Published in final edited form as:

Gastroenterology. 2008 March ; 134(3): 688–695.

Rosiglitazone for Active Ulcerative Colitis:

A Randomized Placebo-Controlled Trial

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Abstract

Background—Thiazolidinedione ligands for the gamma subtype of peroxisome proliferator-activated receptors (PPAR γ), widely used to treat type 2 diabetes mellitus, have been proposed as novel therapies for ulcerative colitis.

Methods—This multicenter randomized, double blind, placebo-controlled clinical trial compared the efficacy of rosiglitazone (AvandiaTM) 4 mg orally twice daily versus placebo twice daily for 12 weeks in 105 patients with mild to moderately active UC. Disease activity was measured with the Mayo Score. The primary endpoint was clinical response (≥ 2 point reduction) at week 12. Clinical remission (Mayo Score ≤ 2), endoscopic remission, and quality of life were secondary outcomes.

Results—After 12 weeks of therapy, 23 patients (44%) treated with rosiglitazone and 12 patients (23%) treated with placebo achieved clinical response ($p=0.04$). Remission was achieved in 9 patients (17%) treated with rosiglitazone and 1 patient (2%) treated with placebo ($p=0.01$). Endoscopic remission was uncommon in either treatment arm (8% rosiglitazone vs. 2% placebo, $p=0.34$). Clinical improvement was evident as early as 4 weeks ($p=0.049$). Quality of life was significantly improved at week 8 ($p=0.01$) but not at week 4 ($p=0.48$) or 12 ($p=0.14$). Serious adverse events were rare.

Conclusions—Rosiglitazone was efficacious in the treatment of mild to moderately active ulcerative colitis.

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Clinical trial registration: clinicaltrials.gov #NCT00065065

Introduction

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily of transcription factors.¹ The thiazolidinedione (TZD) anti-diabetic drugs are ligands for the γ subtype of PPARs. High levels of PPAR γ protein are expressed by adipose tissue and the colonic epithelium, but the role of PPAR γ in the colon is uncertain.^{2, 3} Available evidence suggests a potential anti-inflammatory effect of PPAR γ ligands, including TZDs, particularly in the colon. Treatment with PPAR γ ligands has been demonstrated to attenuate inflammatory cytokine production (e.g. interleukin (IL)-1 β and tumor necrosis factor- α (TNF- α)), inflammatory cell proliferation, and expression of selected adhesion molecules.³ Furthermore, treatment with these compounds reduces colonic inflammation in several murine models of colitis.^{3, 4}

In an uncontrolled, open-label pilot study, we documented that more than 50% of patients with chronic, mild to moderately active ulcerative colitis (UC) refractory to 5-aminosalicylic acid (5-ASA) therapy demonstrated clinical improvement after 12 weeks of therapy with rosiglitazone.⁵ Based on these results, we conducted a placebo-controlled, randomized clinical trial to test whether rosiglitazone is superior to placebo for patients with mild to moderately active UC.

Methods

Design

This randomized, double blind, placebo-controlled clinical trial compared the efficacy of rosiglitazone (Avandia®, GlaxoSmithKline) 4 mg or placebo orally twice daily for 12 weeks in 105 patients with mild to moderately active UC. The dose selected was the highest dose approved for treatment of diabetes mellitus.

Ethical considerations

The study was approved by the Institutional Review Boards of the participating centers.

Participants

Only patients with mild to moderately active UC were eligible. Disease activity was assessed using a slight modification of the Mayo Score.^{6, 7} Mild to moderate disease activity was defined as a score of 4 to 10, inclusive⁵ (Table 1).

Eligible patients were required to have been treated with 5-aminosalicylic acid (5-ASA) compounds at a dose of 2000 mg per day or greater for at least 4 weeks immediately prior to randomization or to have documented intolerance to such therapy. Concomitant therapy with corticosteroids was permitted if the dose was stable for a minimum of 4 weeks prior to randomization and did not exceed prednisone 20mg per day, budesonide 9mg per day, or the equivalent. Concomitant therapy with azathioprine or 6-mercaptopurine was allowed if used for a minimum of 4 months and at a stable dose for a minimum of 2 months prior to randomization. Rectally administered corticosteroids or 5-ASA was allowed if the dose was stable for two weeks prior to randomization. The dose of concomitant medications could not be increased above baseline during the study. Steroid tapering was not allowed. Use of antidiarrheal medications was not permitted.

Patients were excluded if they had evidence of infectious colitis, if they were pregnant or breast feeding, if they had acute or chronic liver disease, abnormal liver associated chemistries, a contraindication to flexible sigmoidoscopy or biopsy, New York Heart Association class III

or IV heart failure, an active malignancy other than non-melanoma skin cancer, or diabetes mellitus requiring medications.

Randomization and masking of treatment assignment

Randomization was in a 1:1 ratio of active drug versus placebo. Computer generated, permuted block randomization was employed by the Data Coordinating Center at the University of Pennsylvania, with randomly assigned block sizes of four to eight used to formulate assignment for each center. Each site was provided with a randomization list and treatment packs. Treatment packs were assigned sequentially at each site according to the randomization list.

Schedule of evaluation

All patients underwent flexible sigmoidoscopy (or colonoscopy) within 30 days prior to randomization (90% within 3 days prior to randomization) and again at the week 12 follow-up visit. Patients were seen at the clinical centers in follow-up after randomization at weeks 2, 4, 8, 12, and 14. Without knowledge of the response rates in either arm, the Data and Safety Monitoring Board (DSMB) requested that the week 2 follow-up evaluation be eliminated with the hopes of minimizing the placebo response rate and maximizing recruitment and retention.⁸⁻¹⁰ Eighteen patients completed the week 2 follow-up visit.

Definition of outcomes

The primary outcome was clinical response, defined as a two points or greater decrease in the Mayo Score from baseline at week 12.¹⁰ Patients who did not complete 12 weeks of follow-up for any reason were defined as treatment failures. Secondary clinical outcome measures included decrease of 3 or more points in the Mayo Score, clinical remission (week 12 Mayo Score ≤ 2) and endoscopic remission (week 12 Mayo Score < 2 and endoscopic score = 0).

Adherence to study medication (defined as the percent of prescribed doses that were consumed) was assessed by pill counts and adverse events were recorded at each study visit.

Protocol violations

During quality assurance checks, 6 patients were identified who were determined to have minor protocol violations that occurred prior to randomization. Decisions on inclusion in the analysis were made prior to knowledge of the patients' treatment assignment or outcomes. These patients were included in the primary intention to treat (ITT) analyses.

Decisions on two additional patients were made without knowledge of treatment assignment. One patient reported use of an anti-diarrhea medication on a single day 3 days prior to their final visit. This patient's Mayo Score for stool frequency, which was based on a 3 day average, was the same at the randomization visit and the week 12 visit. This patient was included in all analyses.

The second patient completed all study visits but refused to undergo flexible sigmoidoscopy at week 12. This patient had a documented 1 point reduction in each of the other components of the Mayo Score compared to baseline (stool frequency 3 to 2, bleeding 2 to 1, and physician global assessment 2 to 1) and had a baseline score of 1 for the sigmoidoscopy component of the Mayo Score. The protocol did not specify how to categorize patients under these circumstances. We elected to categorize this patient as a responder for the primary analysis and for analysis of Mayo Score reduction by 3 points or greater, but not for clinical or endoscopic remission.

Statistical analysis

All analyses used two-sided tests of statistical significance. Comparisons of the descriptive variables of the two arms were performed using the Wilcoxon rank sum test for continuous variables and the chi-square or Fisher's exact test for categorical variables.¹¹ The primary analysis included all randomized patients (i.e., intention to treat). Nominal significance level of 0.05 was adjusted to 0.049 to account for performance of one interim analysis that used a stopping threshold of $p=0.001$. The active treatment arm was compared to placebo using the Mantel-Haenszel (MH) randomization model framework, adjusting for heterogeneity among the randomization centers.¹² In analyses accounting for between center heterogeneity, data were pooled from 4 centers, each enrolling less than 6 patients and in total enrolling 11 patients. Estimates of effect without pooling data from these centers were similar (data not shown).

Logistic regression was used to test for confounding and adjust for potential imbalance between the two arms in the descriptive variables (Table 2).¹³ All variables that affected the crude estimate of the relative risk of effectiveness by 10% or greater were included as candidate confounders in a multivariate model.¹⁴

We assessed improvement in quality of life and a Partial Mayo Score at weeks 4, 8, and 12. The Partial Mayo Score included all components of the Mayo Score other than the endoscopic score, such that the score ranged between 0 and 9.⁵ Of note, Higgins, et al. have demonstrated for the almost identical disease activity index described by Sutherland that the endoscopic component predicts only 0.04% of the variability in measurement of disease activity.¹⁵ A two point decrease in the Partial Mayo Score was defined as a response. Quality of life was measured with the Inflammatory Bowel Disease Questionnaire (IBDQ).¹⁶ Improvement was defined as an increase of 16 points or more.

Sample size

Our initial sample size calculations called for 176 patients to provide 90% power to detect a 26% absolute difference in response rates with an expected response rate of 27% among patients treated with placebo⁸, after inflation by 15% and 5% to account for potential clustering within sites and for planned interim analyses, respectively. Because of slower than anticipated enrollment, the sample size was recalculated assuming a single interim analysis and without inflation for clustering by site. With 105 patients, and one interim analysis, the study would have 80% power to detect an absolute difference of 29% in response rates with the originally assumed 27% response rate in the placebo group. The Data and Safety Monitoring Board recommended that recruitment be terminated when this sample size was achieved.

Role of the funding source

The study was funded by the National Institutes of Health (grant DK059961) who also selected the members of the Data and Safety Monitoring Board. GlaxoSmithKline provided the rosiglitazone and placebo. The study was designed and conducted, the data were analyzed, and the manuscript was written independently by the investigators.

Results

Between September 6, 2002 and January 11, 2006, 157 patients were screened and 105 patients were randomized from 15 centers (Figure 1). The two groups were generally balanced on all factors examined (Table 2). Greater than 80% adherence to the prescribed study medication was observed for 88% -96% and 92% -95% of patients at each study visit in the rosiglitazone and placebo arms, respectively.

After 12 weeks of therapy, 23 patients (44%) treated with rosiglitazone and 12 patients (23%) treated with placebo had achieved the primary outcome of clinical response (Mayo Score decrease of 2 points or more) ($p=0.03$). In logistic regression analysis, age and smoking status were identified as confounders. After adjusting for these factors, the association between treatment with rosiglitazone and clinical response was stronger (unadjusted odds ratio 2.7, 95% confidence interval 1.2 - 6.3, $p=0.02$; adjusted odds ratio 4.0, 95% confidence interval 1.5 - 10.5, $p=0.005$).

Using the more stringent definition of clinical response (3 point or greater reduction in the Mayo Score), 19 patients (37%) treated with rosiglitazone and 7 patients (13%) treated with placebo achieved clinical response ($p=0.01$) (Figure 2a). Clinical remission (Mayo Score ≤ 2) was achieved in 9 patients (17%) treated with rosiglitazone and 1 patient (2%) treated with placebo ($p=0.01$).

Although there were slight imbalances between the groups in selected clinical factors, such as disease distribution and concomitant or prior use of thiopurines, these did not prove to be confounders in the multivariable analyses. Similarly, the pre-specified subgroup analyses generally produced results in the same direction and magnitude as the overall analyses for clinical response (Mayo Score decrease by 2 points or more) and clinical remission (Mayo Score ≤ 2), although the p values and confidence intervals were larger due to the smaller sample sizes (Online supplemental data). Rosiglitazone-treated patients with low Mayo Scores at baseline had higher clinical remission rates (27%) than those with high baseline Mayo Scores (8%); clinical remission was uncommon in placebo-treated patients regardless of the baseline Mayo Score. While response rates were higher with rosiglitazone treatment than with placebo regardless of baseline disease activity, this was only significant among those with high baseline Mayo Scores (50% vs. 17%, $p=0.02$).

In a secondary analysis, we examined the proportion of patients with clinical response (2 point or greater decrease in the Partial Mayo Score) and improvement in quality of life (IBDQ increased by 16 points or greater) at each time point (Figures 2b and 2c). Improvement was numerically more common among rosiglitazone-treated patients for both outcome measures at all time points. However, these differences were only significant at weeks 4 ($p=0.049$) and 12 ($p=0.03$) for the Partial Mayo Score and at week 8 ($p=0.04$) for the IBDQ. At week 12, patients treated with rosiglitazone were more likely to have improvement in each of the components of the Mayo Score, although this was not statistically significant for bleeding (Figure 2d).

Adverse events

Adverse events occurred at similar rates between the two groups (Table 3). Serious adverse events other than worsening of ulcerative colitis were rare. Four patients, all in the placebo arm, underwent colectomy during the study. Decrease in hemoglobin by 2 g/dl or more was observed in 3 patients treated with rosiglitazone and 3 treated with placebo. Among patients who completed 12 weeks of therapy, the mean increase in weight from baseline was 1.8 kg and 0.3 kg for patients treated with rosiglitazone and placebo, respectively ($p=.005$).

As anticipated, edema was more common among patients receiving rosiglitazone ($p=0.008$). Because this could have potentially unmasked the treatment assignment, a post hoc subgroup analysis was conducted among those patients without edema. Response rates were higher in the rosiglitazone group than placebo when defined as reduction in the Mayo Score by ≥ 2 points (42% vs 23%, $p=0.08$) or ≥ 3 points (35% vs. 13%, $p=0.02$). Clinical remission rates were also higher with rosiglitazone (16% vs. 2%, $p=0.02$).

Discussion

Previous in vitro, in vivo, and uncontrolled human studies have suggested a potential anti-inflammatory effect of PPAR γ ligands in the colon. In this double-blind, placebo-controlled clinical trial, 12 weeks of therapy with rosiglitazone was superior to placebo for induction of clinical response and clinical remission among patients with mild to moderately active ulcerative colitis. Although, endoscopic remission was uncommon in both treatment groups, endoscopic improvement was more common with rosiglitazone treatment. Based on the Partial Mayo Score and quality of life data, there was evidence of improvement as early as 4 to 8 weeks.

No specific subgroup of patients was identified that would be most likely to benefit from rosiglitazone therapy. However, the study was relatively small, thereby limiting our power for subgroup analyses. The subsets of patients receiving 5-ASA and those not receiving immunomodulators had nearly identical results as the primary analysis. The magnitude of the beneficial effect was slightly less strong among patients not receiving steroids (see supplemental data). The absolute difference in response rates between rosiglitazone and placebo was greater in the subgroup of patients with moderately active disease at baseline than among those with milder disease. Similar trends have been seen in other placebo-controlled studies of inflammatory bowel diseases.^{9, 10}

Our primary outcome definition was clinical response, defined as a reduction in the Mayo Score of two points or greater. This was established as the primary outcome when the study was designed, based on the results of our preliminary study⁵, and before any validation efforts had been undertaken for this widely used clinical outcome measure. The rationale for selecting a two point reduction as the primary definition of response was that our inclusion criteria required a minimum score of 4 or greater and our definition of remission was a score of 2 or less. Since two points was the minimum reduction in the Mayo Score necessary to achieve a remission (i.e., from baseline of 4 to final score of 2), we concluded that a reduction of 2 points or greater would define a clinical response. Subsequently, Higgins et al. reported that a score of 2 or lower is the optimal cut point to identify patient-defined clinical remission, consistent with the definition used in our study.¹⁷ Recently, others have recommended using a reduction in the Mayo Score of 3 points or greater and at least 30% with an accompanying decrease in the rectal bleeding score of at least 1 point or a rectal bleeding subscore of 0 or 1 to define clinical response, demonstrating that this was associated with improved quality of life.¹⁸ To allow our study results to be comparable to those of other studies that have used this index, prior to examining treatment assignment and outcomes, we added to the analysis plan a secondary analysis using a minimum 3 point reduction in the Mayo Score to define a clinical response. Interestingly, the statistical significance of our findings for clinical outcomes was greater when we used the more stringent definition of response and for clinical remission.

Rosiglitazone treatment was associated with improvement in the endoscopic appearance. However, endoscopic remission rates, while numerically higher in the rosiglitazone group, were not significantly different. This could have been due to the strict criteria that we used to define endoscopic remission. Whether it is necessary to achieve endoscopic remission in order to obtain long term clinical benefits is uncertain, although one would hypothesize that discontinuation of treatments that have failed to achieve complete mucosal healing would lead to more frequent clinical relapse.^{19, 20} Subsequent studies examining the role of rosiglitazone to prevent relapse of ulcerative colitis are warranted.

As anticipated, short term treatment with rosiglitazone was generally well tolerated by patients with ulcerative colitis. Among the most common side-effects were weight gain and edema. We observed significantly more edema and weight gain in the rosiglitazone-treated patients than

among patients receiving placebo. However, interpretation of data on weight gain is difficult in studies of active ulcerative colitis, since some weight gain could result from improvement in disease activity. Of note, the average weight gain in patients completing 12 weeks of rosiglitazone therapy was less than 2 kg.

Other than worsening ulcerative colitis, as would be expected in a clinical trial of active ulcerative colitis, serious adverse events were uncommon. Because the anti-diabetes mechanism of action is through increased sensitization to insulin rather than increased insulin secretion, in the absence of other diabetes therapies, hypoglycemia is not anticipated from treatment with TZD PPAR γ ligands. We observed rare cases of glucose measurements between 60 mg/dl and 70 mg/dl, but these could have been false positive findings since they occurred in similar frequencies in both study arms. No cases of symptomatic hypoglycemia were reported as adverse events. No cases of significant liver injury or congestive heart failure were observed, however patients with underlying liver disease or advanced heart failure were excluded.

PPAR γ may also play a role in cell differentiation and neoplasia. There is conflicting evidence in animal models that TZDs may either promote or inhibit the development of colonic neoplasia.²¹ However, to date, two epidemiological studies in non-ulcerative colitis patients with type 2 diabetes mellitus suggest that TZDs do not increase the risk of colon cancer in humans.^{22, 23} Likewise, adverse effects on other organ systems, such as long bone fractures and myocardial infarction has been suggested from studies focusing mostly on diabetics.^{24, 25} However, the data on risk of myocardial infarction remain controversial, with several studies using similar data sources yielding conflicting results.^{24, 26-28} Nonetheless, a new boxed warning has been added to the rosiglitazone prescribing information about potential increased risk for heart attacks.²⁹ Patients in this study received only 12 weeks of therapy. As such, these data cannot be considered to establish long term safety among patients with ulcerative colitis who may have an increased risk of colon cancer and fracture.^{30, 31}

Although substantial research has focused on the potential anti-inflammatory effects of TZD PPAR γ ligands, their mechanism of action has not been well defined, particularly in the colon. Of particular relevance to the use of these compounds in the treatment of ulcerative colitis is the apparent ability of 5-ASA compounds to bind to PPAR γ .³² In this study, the vast majority of patients were receiving concomitant therapy with 5-ASA medications. The greater affinity to PPAR γ of rosiglitazone than 5-ASA could potentially allow for efficacy among patients inadequately treated with 5-ASA. Alternatively, the anti-inflammatory effects could be mediated by other mechanisms involving the colonic epithelium, where PPAR γ has been shown to be highly expressed², as well as through actions on other cell types such as macrophages^{33, 34}. Finally, PPAR γ receptor-independent effects of TZDs on inflammation have also been described³⁵⁻³⁷. It is interesting that large clinical trials of rosiglitazone as treatment for psoriasis, another inflammatory disease treated with similar medications, did not demonstrate efficacy, suggesting that our observation may not represent a systemic anti-inflammatory effect of TZDs³⁸.

In conclusion, we have demonstrated that short-term therapy with rosiglitazone 4 mg twice daily for 12 weeks was well tolerated and resulted in higher rates of clinical response and clinical remission than placebo for patients with mild to moderately active ulcerative colitis. As with all medications, the magnitude of anticipated benefit must be weighed against the potential for toxicity. This is particularly relevant in light of the recent data regarding the risk of myocardial infarction and fracture associated with use of rosiglitazone. Based on the evidence in this study, we believe that rosiglitazone can be used for short-term treatment of mild to moderately active ulcerative colitis, but such use should be limited to patients who have either failed or are intolerant of standard therapies. Furthermore, such therapy should not be

used in patients with liver disease, congestive heart failure, or in those at particularly high risk for myocardial infarction. Possibly due to the sample size, this study was not able to identify a particular subgroup of patients who are the most likely to benefit from therapy and/or the least likely to experience adverse effects. There will be a temptation to offer rosiglitazone as a maintenance therapy in those patients who respond to short-term treatment. Importantly, however, there are no data on the long-term efficacy and safety of rosiglitazone for maintenance of response on which to base recommendations for such an approach. Ultimately, long-term studies assessing efficacy and safety of maintenance therapy for ulcerative colitis would provide valuable information. Likewise, since large numbers of patients with diabetes are chronically treated with this class of medications at similar doses, further research is needed to better understand the mechanism of action of PPAR γ ligands in the colon given the apparent biological effect observed in this clinical trial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This study was supported by NIH grant DK059961. Drug and placebo were provided by GlaxoSmithKline.

Use of the Inflammatory Bowel Disease Questionnaire, authored by Dr. Jan Irvine was made under license from McMaster University, Hamilton, Canada.

The study was designed and conducted, the data were analyzed, and the manuscript was written independently by the investigators.

Conflict of Interest Statement:

Dr. Lewis reports having received research funding from Centocor, GlaxoSmithKline, and Takeda Pharmaceuticals North America. In addition, he has served as a consultant to Centocor, with payments being made to the Trustees of the University of Pennsylvania. He reports serving as a consultant to P&G Pharmaceuticals, Inc., Berlex, Elan, Synta, Shire, and Millenium. Dr. Lewis has served as an expert witness for legal issues for Prometheus Labs.

Dr. Lichtenstein has received research support from Abbott Corporation, Bristol-Myers Squibb Corporation, Centocor Inc., Intesco Corporation, Millenium Pharmaceuticals, Protein Design Labs, Protomed Scientific, Salix Pharmaceuticals and Shire Pharmaceuticals. He has also received consultant fees from Abbott Corporation, Axcan Corporation, Bristol-Myers Squibb Corporation, Centocor Inc., Elan, Proctor & Gamble, Prometheus Laboratories, Inc., Protein Design Labs, Protomed Scientific, Salix Pharmaceuticals, Schering-Plough Corporation, Serono, Shire Pharmaceuticals, Smith Kline Beecham Corporation, Synta Pharmaceuticals, UCB and Wyeth. Dr. Lichtenstein is on the Speaker's Bureau of the following companies: Axcan Corporation, Centocor, Inc., Proctor & Gamble, Salix Pharmaceuticals, Schering-Plough Corporation, Shire Pharmaceuticals.

Dr. Sands has received consultant fees from Centocor, Inc., Abbott Laboratories, Cerimon Pharmaceuticals, Inc., Shire and Proctor & Gamble Pharmaceuticals, Inc. He has also received research support from Centocor, Inc., Abbott Laboratories and Cerimon Pharmaceuticals Inc.

Dr. Wu has received research support from Johnson & Johnson and Centocor, Inc.

Dr. Deren reports having served as a consultant to Centocor, Inc. and UCB.

Potential investigator conflicts of interest were disclosed to patients in the informed consent process according to each institution's IRB policy.

Appendix

5

Rosiglitazone for Ulcerative Colitis Study Group Clinical Investigators

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Figure 1.
Outcome of patients screened and enrolled in the trial.

Figure 2.

a Proportion of patients achieving the primary and secondary outcomes at week 12. * $p=.03$; † $p=.01$

b Proportion of patients with improvement in the Partial Mayo Score (decrease by 2 points or greater from baseline). * $p=0.049$; † $p=0.03$; # $p=0.06$

c Proportion of patients with improvement in quality of life (IBDQ increase of 16 or more points) after 4, 8, and 12 weeks of therapy. ‡ $p=0.04$

d Proportion of patients with improvement in the individual components of the Mayo Score. Improvement was defined as a reduction of at least 1 point. Patients who withdrew from the study before week 12 were categorized as not having improvement. * $p=0.04$; † $p=0.03$; ‡ $p=0.01$.

Table 1**Components of the Mayo Score****Stool Frequency**

- 0 = Normal
- 1 = 1-2 stools/day more than normal
- 2 = 3-4 stools/day more than normal
- 3 = >4 stools/day more than normal

Rectal bleeding*

- 0 = None
- 1 = Visible blood with stool less than half the time
- 2 = Visible blood with stool half of the time or more
- 3 = Passing blood alone

Mucosal appearance at endoscopy†

- 0 = Normal or inactive disease
- 1 = Mild disease (erythema, decreased vascular pattern, mild friability)
- 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
- 3 = Severe disease (spontaneous bleeding, ulceration)

Physician rating of disease activity

- 0 = Normal
- 1 = Mild
- 2 = Moderate
- 3 = Severe

* A score of 3 for bleeding required patients to have at least 50% of bowel motions accompanied by visible blood and at least one bowel motion with blood alone.

† The mucosal appearance at endoscopy is not included in the Partial Mayo Score

Table 2

Characteristics of the 105 patients enrolled in the study

	Rosiglitazone (n=52)	Placebo (n=53)	p-value
Age (median years, IQR)	42 (31-49)	46 (34-55)	0.07
Sex (%)			0.55
Female	22 (42)	19 (36)	
Male	30 (58)	34 (64)	
Race (%)			
White	48 (92)	50 (94)	0.50
Black	2 (4)	2 (4)	
Asian	2 (4)	0 (0)	
Pacific Islander	0 (0)	1 (2)	
Smoking status			0.35
Current	2 (4)	2 (4)	
Former	8 (15)	14 (26)	
Never	42 (81)	37 (70)	
Duration of UC (median years, IQR)	6 (2.5-11)	8 (2-15)	0.21
Extent of disease			0.35
Proctitis	4 (8)	5 (9)	
Left sided	33 (63)	26 (49)	
Extensive colitis	15 (29)	22 (42)	
Duration of current flare (median weeks, IQR)	13.5 (6-41)	20 (8-52)	0.96
Baseline Mayo Score (median, IQR)	7.5 (6-9)	7 (6-9)	0.96
Concomitant medications			
Mesalamine - oral	41 (80)	41 (77)	>0.99
Mesalamine - rectal	5 (10)	7 (13)	0.76
Corticosteroids - oral	17 (33)	13 (24)	0.39
Corticosteroids - rectal	4 (8)	2 (4)	0.44
Immunomodulators use*	17 (33)	11 (21)	0.19
Prior therapies			
Mesalamine - oral	11 (21)	12 (23)	>0.99
Mesalamine - rectal	14 (27)	14 (26)	>0.99
Corticosteroids - oral	29 (56)	35 (66)	0.32
Corticosteroids - rectal	9 (17)	13 (24)	0.47
Immunomodulators use*	9 (17)	19 (36)	0.05
Anti-TNF α antibodies	9 (17)	7 (13)	0.60

* Azathioprine or 6-mercaptopurine

Table 3**Adverse events by treatment arm**

	Rosiglitazone (n=52)	Placebo (n=53)	P value
Any adverse event - N (%)	37 (71)	35 (66)	0.68
Serious adverse events - N=6 (%)	1(2)	5(9)	0.21
Worsening colitis requiring hospitalization and or colectomy	1(2)	4(8)	0.36
Other*	1(2)	1(2)	>0.99
Adverse events occurring in >5% of patients in either arm** - N (%)			
Edema	9 (17)	1 (2)	0.008
Fatigue	4 (8)	3 (6)	0.72
Fever	3 (6)	2 (4)	0.68
Constitutional symptoms - Other	5 (10)	3 (6)	0.49
Dermatology / Skin - Other	1 (2)	3 (6)	0.62
Colitis	4 (8)	6 (12)	0.74
Diarrhea	3 (6)	7 (13)	0.32
Vomiting	3 (6)	2 (4)	0.68
Gastrointestinal - Other	6 (12)	8 (15)	0.78
Infection	5 (10)	3 (6)	0.49
Musculoskeletal - Other	5 (10)	1 (2)	0.11
Abdominal pain or cramping	4 (8)	2 (4)	0.44
Arthralgia	3 (6)	2 (4)	0.68
Chest pain	3 (6)	1 (2)	0.36
Headache	10 (19)	7 (13)	0.44
Myalgia	4 (8)	0 (0)	0.06
Pain - Other	6 (12)	6 (12)	>0.99
Cough	3 (6)	3 (6)	>0.99
Proteinuria	3 (6)	3 (6)	>0.99
Decrease in hemoglobin concentration by 2gm/dl [†]	4 (8)	4 (8)	>0.99

* One case of bleeding after sigmoidoscopy biopsy and one case of depression. The latter patient underwent colectomy after withdrawal from the study.

** Categorized according to the Common Toxicity Criteria category reported by the investigator. Codes defined as other were grouped even if the free text description identified different adverse events.

[†] Five patients had missing values for baseline hemoglobin concentration