. In 25 patients with steroid-refractory ulcerative colitis given 0.5 MIU of intravenous human natural IFN- $\beta$  or subcutaneous injections of 1 MIU of recombinant IFN- $\beta$ -1a, a remission rate of 88% was described, with a mean response time of 3 weeks.<sup>107</sup> Although there was no difference in efficacy between the 2 forms of IFN- $\beta$ , a subsequent study involving 97 steroid-refractory patients treated with placebo or subcutaneous recombinant IFN- $\beta$ -1a at doses of 1 or 3 MIU 3 times per week for 8 weeks showed remission rates of 38%, 30%, and 56%, respectively.<sup>108</sup> In the most recent placebo-controlled, dose-escalating study of subcutaneous recombinant IFN- $\beta$ -1a at doses of 22, 44, or 88  $\mu$ g 3 times a week, clinical response and remission were achieved in 50% and 30% in the IFN- $\beta$  group, compared with 14% and 0% in the placebo group ( $P = 0.14$  and  $P = 0.02$ , respectively).<sup>109</sup>

Growth factors, including transforming growth factor- $\beta$ , trefoil factors, epidermal growth factor (EGF), and keratinocyte growth factor (KGF), regulate the integrity of the colonic mucosa and maintain its barrier function.<sup>110</sup> The potential use of these growth factors to heal and restore mucosal integrity has stimulated recent studies using KGF and EGF for the treatment of ulcerative colitis. KGF is a potent stimulator of intestinal epithelial cells, and in animal models, colitis has been improved with both recombinant human KGF-1 (fibroblast growth factor-7) and KGF-2 (repifermin; fibroblast growth factor-10). However, in a placebo-controlled trial that enrolled 88 patients with active ulcerative colitis who were randomized to receive intravenous repifermin 1 to 50  $\mu$ g/kg or placebo for 5 consecutive days, there was no significant benefit, although the study did not rule out the possibility of higher dosing or longer treatment intervals.<sup>111</sup> In contrast, EGF, a mitogenic peptide produced by salivary and duodenal Brunner's glands that has been used topically for healing of skin wounds and systemically to treat necrotizing enterocolitis in neonates, was recently evaluated as an enema therapy in conjunction with mesalamine therapy in 24 patients with mild to moderately active ulcerative colitis.<sup>112</sup> After 2 weeks, 10 of 12 patients who received EGF enemas (5  $\mu$ g in 100 mL of an inert carrier) experienced remission, compared with 1 of 12 patients treated with placebo enemas. All 10 patients remained in remission at a 4-week assessment, and this decreased to 8 after 12 weeks. Despite these impressive results, additional confirmation is necessary, and potential benefits need to be balanced against the potential for up-regulation of proto-oncogene expression and the risk of malignant transfor-

mation with EGF therapy in ulcerative colitis or adenomatous polyps.

## Chemopreventive Strategies in Ulcerative Colitis

Recent series have provided optimism regarding the potential for diminishing the risk of neoplasia in patients with ulcerative colitis.<sup>113</sup> There has been increasing although, again, conflicting evidence regarding the potential for mesalamine compounds to reduce the development of dysplasia, cancer, or both in ulcerative colitis.<sup>114,115</sup> There are numerous potential mechanisms by which mesalamine could affect the carcinogenesis sequence, including inhibition of cell growth; proliferation by inhibition of prostaglandins, lipoxygenases, nuclear factor- $\kappa$ B, and MAP kinases; activation of apoptosis; and inhibition of gene transcription by targeting the peroxisome proliferator-activated receptor- $\delta$ .<sup>116</sup> There are also evolving data that ursodeoxycholic acid may provide chemoprotective benefits for patients with ulcerative colitis and primary sclerosing cholangitis.<sup>117,118</sup> Large prospective studies would be helpful to elucidate the dose response and efficacy of the mesalamine compounds and ursodeoxycholic acid alone and in combination as chemopreventive agents in ulcerative colitis. Meanwhile, the data regarding the maintenance benefits of mesalamine are a compelling rationale to continue long-term treatment with additional hope, if not expectation, of chemoprevention, and supplementation with folic acid is also an inexpensive and risk-free recommendation, particularly for patients receiving sulfasalazine.<sup>113</sup>

## Postcolectomy Management

Proctocolectomy and ileo-anal pouch surgeries have become the standard approach to curative resections in young patients with ulcerative colitis. The cosmetic and quality-of-life benefits have been well described and confirmed.<sup>119-121</sup> Now that these operative techniques have matured, the short- and long-term risks and failures have become well established and are acceptable within the gastroenterological and surgical communities.<sup>122,123</sup> However, the recent description of reduced fecundity in women undergoing restorative proctocolectomies has been quite disturbing and requires further evaluation of risk factors and preventive measures to avoid this significant impediment to elective surgical interventions.<sup>124</sup>

Two additional postoperative complications deserve mention: pouchitis and the risk of neoplasia. Pouchitis has been a well-recognized complication of restorative proctocolectomy for ulcerative colitis.<sup>125</sup> Although a re-

cent Cochrane analysis had difficulty identifying evidence-based support, the antibiotics metronidazole and ciprofloxacin have become, at least, empirical standards of treatment of acute<sup>125,126</sup> and chronic<sup>127</sup> pouchitis. Recent clinical trials have also shown a role for the probiotic formulation VSL#3, in high doses, for primary prevention<sup>128</sup> and maintenance of remission after antibiotic therapy.<sup>129,130</sup> This formulation continues to be marketed over the Internet as a food supplement and has yet to be compared with other empirical approaches from the standpoints of safety and efficacy. Additional alternative therapeutic approaches to acute pouchitis have been the use of budesonide enemas<sup>131</sup> or infliximab for patients who develop Crohn's disease in or around the pouch.<sup>132</sup>

## Summary

This review has attempted to update information regarding the current state of medical therapy for ulcerative colitis and its surgical complications. Considerable incremental progress is being made on all fronts. Nevertheless, aside from an expanding array of aminosalicylate formulations, no new therapy has been approved for the treatment of ulcerative colitis over the past several decades. There is consistent evidence for the role of cyclosporine in severe ulcerative colitis and expanding, if not definitive, evidence for purine antimetabolites. The most recent provocative data regarding EGF enemas are the first clinical evidence that epithelial restitution may have a therapeutic role; additional targeted immunosuppressive strategies are under investigation. The future is bright for expanding therapeutic potentials for ulcerative colitis with hopes that predictive factors will be identified that will allow better patient selection for individual agents as they enter into clinical investigation.

## References

- Sutherland L, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2003;CD000543.
- Sutherland L, Roth D, Beck P, May G, Makiyama K. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2002;CD000544.
- Ragunath K, Williams JG. Review article: balsalazide therapy in ulcerative colitis. *Aliment Pharmacol Ther* 2001;15:1549–1554.
- Green JR, Mansfield JC, Gibson JA, Kerr GD, Thornton PC. A double-blind comparison of balsalazide, 6.75 g daily, and sulfasalazine, 3 g daily, in patients with newly diagnosed or relapsed active ulcerative colitis. *Aliment Pharmacol Ther* 2002;16:61–68.
- Mansfield JC, Gjaffer MH, Cann PA, McKenna D, Thornton PC, Holdsworth CD. A double-blind comparison of balsalazide, 6.75 g, and sulfasalazine, 3 g, as sole therapy in the management of ulcerative colitis. *Aliment Pharmacol Ther* 2002;16:69–77.
- Farrell RJ, Peppercorn MA. Equimolar doses of balsalazide and mesalamine: are we comparing apples and oranges? *Am J Gastroenterol* 2002;97:1283–1285.
- Hanauer SB. Caution in the interpretation of safety and efficacy differences in clinical trials comparing aminosalicylates for ulcerative colitis. *Am J Gastroenterol* 2003;98:215–216.
- Johnson LK, Pruitt RE, Green JR. Treatment of ulcerative colitis with balsalazide: response to editorial by Drs. Farrell and Peppercorn and letter to the editor by Dr. Hanauer. *Am J Gastroenterol* 2003;98:216–219.
- Sandborn WJ. Rational selection of oral 5-aminosalicylate formulations and prodrugs for the treatment of ulcerative colitis. (review) *Am J Gastroenterol* 2002;97:2939–2941.
- Kane SV, Bjorkman DJ. The efficacy of oral 5-ASAs in the treatment of active ulcerative colitis: a systematic review. *Rev Gastroenterol Disord* 2003;3:210–218.
- Green JR, Lobo AJ, Holdsworth CD, Leicester RJ, Gibson JA, Kerr GD, Hodgson HJ, Parkins KJ, Taylor MD. Balsalazide is more effective and better tolerated than mesalamine in the treatment of acute ulcerative colitis. The Abacus Investigator Group. *Gastroenterology* 1998;114:15–22.
- Levine DS, Riff DS, Pruitt R, Wruble L, Koval G, Sales D, Bell JK, Johnson LK. A randomized, double blind, dose-response comparison of balsalazide (6.75 g), balsalazide (2.25 g), and mesalamine (2.4 g) in the treatment of active, mild-to-moderate ulcerative colitis. *Am J Gastroenterol* 2002;97:1398–1407.
- Pruitt R, Hanson J, Safdi M, Wruble L, Hardi R, Johanson J, Koval G, Riff D, Winston B, Cross A, Doty P, Johnson LK. Balsalazide is superior to mesalamine in the time to improvement of signs and symptoms of acute mild-to-moderate ulcerative colitis. *Am J Gastroenterol* 2002;97:3078–3086.
- Sandborn WJ, Hanauer SB. Systematic review: the pharmacokinetic profiles of oral mesalazine formulations and mesalazine pro-drugs used in the management of ulcerative colitis. *Aliment Pharmacol Ther* 2003;17:29–42.
- Hanauer S, Schwartz J, Robinson M, Roufai W, Arora S, Cello J, Safdi M. Mesalamine capsules for treatment of active ulcerative colitis: results of a controlled trial. Pentasa Study Group. *Am J Gastroenterol* 1993;88:1188–1197.
- Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987;317:1625–1629.
- Sninsky CA, Cort DH, Shanahan F, Powers BJ, Sessions JT, Pruitt RE, Jacobs WH, Lo SK, Targan SR, Cerda JJ. Oral mesalamine (Asacol) for mildly to moderately active ulcerative colitis. A multicenter study. *Ann Intern Med* 1991;115:350–355.
- Pamukcu R, Hanauer SB, Chang EB. Effect of disodium azodisalicylate on electrolyte transport in rabbit ileum and colon in vitro. Comparison with sulfasalazine and 5-aminosalicylic acid. *Gastroenterology* 1988;95:975–981.
- Cohen RD, Woseth DM, Thisted RA, Hanauer SB. A meta-analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. *Am J Gastroenterol* 2000;95:1263–1276.
- Kruis W, Bar-Meir S, Feher J, Mickisch U, Mlitz H, Faszcyk M, Chowers Y, Lengyele G, Kovacs A, Lakotos L, Stolte M, Vieth M, Greinwald R. The optimal dose of 5-aminosalicylic acid in active ulcerative colitis: a dose-finding study with newly developed mesalamine. *Clin Gastroenterol Hepatol* 2003;1:36–43.
- The Mesalamine Study Group. An oral preparation of mesalamine as long-term maintenance therapy for ulcerative colitis. A randomized, placebo-controlled trial. *Ann Intern Med* 1996;124:204–211.
- Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults. American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 1997;92:204–211.

23. Kane SV, Cohen RD, Aikens JE, Hanauer SB. Prevalence of nonadherence with maintenance mesalamine in quiescent ulcerative colitis. *Am J Gastroenterol* 2001;96:2929–2933.
24. Kane S, Huo D, Aikens J, Hanauer S. Medication nonadherence and the outcomes of patients with quiescent ulcerative colitis. *Am J Med* 2003;114:39–43.
25. Shale MJ, Riley SA. Studies of compliance with delayed-release mesalazine therapy in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2003;18:191–198.
26. Robinson A, Thompson DG, Wilkin D, Roberts C. Guided self-management and patient-directed follow-up of ulcerative colitis: a randomised trial. *Lancet* 2001;358:976–981.
27. Refojo D, Liberman A, Holsboer F, Arzt E. Transcription factor-mediated molecular mechanisms involved in the functional cross-talk between cytokines and glucocorticoids. *Immunol Cell Biol* 2001;79:385–394.
28. Yamamoto Y, Gaynor RB. Therapeutic potential of inhibition of the NF-kappaB pathway in the treatment of inflammation and cancer. *J Clin Invest* 2001;107:135–142.
29. Nikolaus S, Folsch U, Schreiber S. Immunopharmacology of 5-aminosalicylic acid and of glucocorticoids in the therapy of inflammatory bowel disease. *Hepatogastroenterology* 2000;47:71–82.
30. Gelbmann CM. Prediction of treatment refractoriness in ulcerative colitis and Crohn's disease—do we have reliable markers? *Inflamm Bowel Dis* 2000;6:123–131.
31. Lindgren SC, Flood LM, Kilander AF, Lofberg R, Persson TB, Sjodahl RI. Early predictors of glucocorticosteroid treatment failure in severe and moderately severe attacks of ulcerative colitis. *Eur J Gastroenterol Hepatol* 1998;10:831–835.
32. Schottelius A, Wedel S, Weltrich R, Rohde W, Buttgerit F, Schreiber S, Lochs H. Higher expression of glucocorticoid receptor in peripheral mononuclear cells in inflammatory bowel disease. *Am J Gastroenterol* 2000;95:1994–1999.
33. Flood L, Lofberg R, Stierna P, Wikstrom AC. Glucocorticoid receptor mRNA in patients with ulcerative colitis: a study of responders and nonresponders to glucocorticosteroid therapy. *Inflamm Bowel Dis* 2001;7:202–209.
34. Webster JC, Oakley RH, Jewell CM, Cidowski JA. Proinflammatory cytokines regulate human glucocorticoid receptor gene expression and lead to the accumulation of the dominant negative beta isoform: a mechanism for the generation of glucocorticoid resistance. *Proc Natl Acad Sci U S A* 2001;98:6865–6870.
35. Honda M, Orii F, Ayabe T, Imai S, Ashida T, Obara T, Kohgo Y. Expression of glucocorticoid receptor beta in lymphocytes of patients with glucocorticoid-resistant ulcerative colitis. *Gastroenterology* 2000;118:859–866.
36. Faubion WA Jr, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology* 2001;121:255–260.
37. Kornbluth A, Marion JF, Salomon P, Janowitz HD. How effective is current medical therapy for severe ulcerative and Crohn's colitis? An analytic review of selected trials. *J Clin Gastroenterol* 1995;20:280–284.
38. Sood A, Midha V, Sood N, Awasthi G. A prospective, open-label trial assessing dexamethasone pulse therapy in moderate to severe ulcerative colitis. *J Clin Gastroenterol* 2002;35:328–331.
39. Rembacken BJ, Snelling AM, Hawkey PM, Chambers DM, Axon AT. Non-pathogenic *Escherichia coli* versus mesalazine for the treatment of ulcerative colitis: a randomised trial. *Lancet* 1999;354:635–639.
40. Friend DR. Review article: issues in oral administration of locally acting glucocorticosteroids for treatment of inflammatory bowel disease. *Aliment Pharmacol Ther* 1998;12:591–603.
41. Lofberg R, Danielsson A, Suhr O, Nilsson A, Schioler R, Nyberg A, Hultcrantz R, Kollberg B, Gillberg R, Willen R, Persson T, Salde L. The Mesalamine Study Group. Oral budesonide versus prednisolone in patients with active extensive and left-sided ulcerative colitis. *Gastroenterology* 1996;110:1713–1718.
42. Rizzello F, Gionchetti P, D'Arienzo A, Manguso F, Di Matteo G, Annese V, Valpiani D, Casetti T, Adamo S, Prada A, Castiglione GN, Varoli G, Campieri M. Oral beclometasone dipropionate in the treatment of active ulcerative colitis: a double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2002;16:1109–1116.
43. Marshall JK, Irvine EJ. Putting rectal 5-aminosalicylic acid in its place: the role in distal ulcerative colitis. *Am J Gastroenterol* 2000;95:1628–1636.
44. Lichtiger S, Present DH. Preliminary report: cyclosporin in treatment of severe active ulcerative colitis. *Lancet* 1990;336:16–19.
45. Lichtiger S, Present DH, Kornbluth A, Geleert I, Bauer J, Galler G, Michelassi F, Hanauer S. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994;330:1841–1845.
46. Sandborn WJ. Cyclosporine in ulcerative colitis: state of the art. *Acta Gastroenterol Belg* 2001;64:201–204.
47. D'Haens G, Lemmens L, Geboes K, Vandeputte L, Van Acker F, Mortelmans L, Peeters M, Vermeire S, Penninckx F, Nevens F, Hiele M, Rutgeerts P. Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. *Gastroenterology* 2001;120:1323–1329.
48. Rayner CK, McCormack G, Emmanuel AV, Kamm MA. Long-term results of low-dose intravenous cyclosporin for acute severe ulcerative colitis. *Aliment Pharmacol Ther* 2003;18:303–308.
49. Van Assche G, D'Haens G, Noman M, Vermeire S, Hiele M, Asnong K, Arts J, D'Hoore A, Penninckx F, Rutgeerts P. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. *Gastroenterology* 2003;125:1025–1031.
50. Rowe FA, Walker JH, Karp LC, Vasiliauskas EA, Plevy SE, Targan SR. Factors predictive of response to cyclosporin treatment for severe, steroid-resistant ulcerative colitis. *Am J Gastroenterol* 2000;95:2000–2008.
51. Actis GC, Ottobrelli A, Pera A, Barletti C, Ponti V, Pinna-Pintor M, Verme G. Continuously infused cyclosporine at low dose is sufficient to avoid emergency colectomy in acute attacks of ulcerative colitis without the need for high-dose steroids. *J Clin Gastroenterol* 1993;17:10–13.
52. Actis GC, Aimo G, Priolo G, Moscato D, Rizzetto M, Pagni R. Efficacy and efficiency of oral microemulsion cyclosporin versus intravenous and soft gelatin capsule cyclosporin in the treatment of severe steroid-refractory ulcerative colitis: an open-label retrospective trial. *Inflamm Bowel Dis* 1998;4:276–279.
53. Navazo L, Salata H, Morales S, Dorta MC, Perez F, de las Casas D, Aviles J. Oral microemulsion cyclosporine in the treatment of steroid-refractory attacks of ulcerative and indeterminate colitis. *Scand J Gastroenterol* 2001;36:610–614.
54. Bousvaros A, Kirschner BS, Werlin SL, Parker-Hartigan L, Daum F, Freeman KB, Balint JP, Day AS, Griffiths AM, Zurakowski D, Ferry GD, Leichtner AM. Oral tacrolimus treatment of severe colitis in children. *J Pediatr* 2000;137:794–799.
55. Matsushashi N, Nakajima A, Watanabe K, Komono Y, Suzuki A, Ohnishi S, Omata M, Kondo K, Usui Y, Iwadare JI, Wantanabe T, Nagawa H, Muto T. Tacrolimus in corticosteroid-resistant ulcerative colitis. *J Gastroenterol* 2000;35:635–640.
56. Fleshner PR, Michelassi F, Rubin M, Hanauer SB, Plevy SE, Targan SR. Morbidity of subtotal colectomy in patients with severe ulcerative colitis unresponsive to cyclosporin. *Dis Colon Rectum* 1995;38:1241–1245.
57. Hyde GM, Jewell DP, Kettlewell MG, Mortensen NJ. Cyclosporin for severe ulcerative colitis does not increase the rate of peri-

- operative complications. *Dis Colon Rectum* 2001;44:1436–1440.
58. Su CG, Stein RB, Lewis JD, Lichtenstein GR. Azathioprine or 6-mercaptopurine for inflammatory bowel disease: do risks outweigh benefits? *Dig Liver Dis* 2000;32:518–531.
  59. Fraser AG, Orchard TR, Jewell DP. The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. *Gut* 2002;50:485–489.
  60. Jewell DP, Truelove SC. Azathioprine in ulcerative colitis: final report on controlled therapeutic trial. *Br Med J* 1974;4:627–630.
  61. Rosenberg JL, Wall AJ, Levin B, Binder HJ, Kirsner JB. A controlled trial of azathioprine in the management of chronic ulcerative colitis. *Gastroenterology* 1975;69:96–99.
  62. Kirk AP, Lennard-Jones JE. Controlled trial of azathioprine in chronic ulcerative colitis. *Br Med J* 1982;284:1291–1292.
  63. Hawthorne AB, Logan RF, Hawkey CJ, Foster PN, Axon AT, Swarbrick ET, Scott BB, Lennard-Jones JE. Randomised controlled trial of azathioprine withdrawal in ulcerative colitis. *BMJ* 1992;305:20–22.
  64. Campbell S, Ghosh S. Effective maintenance of inflammatory bowel disease remission by azathioprine does not require concurrent 5-aminosalicylate therapy. *Eur J Gastroenterol Hepatol* 2001;13:1297–1301.
  65. Lobo AJ, Foster PN, Burke DA, Johnston D, Axon AT. The role of azathioprine in the management of ulcerative colitis. *Dis Colon Rectum* 1990;33:374–377.
  66. Adler DJ, Korelitz BI. The therapeutic efficacy of 6-mercaptopurine in refractory ulcerative colitis. *Am J Gastroenterol* 1990;85:717–722.
  67. George J, Present DH, Pou R, Bodian C, Runin PH. The long-term outcome of ulcerative colitis treated with 6-mercaptopurine. *Am J Gastroenterol* 1996;91:1711–1714.
  68. Mate-Jimenez J, Hermida C, Cantero-Perona J, Moreno-Otero R. 6-Mercaptopurine or methotrexate added to prednisone induces and maintains remission in steroid-dependent inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2000;12:1227–1233.
  69. Actis GC, Bresso F, Astegjano M, Demarchi B, Sapone N, Boscaglia C, Rizzetto M. Safety and efficacy of azathioprine in the maintenance of ciclosporin-induced remission of ulcerative colitis. *Aliment Pharmacol Ther* 2001;15:1307–1311.
  70. Cohen RD, Stein R, Hanauer SB. Intravenous cyclosporin in ulcerative colitis: a five-year experience. *Am J Gastroenterol* 1999;94:1587–1592.
  71. Falasco G, Zinicola R, Forbes A. Review article: immunosuppressants in distal ulcerative colitis. *Aliment Pharmacol Ther* 2002;16:181–187.
  72. Mahadevan U, Loftus EV Jr, Tremaine WJ, Pemberton JH, Harnsen WS, Schleck CD, Zinsmeister AR, Sandborn WJ. Azathioprine or 6-mercaptopurine before colectomy for ulcerative colitis is not associated with increased postoperative complications. *Inflamm Bowel Dis* 2002;8:311–316.
  73. Cuffari C, Hunt S, Bayless T. Utilisation of erythrocyte 6-thioguanine metabolite levels to optimise azathioprine therapy in patients with inflammatory bowel disease. *Gut* 2001;48:642–646.
  74. Campbell S, Ghosh S. Is neutropenia required for effective maintenance of remission during azathioprine therapy in inflammatory bowel disease? *Eur J Gastroenterol Hepatol* 2001;13:1073–1076.
  75. Dubinsky MC. Optimizing immunomodulator therapy for inflammatory bowel disease. *Curr Gastroenterol Rep* 2003;5:506–511.
  76. Tiede I, Fritz G, Strand S, Poppe D, Dvorsky R, Strand D, Lehr HA, Wirtz S, Becker C, Atreya R, Mudter J, Hildner K, Bartsch B, Holtmann M, Blumberg R, Walczak H, Iven H, Galle PR, Ahmadian MR, Neurath MF. CD28-dependent Rac1 activation is the molecular target of azathioprine in primary human CD4+ T lymphocytes. *J Clin Invest* 2003;111:1133–1145.
  77. Sands BE, Tremaine WJ, Sandborn WJ, Rutgeerts PJ, Hanauer SB, Mayer L, Targan SR, Podolsky DK. Infliximab in the treatment of severe, steroid-refractory ulcerative colitis: a pilot study. *Inflamm Bowel Dis* 2001;7:83–88.
  78. Chey WY, Hussain A, Ryan C, Potter GD, Shah A. Infliximab for refractory ulcerative colitis. *Am J Gastroenterol* 2001;96:2373–2381.
  79. Chey WY. Infliximab for patients with refractory ulcerative colitis. *Inflamm Bowel Dis* 2001;7(Suppl 1):S30–S33.
  80. Kaser A, Mairinger T, Vogel W, Tilg H. Infliximab in severe steroid-refractory ulcerative colitis: a pilot study. *Wien Klin Wochenschr* 2001;113:930–933.
  81. Kohn A, Prantera C, Pera A, Cosentino R, Sostegni R, Daperno M. Anti-tumour necrosis factor alpha (infliximab) in the treatment of severe ulcerative colitis: result of an open study on 13 patients. *Dig Liver Dis* 2002;34:626–630.
  82. Su C, Salzberg BA, Lewis JD, Deren JJ, Kornbluth A, Katzka DA, Stein RB, Adler DR, Lichtenstein GR. Efficacy of anti-tumor necrosis factor therapy in patients with ulcerative colitis. *Am J Gastroenterol* 2002;97:2577–2584.
  83. Actis GC, Bruno M, Pinna-Pintor M, Rossini FP, Rizzetto M. Infliximab for treatment of steroid-refractory ulcerative colitis. *Dig Liver Dis* 2002;34:631–634.
  84. Gornet JM, Couve S, Hassani Z, Delchier JC, Marteau P, Cosnes J, Bouhnik Y, Dupas JL, Modigliani R, Taillard F, Lemann M. Infliximab for refractory ulcerative colitis or indeterminate colitis: an open-label multicentre study. *Aliment Pharmacol Ther* 2003;18:175–181.
  85. Probert CS, Hearing SD, Schreiber S, Kuhbacher T, Ghosh S, Arnott ID, Forbes A. Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomised controlled trial. *Gut* 2003;52:998–1002.
  86. Evans RC, Clarke L, Heath P, Stephens S, Morris AI, Rhodes JM. Treatment of ulcerative colitis with an engineered human anti-TNFalpha antibody CDP571. *Aliment Pharmacol Ther* 1997;11:1031–1035.
  87. Masuda H, Iwai S, Tanaka T, Hayakawa S. Expression of IL-8, TNF- $\alpha$  and IFN- $\gamma$  mRNA in ulcerative colitis, particularly in patients with inactive phase. *J Clin Lab Immunol* 1995;46:111–123.
  88. Reinecker HC, Steffen M, Witthoef T, Pflueger I, Schreiber S, MacDermott RP, Raedler A. Enhanced secretion of tumour necrosis factor-alpha, IL-6, and IL-1 beta by isolated lamina propria mononuclear cells from patients with ulcerative colitis and Crohn's disease. *Clin Exp Immunol* 1993;94:174–181.
  89. Nielsen OH, Gionchetti P, Ainsworth M, Vainer B, Campieri M, Borregaard N, Kjeldsen L. Rectal dialysate and fecal concentrations of neutrophil gelatinase-associated lipocalin, interleukin-8, and tumor necrosis factor-alpha in ulcerative colitis. *Am J Gastroenterol* 1999;94:2923–2928.
  90. Saiki T, Mitsuyama K, Toyonaga A, Ishida H, Tanikawa K. Detection of pro- and anti-inflammatory cytokines in stools of patients with inflammatory bowel disease. *Scand J Gastroenterol* 1998;33:616–622.
  91. Watkins PE, Warren BF, Stephens S, Ward P, Foulkes R. Treatment of ulcerative colitis in the cottontop tamarin using antibody to tumour necrosis factor alpha. *Gut* 1997;40:628–633.
  92. Iyer S, Kontoyiannis D, Chevrier D, Woo J, Mori N, Cornejo M, Kollias G, Buelow R. Inhibition of tumor necrosis factor mRNA translation by a rationally designed immunomodulatory peptide. *J Biol Chem* 2000;275:17051–17057.
  93. Iyer S, Lahana R, Buelow R. Rational design and development of RDP58. *Curr Pharm Des* 2002;8:2217–2229.
  94. Travis S, Yap L, Hawkey CJ. Novel and effective therapy for

- ulcerative colitis results of parallel, prospective, placebo-controlled trials (abstr). *Am J Gastroenterol* 2003;98:S239.
95. Gordon FH, Hamilton MI, Donoghue S, Greenlees C, Palmer T, Rowley-Jones D, Dhillon AP, Amlot PL, Pounder RE. A pilot study of treatment of active ulcerative colitis with natalizumab, a humanized monoclonal antibody to alpha-4 integrin. *Aliment Pharmacol Ther* 2002;16:699–705.
  96. Feagan B, Greenberg GR, Wild G. A randomized controlled trial of a humanized alpha4beta7 antibody in ulcerative colitis. (abstr) *Am J Gastroenterol* 2003;98:S248–S249.
  97. Miner P, Bane B, Bradley J. ICAM-1 antisense inhibition by enema improves pouchitis and suggests long-term mucosal healing in patients with chronic unremitting disease (abstr). *Am J Gastroenterol* 2003;98:S246–S247.
  98. Van Assche G, Dalle I, Noman M, Aerden I, Swijsen C, Asnong K, Maes B, Ceuppens J, Geboes K, Rutgeerts P. A pilot study on the use of the humanized anti-interleukin-2 receptor antibody daclizumab in active ulcerative colitis. *Am J Gastroenterol* 2003;98:369–376.
  99. Creed TJ, Norman MR, Probert CS, Harvey RF, Shaw IS, Smithson J, Anderson J, Moorghen M, Gupta J, Shepherd NA, Dayan CM, Hearing SD. Basiliximab (anti-CD25) in combination with steroids may be an effective new treatment for steroid-resistant ulcerative colitis. *Aliment Pharmacol Ther* 2003;18:65–75.
  100. Cole MS, Stellrecht KE, Shi JD, Homola M, Hsu DH, Anasetti C, Vasquez M, Tso JY. HuM291, a humanized anti-CD3 antibody, is immunosuppressive to T cells while exhibiting reduced mitogenicity in vitro. *Transplantation* 1999;68:563–571.
  101. Plevy SE, Salzberg BA, Regueiro M. A humanized anti-CD3 monoclonal antibody, visilizumab, for treatment of severe steroid-refractory ulcerative colitis: preliminary results of a phase I study (abstr). *Gastroenterology* 2003;124:A7
  102. Carpenter PA, Appelbaum FR, Corey L, Deeg HJ, Doney K, Gooley T, Krueger J, Martin P, Pavlovic S, Sanders J, Slattery J, Levitt D, Storb R, Woolfrey A, Anasetti C. A humanized non-FcR-binding anti-CD3 antibody, visilizumab, for treatment of steroid-refractory acute graft-versus-host disease. *Blood* 2002;99:2712–2719.
  103. Cottone M, Magliocco A, Trallori G, Brignola C, Vandelli C, Ardizzone S, Meucci G, Zannoni F, Di Maio G, Astegiano M. Clinical course of inflammatory bowel disease during treatment with interferon for associated chronic active hepatitis. *Ital J Gastroenterol* 1995;27:3–4.
  104. Sumer N, Palabiyikoglu M. Induction of remission by interferon-alpha in patients with chronic active ulcerative colitis. *Eur J Gastroenterol Hepatol* 1995;7:597–602.
  105. Madsen SM, Schlichting P, Davidsen B, Nielsen OH, Federspiel B, Riis P, Munkholm P. An open-labeled, randomized study comparing systemic interferon-alpha-2A and prednisolone enemas in the treatment of left-sided ulcerative colitis. *Am J Gastroenterol* 2001;96:1807–1815.
  106. Tilg H, Vogelsang H, Ludwiczek O. A randomized placebo-controlled trial of pegylated interferon alpha in active ulcerative colitis (abstr). *Gastroenterology* 2003;124:A62.
  107. Musch E, Andus T, Malek M. Induction and maintenance of clinical remission by interferon-beta in patients with steroid-refractory active ulcerative colitis—an open long-term pilot trial. *Aliment Pharmacol Ther* 2002;16:1233–1239.
  108. Musch E, Raedler A, Andus T. A phase II placebo-controlled, randomized, multicenter study to evaluate efficiency and safety of interferon beta-1a in patients with ulcerative colitis. (abstr) *Gastroenterology* 2002;122:A431.
  109. Nikolaus S, Rutgeerts P, Fedorak R, Steinhart AH, Wild GE, Theuer D, Mohrle J, Schreiber S. Interferon beta-1a in ulcerative colitis: a placebo controlled, randomised, dose escalating study. *Gut* 2003;52:1286–1290.
  110. Beck PL, Podolsky DK. Growth factors in inflammatory bowel disease. *Inflamm Bowel Dis* 1999;5:44–60.
  111. Sandborn WJ, Sands BE, Wolf DC, Valentine JF, Safdi M, Katz S, Isaacs KL, Wruble LD, Katz J, Present DH, Loftus EV Jr, Graeme-Cook F, Odenheimer DJ, Hanauer SB. Repifermin (keratinocyte growth factor-2) for the treatment of active ulcerative colitis: a randomized, double-blind, placebo-controlled, dose-escalation trial. *Aliment Pharmacol Ther* 2003;17:1355–1364.
  112. Sinha A, Nightingale J, West KP, Berlanga-Acosta J, Playford RJ. Epidermal growth factor enemas with oral mesalamine for mild-to-moderate left-sided ulcerative colitis or proctitis. *N Engl J Med* 2003;349:350–357.
  113. Croog VJ, Ullman TA, Itzkowitz SH. Chemoprevention of colorectal cancer in ulcerative colitis. *Int J Colorectal Dis* 2003;18:392–400.
  114. Eaden J. Review article: the data supporting a role for aminosalicylates in the chemoprevention of colorectal cancer in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2003;18(Suppl 2):15–21.
  115. Bernstein CN, Blanchard JF, Metge C, Yogendran M. Does the use of 5-aminosalicylates in inflammatory bowel disease prevent the development of colorectal cancer? *Am J Gastroenterol* 2003;98:2784–2788.
  116. Allgayer H. Review article: mechanisms of action of mesalazine in preventing colorectal carcinoma in inflammatory bowel disease. *Aliment Pharmacol Ther* 2003;18(Suppl 2):10–14.
  117. Tung BY, Emond MJ, Haggitt RC, Bronner MP, Kimmey MB, Kowdley KV, Brentnall TA. Ursodiol use is associated with lower prevalence of colonic neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. *Ann Intern Med* 2001;134:89–95.
  118. Pardi DS, Loftus EV Jr, Kremers WK, Keach J, Lindor KD. Ursodeoxycholic acid as a chemopreventive agent in patients with ulcerative colitis and primary sclerosing cholangitis. *Gastroenterology* 2003;124:889–893.
  119. Berndtsson I, Oresland T. Quality of life before and after proctocolectomy and IPAA in patients with ulcerative proctocolitis—a prospective study. *Colorectal Dis* 2003;5:173–179.
  120. Delaney CP, Fazio VW, Remzi FH, Hammel J, Church JM, Hull TL, Senagore AJ, Strong SA, Lavery IC. Prospective, age-related analysis of surgical results, functional outcome, and quality of life after ileal pouch-anal anastomosis. *Ann Surg* 2003;238:221–228.
  121. Michelassi F, Lee J, Rubin M, Fichera A, Kasza K, Karrison T, Hurst RD. Long-term functional results after ileal pouch anal restorative proctocolectomy for ulcerative colitis: a prospective observational study. *Ann Surg* 2003;238:433–441; discussion 442–445.
  122. Stein RB, Lichtenstein GR. Complications after ileal pouch-anal anastomosis. *Semin Gastrointest Dis* 2000;11:2–9.
  123. Tulchinsky H, Hawley PR, Nicholls J. Long-term failure after restorative proctocolectomy for ulcerative colitis. *Ann Surg* 2003;238:229–234.
  124. Ording O, Olsen K, Juul S, Berndtsson I, Oresland T, Laurberg S. Ulcerative colitis: female fecundity before diagnosis, during disease, and after surgery compared with a population sample. *Gastroenterology* 2002;122:15–19.
  125. Mahadevan U, Sandborn WJ. Diagnosis and management of pouchitis. *Gastroenterology* 2003;124:1636–1650.
  126. Sandborn W, McLeod R, Jewell D. Pharmacotherapy for inducing and maintaining remission in pouchitis. *Cochrane Database Syst Rev* 2000:2.
  127. Mimura T, Rizzello F, Helwig U, Poggioli G, Schreiber S, Talbot IC, Nicholls RJ, Gionchetti P, Campieri M, Kamm MA. Four-week open-label trial of metronidazole and ciprofloxacin for the treatment of recurrent or refractory pouchitis. *Aliment Pharmacol Ther* 2002;16:909–917.

128. Gionchetti P, Rizzello F, Helwig U, Venturi A, Lammers KM, Brigidi P, Vitali B, Poggioli G, Miglioli M, Campieri M. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. *Gastroenterology* 2003;124:1202–1209.
129. Gionchetti P, Rizzello F, Venturi A, Brigidi P, Matteuzzi D, Baz-zocchi G, Poggioli G, Miglioli M, Campieri M. Oral bacterio-therapy as maintenance treatment in patients with chronic pou-chitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000;119:305–309.
130. Mimura T, Rizzello F, Helwig U, Poggioli G, Schreiber S, Talbot IC, Nicholls RJ, Gionchetti P, Campieri M, Kamm MA. Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. *Gut* 2004;53:108–114.
131. Sambuelli A, Boerr L, Negreira S, Gil A, Camartino G, Huernos S, Kogan Z, Cabanne A, Graziano A, Peredo H, Doldan I, Gonzalez O, Sugai E, Lumi M, Bai JC. Budesonide enema in pouchitis—a double-blind, double-dummy, controlled trial. *Aliment Pharmacol Ther* 2002;16:27–34.
132. Colombel JF, Ricart E, Loftus EV Jr, Tremaine WJ, Young-Fadok T, Dozois EJ, Wolff BG, Devine R, Pemberton JH, Sandborn WJ. Management of Crohn's disease of the ileoanal pouch with infliximab. *Am J Gastroenterol* 2003;98:2239–2244.

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