

ORIGINAL ARTICLE

Epidermal Growth Factor Enemas with Oral Mesalamine for Mild-to-Moderate Left-Sided Ulcerative Colitis or Proctitis

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ABSTRACT

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BACKGROUND

Epidermal growth factor (EGF) is a potent mitogenic peptide produced by salivary glands. We examined whether EGF enemas are an effective treatment for active left-sided ulcerative colitis and ulceration limited to the rectum (proctitis).

METHODS

In a randomized, double-blind clinical trial conducted at Leicester Royal Infirmary, 12 patients with mild-to-moderate left-sided ulcerative colitis received daily enemas of 5 µg of EGF in 100 ml of an inert carrier and 12 received daily enemas with carrier alone for 14 days. All also began to receive 1.2 g of oral mesalamine per day or had their dose increased by 1.2 g per day. Patients were assessed clinically at 0, 2, 4, and 12 weeks and by sigmoidoscopy and biopsy at 0, 2, and 4 weeks. The primary end point was disease remission (defined by a St. Marks score of 4 or less without sigmoidoscopic evidence of inflammation) at two weeks. Secondary end points were clinically significant improvements in disease activity (defined by a decrease of more than 3 points in the St. Marks score or the ulcerative colitis disease-activity index) at two and four weeks. Analyses were performed according to the intention-to-treat principle.

RESULTS

After two weeks, 10 of the 12 patients given EGF enemas were in remission, as compared with 1 of 12 in the control group (83 percent vs. 8 percent, $P < 0.001$). At the 2-week assessment, disease-activity scores, sigmoidoscopic score, and histologic scores were all significantly better in the EGF group than in the placebo group ($P < 0.01$ for all comparisons), and this benefit was maintained at 4 weeks and at 12 weeks.

CONCLUSIONS

This study provides preliminary data suggesting that EGF enemas are an effective treatment for active left-sided ulcerative colitis.

ULCERATIVE COLITIS IS A RELAPSING disease of unknown cause characterized by bloody diarrhea. Therapy usually involves 5-aminosalicylates, which are of limited benefit, with a response rate between 30 and 80 percent, depending on the end point used,¹ or corticosteroids such as prednisolone, although resistance and dependency can become problematic with corticosteroids.² Immunosuppressive drugs, such as azathioprine, are beneficial but may have serious side effects.³ New therapeutic approaches are therefore needed.

Recombinant peptides are increasingly being used for clinical purposes; for example, epoetin is used for anemia related to renal failure. Human epidermal growth factor (EGF) is a potent mitogenic peptide produced by salivary and duodenal Brunner's glands,⁴ which stimulates several components of the healing response.⁵ Preliminary studies in humans suggest that topical EGF enhances healing of skin wounds⁶ and that systemic EGF is beneficial for necrotizing enterocolitis in neonates.⁷ We therefore examined the value of luminal (enema) EGF therapy for patients with active left-sided ulcerative colitis or proctitis (ulceration limited to the rectum).

METHODS

PATIENTS

Subjects were recruited from patients with active colitis who attended the emergency colitis clinic (thus including patients with acute relapse) and regular outpatient clinics at Leicester Royal Infirmary. Entry criteria were a worsening of symptoms requiring additional therapy and mild-to-moderate disease, as indicated by a score of at least 5 on the St. Marks index⁸ (in which a score of 12 indicates the most severe disease) with a score of at least 1 (on a scale of 0 [normal] to 3 [most severe inflammation]) on sigmoidoscopy.⁸ Patients were excluded if they required hospitalization or intravenous corticosteroid therapy or if they were taking topical or systemic corticosteroids, if their treatment had changed in the three months before the study began, or if inflammation extended proximally to the left side of the colon (i.e., beyond the splenic flexure on fiberoptic endoscopy). Patients who had had no changes in their immunosuppressive-therapy regimen in the three months before recruitment to the study were eligible.

STUDY DESIGN

Patients were randomly assigned in a double-blind fashion to receive an EGF or placebo enema for 14 days. A permuted-block design was used to achieve equal numbers in each group. To ensure that all patients received an active treatment, all patients received a pH-dependent, slow-release oral preparation of mesalamine (Asacol, GlaxoSmithKline). Patients who were not taking mesalamine at recruitment began to take 1.2 g per day, whereas patients who were already taking mesalamine had their dose increased by 1.2 g per day. Patients were assessed clinically, sigmoidoscopically, and histologically at the start of the study, at two weeks, and at four weeks. At the two-week assessment, the enema medication was discontinued but mesalamine therapy was continued at the same dose. At the four-week assessment, patients who were in remission reverted to their original pretrial regimen (no treatment or continued mesalamine), whereas those with active disease had their medication increased or changed according to clinical need; in most cases, additional corticosteroid therapy or mesalamine therapy or both were given. The four-week assessment marked the end of the trial period, although all patients underwent a final clinical review 12 weeks after entry. The study remained double-blind until after the 12-week review.

The study was approved by the Leicestershire Research Ethics Committee. All patients gave written informed consent.

ENEMAS

Patients received daily enemas containing EGF or carrier alone. Human recombinant EGF (Heber Biotec, a commercial subsidiary of the Center for Genetic Engineering and Biotechnology, Havana, Cuba), expressed in *Saccharomyces cerevisiae*, comprises 60 percent EGF₁₋₅₂ (the EGF protein, lacking one terminal amino acid) and 40 percent EGF₁₋₅₁ (the EGF protein, lacking two terminal amino acids) and has bioactivity equivalent to that of full-length EGF₁₋₅₃.⁹ The EGF enema consisted of 5 µg of EGF in 100 ml of a degraded and modified gelatin carrier solution (Haemaccel 3.5 percent, Beacon Pharmaceuticals). This dose of EGF was chosen because it is similar to the concentration required to induce the maximal restitution response in intestinal cell lines.¹⁰ A two-week period of enema therapy was chosen to maximize the likelihood of patients' compliance and because most standard therapies cur-

rently used, such as corticosteroid therapy, usually have a positive result within this period. Placebo enema consisted of modified gelatin carrier alone and was indistinguishable from the EGF enema. Preliminary studies involving the incorporation of [³H]thymidine into rat intestinal epithelium cells¹⁰ confirmed that the inert carrier did not influence cell proliferation when it was given alone and that the biologic activity of the EGF remained stable during passage through the syringe and catheter, as previously described (data not shown).⁹

Patients were taught to administer the enema themselves in the supine position before going to bed, using a 10-French rectal catheter attached to a 100-ml syringe. The patients gave themselves an enema once a day for 14 days (they were instructed to retain the preparation as long as possible) and then lay on each side for 15 minutes to ensure maximal contact of the enema preparation with the mucosa.

CLINICAL SCORING AND DEFINITION OF REMISSION

At each assessment, patients completed a symptom questionnaire and underwent a clinical examination to generate three indexes of disease activity. The St. Marks index⁸ and the ulcerative colitis disease-activity index¹¹ provide an assessment of disease activity based on a combination of symptoms, signs, and sigmoidoscopic findings, with scores ranging from 0 to 12 and 0 to 22, respectively. In both cases, lower scores mean less disease activity. We also analyzed the data using a simplified symptom score, which does not require information from sigmoidoscopy; patients were given a clinical-severity score that was based on an aggregate assessment of stool consistency, visible blood in stool, and nocturnal defecation, with a score of 0 or 1 for each, for a maximal score of 3.¹²

Remission was defined by a St. Marks score of 4 or less with no inflammation on sigmoidoscopy. We also present the data using the ulcerative colitis disease-activity index, for which we defined remission as a score of 0 or 1 (no blood in stool), and using the simplified symptom score, for which we defined remission as a score of 0.¹² A clinical response was defined as a decrease of more than three points in the score on either the St. Marks index or the ulcerative colitis disease-activity index.

BLOOD TESTS

At each visit, 10 ml of venous blood was obtained for the determination of the hemoglobin level, white-

cell count, platelet count, albumin level, and C-reactive protein level.

SIGMOIDOSCOPIC AND HISTOLOGIC SCORING

During the initial visit, all patients underwent a limited colonoscopic examination as far as the splenic flexure, at approximately 50 cm, and always above the upper limit of macroscopic disease. The second and third examinations were limited to the distal 25 cm. The mucosal appearance was given a score of 0, 1, 2, or 3, with 0 representing normal,¹³ and three mucosal-biopsy specimens were obtained from a point halfway along the inflamed section of colon at the initial examination and at the same level at subsequent examinations for histologic grading. The biopsy specimens were fixed in formalin, sectioned, stained with hematoxylin and eosin, and given a score of 0, 1, 2, or 3⁸; a score of 0 represented normal histologic findings. Mucosal-biopsy specimens were assessed in a blinded fashion by a single investigator.

STUDY END POINTS

The primary end point of the study was disease remission (as defined by a St. Marks score of 4 or less) at two weeks. Secondary end points were clinically significant improvements in the clinical and histologic scores at two and four weeks.

STATISTICAL ANALYSIS

With 12 patients per group, the study had 80 percent power to detect a significant difference in proportions between a 10 percent rate of remission in the placebo group and a 60 percent rate of remission in the EGF group at a P value of 0.05 when the data were evaluated with use of a chi-square test. Data were analyzed in a blinded fashion according to the intention-to-treat principle. The Wilcoxon signed-rank test for paired samples was used to compare differences within treatment groups, and the Mann-Whitney U test was used to compare differences between the groups. Fisher's exact test was used to compare remission rates in the two groups. A planned interim analysis was conducted after 15 patients had completed the trial. All reported P values are based on two-sided t-tests.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Twenty-four patients (12 of whom were men) were recruited between March 1999 and January 2001.

Five patients in the placebo group and four in the EGF group had proctitis. One patient in the EGF group was taking azathioprine at recruitment, and the dose had been unchanged for more than three months before recruitment. No patients were receiving long-term topical mesalamine therapy at the time of recruitment.

There were no significant differences between the groups in any of the recorded base-line symptoms, signs, or hematologic, biochemical, sigmoidoscopic, or histologic characteristics (Table 1). The median daily dose of mesalamine at both two and four weeks was 2.4 g (range, 1.2 to 2.8) in both groups. All 24 patients gave themselves the enema and retained the solution for more than 45 minutes per day for 14 days.

TWO-WEEK ASSESSMENT

At the end of the two weeks of enemas, all 12 patients in the EGF group had significant decreases in the St. Marks score ($P=0.005$) (Table 2) and the score on the ulcerative colitis disease-activity index ($P<0.001$) (Fig. 1A), as compared with 2 of 12 patients in the placebo group. Remission as defined by a St. Marks score of 4 or less was achieved in 10 of 12 patients in the EGF group, as compared with 1 of 12 in the placebo group ($P<0.001$). Remission as defined by a score on the ulcerative colitis disease-activity index of 0 or 1 was achieved in 4 of 12 patients in the EGF group, as compared with 0 patients in the placebo group ($P=0.09$). Remission as defined by a simplified symptom score of 0 was achieved in 10 of 12 patients in the EGF group, as compared with 1 of 12 in the placebo group ($P<0.001$) (Fig. 1B). In both groups, hematologic and biochemical measurements were normal at the initial visit and remained so (Table 3). No side effects were reported by any of the patients who were taking EGF.

Since only 6 of the 24 patients were not taking mesalamine at the time of recruitment, formal statistical analysis of this subgroup was not possible. However, the median St. Marks score improved by 6 points in the EGF group (three of three patients were in remission) and by 4 points in the placebo group (one of three were in remission).

Nine patients had proctitis. This number was insufficient for formal subgroup analysis, although the median St. Marks score improved by 6.5 points in the EGF group (four of four patients were in remission) and by 1 point in the placebo group (one of five was in remission).

Table 1. Base-Line Characteristics of the Patients.*

Variable	Placebo Group (N=12)	EGF Group (N=12)
Male sex (no. of patients)	6	6
Age (yr)		
Median	36	44
Range	20–56	21–64
Duration of colitis (mo)		
Median	72	60
Range	4–144	6–192
Duration of exacerbation (wk)		
Median	3	4
Range	1–10	1–6
Ongoing mesalamine therapy at entry		
No. of patients	9	9
Median dose (g/day)	1.2	1.2
Dose range (g/day)	1.2–1.6	0.4–1.6
St. Marks score†		
Median	9	10
Range	7–14	7–13
UCDAI score‡		
Median	9	9.5
Range	7–11	7–12
Simplified symptom score§		
Median	2	2.5
Range	1–3	1–3
Sigmoidoscopic score		
Median	2.5	3
Range	2–3	2–3
Histologic score		
Median	3	3
Range	1–3	2–3
Hemoglobin (g/dl)		
Median	13.2	13.3
Range	12.0–15.2	11.4–15.8
White cells ($\times 10^{-3}/\text{mm}^3$)		
Median	6.9	8.0
Range	4.0–8.4	5.4–18
Platelets ($\times 10^{-3}/\text{mm}^3$)		
Median	283	299
Range	236–409	223–455
Albumin (g/liter)		
Median	43	44
Range	39–52	36–49
C-reactive protein (mg/liter)		
Median	0	0
Range	0–32	0–8

* EGF denotes epidermal growth factor, and UCDAI ulcerative colitis disease-activity index.

† A score of 4 or less represented remission, with no inflammation on sigmoidoscopy.

‡ A score of 0 or 1 represented remission, with no visible blood in stool.

§ A score of 0 represented remission.

Table 2. Changes in Disease Activity among Patients Who Received Epidermal Growth Factor (EGF) or Placebo Enemas for 14 Days in Addition to Mesalamine.

Variable	Before Treatment	At 2 Weeks	At 4 Weeks*
	<i>median (interquartile range)</i>		
St. Marks score†			
EGF	10 (8.75–10.25)	3 (2–4.25)‡	2 (1–3)‡
Placebo	9 (9–10)	8.5 (6–11)	6.5 (3–8.75)
P value	0.74	0.005	0.04
Simplified symptom score§			
EGF	2.5 (2–3)	0 (0–0.75)‡	0 (0–0)‡
Placebo	2 (2–2)	2 (1–2.75)	1.5 (0.25–2.75)
P value	0.26	0.002	0.02
Sigmoidoscopic score			
EGF	3 (2–3)	1 (1–1)‡	1 (0–1.75)‡
Placebo	2.5 (2–3)	2 (2–3)	2 (1–3)
P value	0.51	<0.001	0.04
Histologic score¶			
EGF	3 (3–3)	2 (1–2)‡	1 (1–2)‡
Placebo	3 (2–3)	3 (2–3)	2.5 (1.75–3)
P value	0.26	0.002	0.05

* Data were missing for two patients in the placebo group who were withdrawn from the study at two weeks because of worsening symptoms.

† A score of 4 or less represented remission, with no inflammation on sigmoidoscopy.

‡ P<0.01 for the comparison with the value before treatment.

§ A score of 0 represented remission, with no visible blood in stool.

¶ No dysplasia was observed in any biopsy specimen at any time.

Two patients in the placebo group were withdrawn from the study at two weeks because of a worsening of symptoms (diarrhea with blood) and disease activity, although the investigators were unaware of the patients' treatment assignments. This represents failure of treatment, and these patients were included in the denominator for all chi-square tests. Since they were not assessed after their withdrawal from the study, their data were not included in calculations of the median values, ranges, and statistical analyses (Wilcoxon and Mann-Whitney tests) relating to disease activity. Significant improvements in clinical, sigmoidoscopic, and histologic measurements were found in the EGF group but not in the placebo group (Table 2).

FOUR-WEEK ASSESSMENT

At four weeks, disease-activity scores in the EGF group were significantly better than both pretreatment values and the four-week values in the placebo group (Table 2 and Fig. 1A). When remission was defined according to the St. Marks score, 10 of 12

patients were in remission in the EGF group, as compared with 3 of 12 in the placebo group (P=0.012). When remission was defined according to the score on the ulcerative colitis disease-activity index, 7 of 12 patients were in remission in the EGF group, as compared with 1 of 12 in the placebo group (P=0.03). When remission was defined according to the simplified symptom score, 10 of 12 patients in the EGF group were in remission, as compared with 3 of 12 in the placebo group (P=0.01) (Fig. 1B).

12-WEEK ASSESSMENT

Since patients did not undergo sigmoidoscopy at the 12-week assessment, we could not calculate the St. Marks score or the score on the ulcerative colitis disease-activity index. However, 8 of 12 patients (67 percent) who had been treated with EGF and who were in histologic remission at four weeks remained in remission defined according to the simplified symptom score, as compared with only 1 in the placebo group (8 percent) (P=0.009). Nine of the 12 patients in the placebo group (75 percent) required oral or rectal corticosteroid treatment or both: oral prednisolone and foam enemas in 2, prednisolone foam enemas in 4, and prednisolone suppositories in 3. Four of the 12 patients in the EGF group (33 percent) required rectal corticosteroid treatment alone (prednisolone foam enemas) between 4 and 12 weeks.

SUBSEQUENT REVIEW

We reviewed the patients' records retrospectively to determine the number who subsequently received corticosteroid treatment. The decision to use corticosteroids was made by the attending physician on the basis of his or her normal clinical criteria. By 6 months, 6 of the 12 EGF-treated patients had required local or systemic corticosteroids, and by the last review, at a median of 16 months, 8 of the 12 had required local or systemic corticosteroids. By six months, all the patients in the placebo group had required local or systemic corticosteroids.

DISCUSSION

We found that once-daily EGF enemas induced rapid improvements in active left-sided ulcerative colitis or proctitis when administered in combination with oral mesalamine. The condition of all patients who received EGF improved within two weeks, and 10 of 12 (83 percent) were in remission according to the

St. Marks score. In contrast, only two patients who received placebo plus mesalamine had an improvement, and only one of the two was in remission. After 12 weeks there was no clinical evidence of early relapse in patients in whom remission was achieved with EGF therapy. Previous studies have reported response rates to placebo of 16 to 52 percent,¹⁴ although the number of patients who have a spontaneous full remission is probably much lower. Mesalamine is a well-established agent for colitis therapy that is superior to placebo,¹⁵ has dose-dependent efficacy,¹⁶ and is useful when given both topically and orally for distal colonic disease.¹⁷ The lack of a major response to mesalamine therapy in our study is probably related to the relatively small additional oral dose used (1.2 g per day).

EGF is a 1207-amino-acid precursor¹⁸ that is processed to a polypeptide of 53 amino acids (EGF₁₋₅₃). Circulating levels of EGF are low and consist mostly of the EGF₁₋₅₂ form,¹⁹ which is bound to platelets and not readily available to the gastrointestinal mucosa. Although EGF enters the proximal gastrointestinal tract as EGF₁₋₅₃, it is susceptible to progressive digestion as it proceeds distally. In acidic gastric juice, it is cleaved mainly to EGF₁₋₄₉, reducing its activity by 75 percent.²⁰ Once EGF enters the small intestine, it is rapidly digested by pancreatic proteases within the lumen but may be partially protected against digestion by the presence of food.²¹ Under physiologic conditions, it is therefore likely that very little luminal EGF derived from the upper intestine reaches the colon, and any orally administered EGF is unlikely to reach the distal bowel unless it is protected from digestion. Administration of EGF as an enema has the advantage of delivering the peptide to the injured area in a readily

Figure 1. Changes in the Ulcerative Colitis Disease-Activity Index (Panel A) and the Simplified Symptom Score (Panel B) among Patients Who Received Epidermal Growth Factor or Placebo Enemas for 14 Days in Addition to Mesalamine.

Values in Panel A are expressed as the group medians and interquartile ranges. P values are for the comparison between groups. The asterisk denotes $P=0.02$ as compared with the initial value. The daggers denote $P<0.001$ as compared with the initial value. Scores for the ulcerative colitis disease-activity index range from 0 to 22, with lower scores indicating less disease activity. The simplified symptom score was based on an aggregate assessment of stool consistency, visible blood in stool, and nocturnal defecation,¹² with a score of 0 or 1 for each and a maximal score of 3. A score of 0 represented remission.

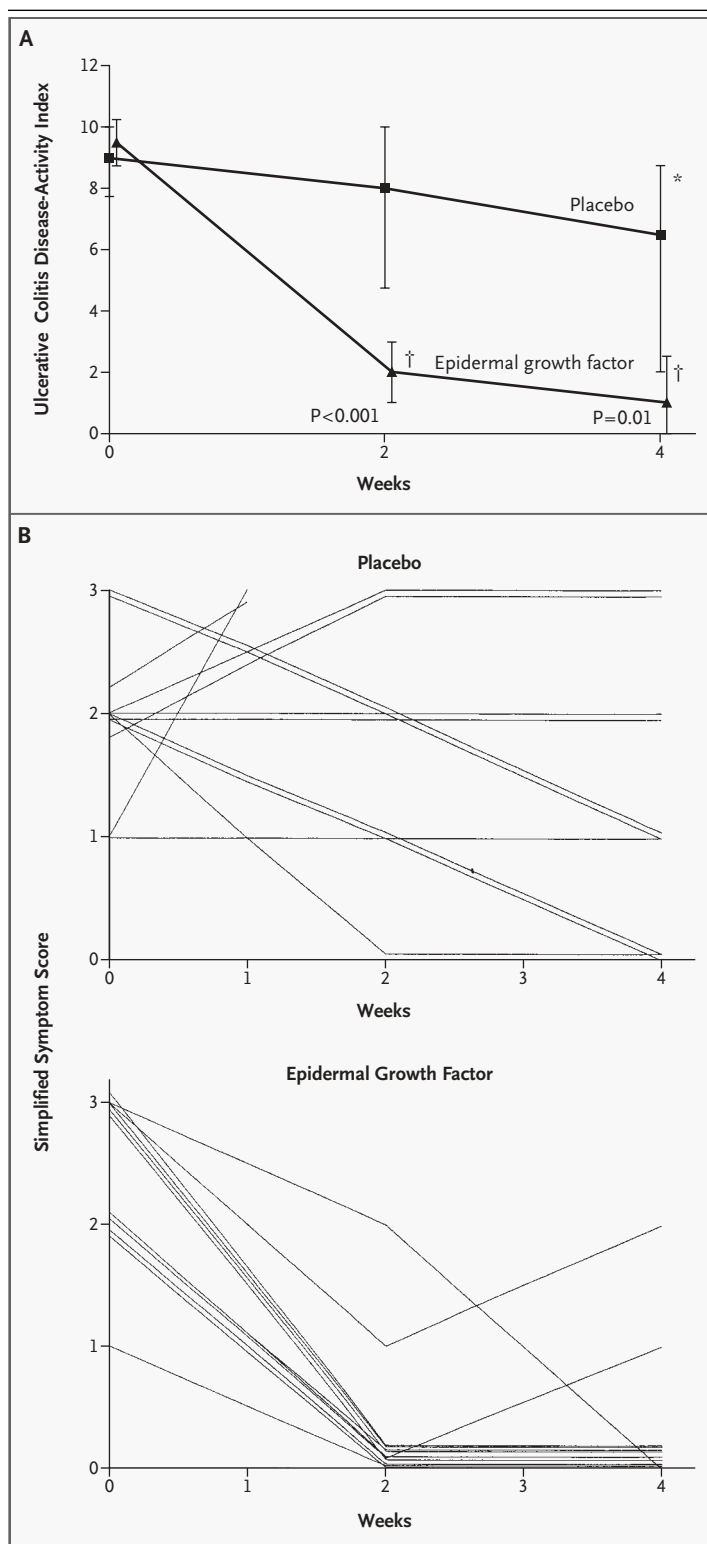


Table 3. Changes in Other Variables among Patients Who Received Epidermal Growth Factor (EGF) or Placebo Enemas for 14 Days in Addition to Mesalamine.*

Variable	Before Treatment	At 2 Weeks	At 4 Weeks
	<i>median (interquartile range)</i>		
Hemoglobin (g/dl)			
EGF	13.3 (12.7–14.4)	12.5 (11.7–13.7)	12.8 (12.2–13.6)
Placebo	13.2 (12.4–14.8)	13.4 (12.7–14.2)	13.1 (12.4–14.2)
White cells ($\times 10^{-3}/\text{mm}^3$)			
EGF	8.0 (7.1–12.9)	7.0 (6.2–11.8)	7.8 (6.0–10.4)
Placebo	6.9 (5.6–8.1)	6.9 (6–7.5)	6.3 (5.8–7.5)
Platelets ($\times 10^{-3}/\text{mm}^3$)			
EGF	299 (223–465)	335 (240–403)	315 (268–374)
Placebo	283 (236–401)	285 (276–358)	305 (251–359)
Albumin (g/liter)			
EGF	44 (36–49)	42 (35–48)	43 (33–51)
Placebo	43 (39–52)	42 (38–52)	43 (37–46)
C-reactive protein (mg/liter)			
EGF	0 (0–1.3)	0 (0–0)	0 (0–0)
Placebo	0 (0–1)	0 (0–0)	0 (0–2.8)

* Data were missing for two patients in the placebo group who were withdrawn from the study at two weeks because of worsening symptoms. There were no significant differences between or within the groups.

available, intact, active form. To ensure that adequate active EGF reached the inflamed mucosa, we administered an enema containing 100 times the concentration of EGF found in gastric juice (500 ng per liter),^{20,22} an amount sufficient to stimulate the proliferation of intestinal cells in vitro.^{10,19,20}

EGF probably acts through several mechanisms. It is a potent stimulant of cell migration (restitution) and cell proliferation,^{10,20} both of which are important in reestablishing epithelial continuity.⁵ EGF also reduces injury and stimulates repair in animal models of gastric, small intestinal, and colonic injury,^{9,20,23–25} although the exact mechanisms of this effect remain unclear. In our patients, it is likely that EGF facilitated the reformation of the epithelial barrier, and this in turn reduced the secondary inflammatory response to luminal antigens. Most studies of the distribution of EGF receptors in the normal human bowel suggest that they are restricted to the basolateral membranes.²⁶ Our luminal therapy probably stimulated repair by means of EGF

receptors exposed at the sites of injury, in keeping with the role of EGF as a luminal surveillance peptide.⁵ Other potential mechanisms include an increase in the numbers of receptors²⁷ and an alteration in the distribution of receptors to include apical membranes.²⁸

The cause of ulcerative colitis is unclear but probably involves an imbalance between aggressive factors and mucosal defense and repair. Since EGF is important in repair mechanisms, a local or generalized defect in its production, its receptor, or the rate of its destruction may be etiologic factors. Reduced plasma levels of EGF are found in neonates with necrotizing enterocolitis,⁷ and when the EGF receptor is deleted in mice,²⁹ bowel ulceration results.

The use of recombinant peptides for so-called hollow-organ gastrointestinal conditions is at a preliminary stage.³⁰ Many of the favorable outcomes reported with the use of recombinant peptides in animal models of gastrointestinal disease are seen only if the peptides are administered before exposure to the damaging agent, limiting their clinical relevance. Systemic therapy with potent growth factors, such as EGF, could theoretically stimulate premalignant lesions in distant organs. It is therefore prudent to limit systemic therapy to life-threatening conditions, as occurred in the case of a child with necrotizing enterocolitis⁷ and in a child with congenital microvillous atrophy.³¹ Luminal therapy overcomes many of these problems, since EGF will only influence the growth and repair of the damaged areas, where the basolateral receptors are exposed. Although we found no colonic dysplasia in this short-term study, serial biopsies of the affected area in patients given exogenous EGF seem appropriate until potential safety issues have been addressed.

In summary, our finding that EGF enemas reduced disease activity and induced clinical remission expands on previous studies in vitro and in animal models. To determine optimal doses and delivery methods, larger studies that directly compare EGF with high-dose mesalamine or corticosteroids appear to be warranted.

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REFERENCES

1. Hanauer SB. Medical therapy of ulcerative colitis. *Lancet* 1993;342:412-7.
2. Farrell RJ, Peppercorn MA. Ulcerative colitis. *Lancet* 2002;359:331-40.
3. Podolsky DK. Inflammatory bowel disease. *N Engl J Med* 2002;347:417-29.
4. Heitz PU, Kasper M, van Noorden S, Polak JM, Gregory H, Pearse AG. Immunohistochemical localisation of urogastrone to human duodenal and submandibular glands. *Gut* 1978;19:408-13.
5. Playford RJ. Peptides and gastrointestinal mucosal integrity. *Gut* 1995;37:595-7.
6. Brown GL, Nanney LB, Griffen J, et al. Enhancement of wound healing by topical treatment with epidermal growth factor. *N Engl J Med* 1989;321:76-9.
7. Sullivan PB, Brueton MJ, Tabara ZB, Goodlad RA, Lee CY, Wright NA. Epidermal growth factor in necrotising enteritis. *Lancet* 1991;338:53-4.
8. Powell-Tuck J, Day DW, Buckell NA, Wadsworth J, Lennard-Jones JE. Correlations between defined sigmoidoscopic appearances and other measures of disease activity in ulcerative colitis. *Dig Dis Sci* 1982;27:533-7.
9. Calnan DP, Fagbemi A, Berlanga-Acosta J, et al. Potency and stability of C terminal truncated human epidermal growth factor. *Gut* 2000;47:622-7.
10. Chinery R, Playford RJ. Combined intestinal trefoil factor and epidermal growth factor is prophylactic against indomethacin-induced gastric damage in the rat. *Clin Sci (Lond)* 1995;88:401-3.
11. Sutherland LR, Martin F, Greer S, et al. 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. *Gastroenterology* 1987;92:1894-8.
12. Sinha A, Nightingale J, West KP. A simple method of grading the activity of ulcerative colitis using patient symptoms. *Gastroenterology* 2000;118:Suppl 2:A316. abstract.
13. Baron JH, Connell AM, Lennard-Jones JE. Variation between observers in describing mucosal appearances in proctocolitis. *Brit Med J* 1964;1:89-92.
14. Meyers S, Janowitz HD. The "natural history" of ulcerative colitis: an analysis of the placebo response. *J Clin Gastroenterol* 1989;11:33-7.
15. Klotz U. The role of aminosaliclates at the beginning of the new millennium in the treatment of chronic inflammatory bowel disease. *Eur J Clin Pharmacol* 2000;56:353-62.
16. Sutherland LR, May GR, Shaffer EA. Sulfasalazine revisited: a meta-analysis of 5-aminosalicylic acid in the treatment of ulcerative colitis. *Ann Intern Med* 1993;118:540-9.
17. Safdi M, DeMicco M, Sninsky C, et al. A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. *Am J Gastroenterol* 1997;92:1867-71.
18. Bell GI, Fong NM, Stempien MM, et al. Human epidermal growth factor precursor: cDNA sequence, expression in vitro and gene organization. *Nucleic Acids Res* 1986;14:8427-46.
19. Araki F, Nakamura H, Nojima N, Tsukumo K, Sakamoto S. Stability of recombinant human epidermal growth factor in various solutions. *Chem Pharm Bull (Tokyo)* 1989;37:404-6.
20. Playford RJ, Marchbank T, Calnan DP, et al. Epidermal growth factor is digested to smaller, less active forms in acidic gastric juice. *Gastroenterology* 1995;108:92-101.
21. Playford RJ, Woodman AC, Clark P, et al. Effect of luminal growth factor preservation on intestinal growth. *Lancet* 1993;341:843-8.
22. Kelly SM, Jenner JR, Dickinson RJ, Hunter JO. Increased gastric juice epidermal growth factor after non-steroidal anti-inflammatory drug ingestion. *Gut* 1994;35:611-4.
23. Itoh M, Imai S, Joh T, et al. Protection of gastric mucosa against ethanol-induced injury by intragastric bolus administration of epidermal growth factor combined with hydroxypropylcellulose. *J Clin Gastroenterol* 1992;14:Suppl 1:S127-S130.
24. Berlanga J, Prats P, Ramirez D, et al. Prophylactic use of epidermal growth factor reduces ischemia/reperfusion intestinal damage. *Am J Pathol* 2002;16:373-9.
25. Procaccino F, Reinshagen M, Hoffmann P, et al. Protective effect of epidermal growth factor in an experimental model of colitis in rats. *Gastroenterology* 1994;107:12-7.
26. Playford RJ, Hanby AM, Gschmeissner S, Peiffer LP, Wright NA, McGarrity T. The epidermal growth factor receptor (EGF-R) is present on the basolateral, but not the apical, surfaces of enterocytes in the human gastrointestinal tract. *Gut* 1996;39:262-6.
27. Hoffmann P, Reinshagen M, Zeeh JM, et al. Increased expression of epidermal growth factor-receptor in an experimental model of colitis in rats. *Scand J Gastroenterol* 2000;35:1174-80.
28. Wright NA, Poulosom R, Stamp F, et al. Trefoil peptide gene expression in gastrointestinal epithelial cells in inflammatory bowel disease. *Gastroenterology* 1993;104:12-20.
29. Miettinen PJ, Berger JE, Meneses J, et al. Epithelial immaturity and multiorgan failure in mice lacking epidermal growth factor receptor. *Nature* 1995;376:337-41.
30. Playford RJ. Recombinant peptides for gastrointestinal ulceration: still early days. *Gut* 1997;40:286-7.
31. Drumm B, Cutz E, Tomkins KB, Cook D, Hamilton JR, Sherman P. Urogastrone/epidermal growth factor in treatment of congenital microvillous atrophy. *Lancet* 1988;1:111-2.

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