Original Article

Clinical Experience with Tumor Necrosis Factor-alpha Inhibitor Treatment for Moderate to Severe Ulcerative Colitis from a Single Institute

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Key Words
Ulcerative colitis;
Anti-tumor necrosis factor-alpha;
Biologics;
Golimumab

Topic. The clinical experience with tumor necrosis factor-alpha (TNF-α) inhibitor treatment for moderate to severe ulcerative colitis from a single institute.
Purpose. To review experiences from a single hospital in treating moderate to severe ulcerative colitis with a TNF-α inhibitor (golimumab).
Methods. We retrospectively reviewed the clinical results [Mayo score, endoscopic score, mucosal healing rate, normal and inactive mucosal disease, serum C-reactive protein (CRP) level, serum erythrocyte sedimentation rate (ESR) level, white blood cell (WBC) count, and withdraw rate of steroid usage] of patients with moderate to severe ulcerative colitis (UC) treated in the Taichung Veterans General Hospital, Taiwan from July 1982 to October 2018. Treatment outcomes were recorded regularly in the outpatient clinic. The follow-up period included the following: (a) week 0, receive the inducing dose, (b) week 4, post-treatment follow-up 1, (c) week 14, post-treatment follow-up 2, and (d) week 38, post-treatment follow-up 3.
Results. Among 107 patients diagnosed in our hospital, 23 patients (23/107, 21.5%) had moderate to severe UC and received golimumab treatment. We found significant decreases in patients' Mayo scores (mean score, from 9.6 to 3.7), endoscopic subscores (mean score, from 2.04 to 1), CRP level, WBC count, and ESR. The percentage of patients receiving steroids also decreased (from 95.7% to 38.9 %).
Conclusion. TNF-α inhibitor therapy was effective for inducing and maintaining patients' clinical response for an average follow-up of 38 weeks.
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Inflammatory bowel disease is common in Western countries but rare in Asia-Pacific areas.[1] Ulcerative colitis (UC) is an idiopathic, inflammatory gastrointestinal disease of the colon. The prevalence rate of UC in Taiwan has increased from 0.59 to 1.07 per 10^5 inhabitants/year over 12 years (1998-2010).[2] Current UC managements are based on clinical symptoms and laboratory data that guide treatment options. Treatment protocols can also be tailored for individual patients based on their response and progression.[3] Most patients with UC are in the age group of 30-40 years at diagnosis;[4] thus, hospital admission or disease burden

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could affect their jobs. Therefore, new available biological agents were introduced to help these patients and maintain their daily work. This study aimed to review experiences from a single hospital in treating moderate to severe ulcerative colitis with a tumor necrosis factor-alpha (TNF-α) inhibitor (golimumab).

Material and Methods

Ethical statements

The study was approved by an institutional review board of Taichung Veterans General Hospital. All patients provided treatment informed consent for study inclusion.

Study design and population

We retrospectively reviewed patients treated with golimumab for moderate to severe UC at the Taichung Veterans General Hospital, Taiwan from July 1982 to October 2018. We excluded patients with suspected tuberculosis infection according to results of the quantiferon test and chest imaging (TNF-α inhibitor use has been linked to re-activation of tuberculosis[5]), and those with hepatitis B and hepatitis C patients. Clinical evaluations were performed every 3 months, and blood tests and sigmoidoscopy were conducted every 6 months and 9 months, respectively. Laboratory data were collected during outpatient clinic follow-ups. Treatment outcomes were recorded in the outpatient clinic at multiple specified times.

Mayo scores/disease activity index

The Mayo scores were first described by Schroeder et al.[6] in 1987 and they are the most commonly used activity indices in placebo-controlled clinical trials for UC. The scores have four categories (rectal bleeding, stool frequency, endoscopic findings and physician assessment), and each category is rated with 0-3 points from mild to severe symptoms. The total score is the summed score of the four categories ranging from 0 to 12 points and classified into four levels: remission (0-2), mild (3-5), moderate (6-10), or severe (> 10).

Endoscopic score

The patients attended regular follow-up visits in our outpatient clinic. Colonoscopy was performed by a colorectal surgeon for the evaluation of endoscopic scores. Scores between 0 and 1 were considered a positive indicative of mucosa healing, and scores of 0 indicated normality or no mucosal disease.

Evaluation of clinical response and clinical remission

The evaluation of clinical response and clinical remission after golimumab treatments followed the definitions of the Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment (PURSUIT)[7] study group. Clinical response was defined as a decrease from baseline in the Mayo score by 30% and 3 points, accompanied by either a rectal bleeding subscore of 0 to 1 or a decrease from baseline in the rectal bleeding subscore of 1. Clinical remission was defined as Mayo score 2, with no individual subscore > 1. Mucosal healing was defined as Mayo subscore of 0 to 1.

Golimumab administration

Patients diagnosed with UC were considered to have moderate-to-severe disease activity, with Mayo scores of 6 to 12. These patients showed poor responses to any one or more of the following conventional therapies: aminosalicylates, oral corticosteroid, azathioprine (AZA), and immune-modulatory agents. After providing informed consent, patients received golimumab via subcutaneously injections as induction therapy (200-mg injection at week 0 and 100-mg injection 14 days after the first injection) and then maintenance doses (100-mg subcutaneous injections) in the following months, which is in complies with our government allowed payment guidelines.[8] For induction therapy, we prescribed aminosalicylates for combination treatment in either oral or enema form and

sometimes adjusted or de-escalated the dosage during the maintenance therapy period.

Results

Patient demographics and characteristics

The basic data of 23 patients with moderate to severe UC are shown in Table 2. The male-to-female ratio was 17:6. Patients' mean age was 54.5 years (range, 36-78 years). The mean disease duration of UC was 11 years; mean Mayo score ranged from 9 to 10, showing a moderate to severe disease condition. Based on chart reviews, nearly all of the patients (95.7%) received corticosteroids before golimumab administration, and eight patients (34.8%) received high doses of steroids. Half of them (52.1%) received immunemodulatory drugs (AZA, 11 patients; hydroxychloroquine, one patient; and adalimumab, one patient). Patients' mean CRP level, WBC count and ESR are also listed in Table 1. Two of 23 patients (8.7%) underwent an operation because of UC complications before receiving golimumab (total colectomy plus end ileostomy during diagnostic period, one patient; total colectomy plus ileo-rectal anastomosis because of bowel perforation during an outpatient clinic follow-up, one patient). There was no UC-associated cancer in this group of patients.

Clinical response and clinical remission rate

The clinical response rates for patients with moderate to severe UC are shown in Fig. 1. Great responses were found throughout the periods of induction (95.7% during week 4) and maintenance therapy (100% during week 14 and 95.7% during week 38). In one patient, another TNF-α inhibitor (adalimumab) was adjusted because of disease relapse during week 25. Median Mayo scores showed a decreasing trend from 9.6 to 3.7 after giving golimumab treatment during the 38 weeks (Fig. 2). Medication greatly improved patients' symptoms and signs. However, no patient was able to reach clinical remission during the period of induction or maintenance therapy.

Mucosa healing rate

Colonoscopic findings of endoscopic sub-scores showed improvement of mucosa healing (Fig. 3). Significant changes were found during weeks 14 and 38 compared with week 0. The normal or inactive mucosal disease rate was low (one patient, 4.5%).

Corticosteroid withdrawal rate

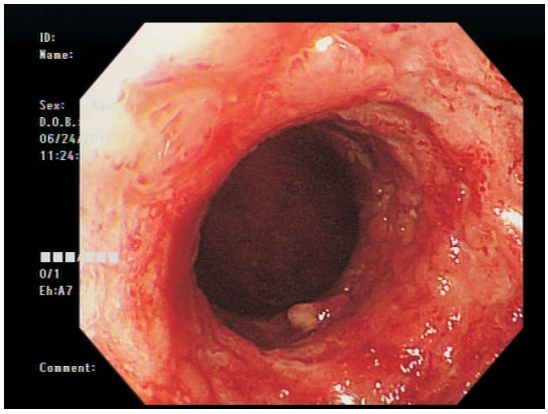
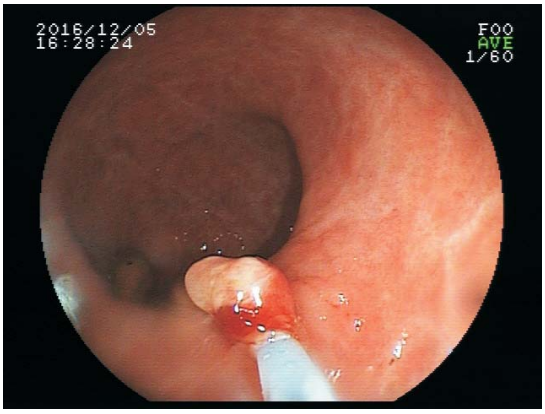
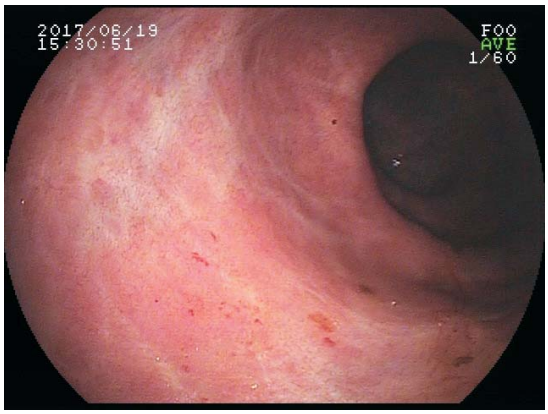
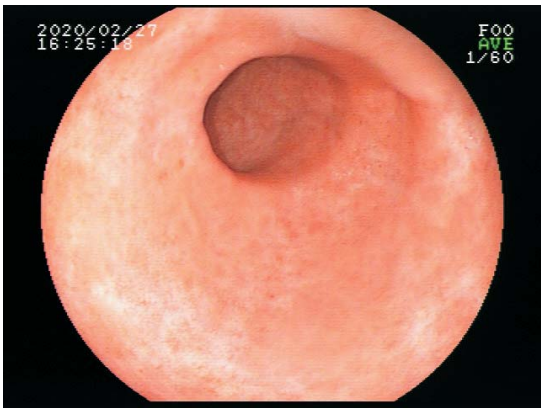
Corticosteroid usage was found in nearly all of the

Table 1. Patient demographics and characteristics

	n = 23
Age (y)	
Mean ± SD	54.5 ± 12.6
Median (IQR)	52 (43-59)
Disease duration (y)	
Mean ± SD	11.24 ± 5.04
Median (IQR)	12 (7.375-15)
Mayo score (0-12)	
Mean ± SD	9.6 ± 1.07
Median (IQR)	9 (9-10)
Endoscopy score (0-3)	
0	0%
1	13%
2	70%
3	17%
CRP level (mg/dl)	
Mean ± SD	0.97 ± 1.6
Median (IQR)	0.36 (0.06-1.01)
WBC (IU)	
Mean ± SD	8785 ± 3104
Median (IQR)	8540 (6982-10395)
ESR level (mm/hr)	
Mean ± SD	22.6 ± 17.1
Median (IQR)	18 (12.5-30.5)
Receiving any UC medications, n (%)	
Corticosteroids	22 (95.7)
≥ 20 mg/d pEq	8 (34.8)
< 20 mg/d pEq	14 (60.8)
Aminosalicylates	23 (100)
Immunomodulatory drug	12 (52.1)
Extent of disease, n (%)	
Limited to the left side of the colon	16 (70%)
Extensive	7 (30%)
Received operative treatment, n (%)	2/23 (8.7%)

SD, standard deviation; IQR, interquartile range; CRP, C-reactive protein; WBC, white blolod cell; ESR, erythrocyte sedimentation rate; UC, ulcerative colitis.

Table 2. Corresponding endoscopy images in one patient's disease process

	
Poor compliance of oral and enema form Mesalazine, subscore: 3 (2016/6)	Post discharge six months, subscore: 1 (2016/12)
	
Golimumab week 16, subscore: 2 (2017/06)	The maintenance efect of golimumab approach mucosal healing effect even at week 104, subscore: 1 (2020/2)

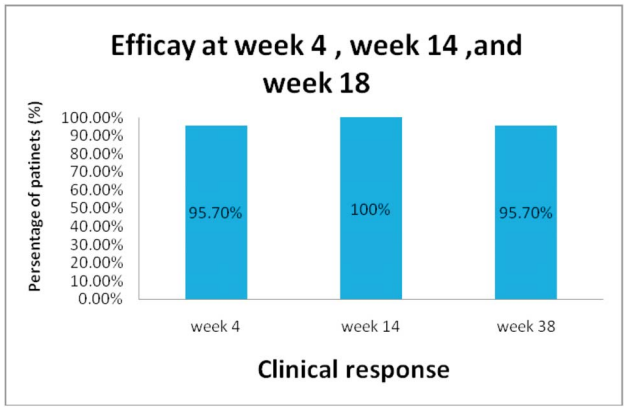


Fig. 1. The clinical response rates for patients with moderate to severe UC.

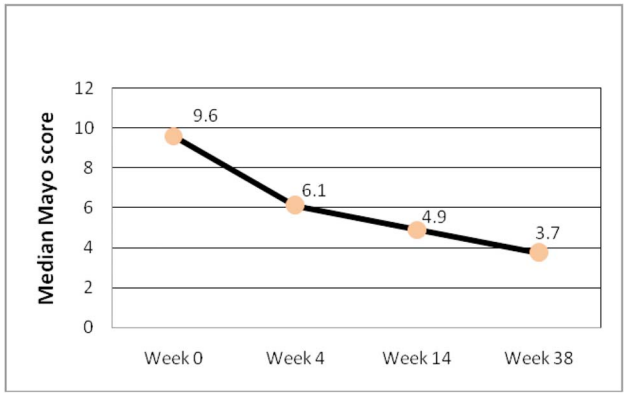


Fig. 2. Median Mayo score showed decreasing trend after giving golimumab treatment.

patients before golimumab treatment. Significant withdrawal was found during the follow-up period (Fig. 4). In the extended week 52, seven patients used steroids: one patient was given a steroid by a neurosurgeon because of an underlying pituitary tumor condition post operatively; one patient's medications were adjusted with AZA combined with a steroid; and the remaining five patients had a disease flare-up that re-

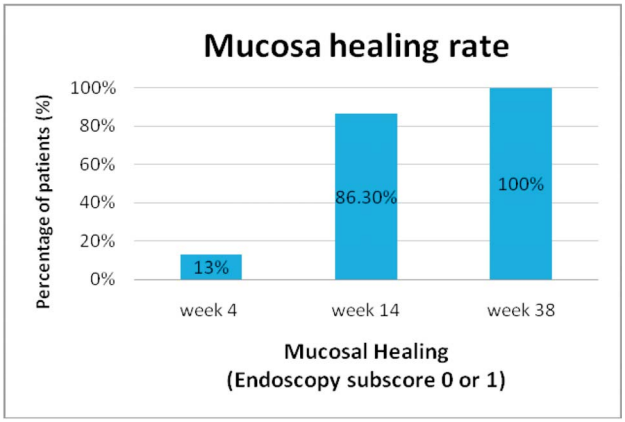


Fig. 3. Endoscopic sub-scores showed improvement of mucosal healing.

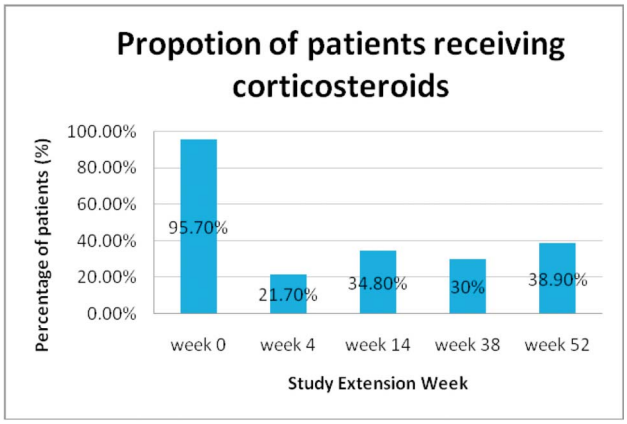


Fig. 4. Propotion of patients receiving corticosteroids decreased during the follow-up period.

quired steroid administration. We compared the steroid-free group (12 patients) with the steroid dependent-group (seven patients) in week 38 (Table 3) and tried to identify risk factors for poor response to golimumab. No inter-group difference was found, despite a longer disease duration in the steroid-dependent group than in the steroid-free group.

Biochemical data activity

CRP levels were available in 18 patients, and data showed that at a median of 31.4 weeks after induction therapy, the baseline CRP level decreased from a median of 0.91 mg/dl (range, 0.01-5.59 mg/dl) to 0.32 mg/dl (range, 0.013-2.92 mg/dl) ($p = 0.06$). ESR values were available in 15 patients, and data showed that at a median of 34.8 weeks after induction therapy, the baseline ESR decreased from a median of 23.8 mm/hr (range, 4-64 mm/hr) to 15.27 mm/hr (range, 3-59 mm/hr). WBC counts were available in 20 patients; the data showed that at a median of 32.2 weeks after induction, the WBC count decreased from a median of 8410/UL (range, 2990-14680/UL) to 8163/UL (range, 4490-11420/UL) ($p = 0.76$).

Safety

Adverse effects were observed during the study: three patients had moon faces, four had weight gain, three complained of insomnia, two had hyperglycemia, one developed a skin rash, and one had osteoporosis. No infection or malignancy was reported during treatment.

Representative case

A 37-year-old woman was diagnosed with UC since 2005. She received oral and enema forms of

Table 3. Risk factors for poor response to golimumab

Variable	Steroid free group (n = 12)	Steroid dependent group (n = 7)	*p* value
Age (y)	51.75 ± 12.91	49.86 ± 10.64	0.31
Duration (y)	10.28 ± 4.46	12.53 ± 3.63	0.08
Female sex, n (%)	4 (33.3)	4 (16.7)	0.24
Initial Mayo score	9.58 ± 0.96	9.14 ± 0.34	0.18
Initial endoscopic score	1.83 ± 0.55	2.14 ± 0.34	0.17
Initial CRP level (mg/dl)	0.86 ± 1.39	2 ± 2.46	0.25
Initial ESR level (mm/hr)	22.12 ± 17.35	24.6 ± 21.03	0.47
Initial WBC counts (IU)	8212 ± 2517	8551 ± 1853	0.41

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell.

aminosalicylates (mesalazine) but had poor compliance and irregular outpatient clinic follow-up visits. An episode of abdominal pain with bloody stool was noted since June 2016, and she was admitted to our hospital. We reviewed and adjusted her medications during the hospitalization. After discharge at 6 months, her endoscopic subscore decreased from 3 to 1. However, her condition deteriorated since Februry 2017 and became severe (Mayo score = 11). Then we administrated golimumab during the same month as induction therapy. After further follow-up, her symptoms improcvced, and the endoscopic subscore indicated mild disease (subscore = 1). Even 3 years (144 weeks) later after discontinuing golimumab treatment, the endoscopic subscore still indicated mild disease. The corresponding images are shown in Table 2.

Discussion

Golimumab was first approved for the treatment of moderate to severe UC in 2013 by the United States Food and Drug Administration (FDA) before it was included in the package benefits provided by our government's National Health Insurance system in 2016. Many biologics have been available and used in recent years.[9] However, no study in Taiwan has reported specifically on the efficacy and safety of golimumab treatment. Here, we 'performed a real world' observational study of 23 patients with moderate to severe UC who had received golimumab treatment.

Taiwan's FDA approved the use of golimumab in September 2016 for the earlier treatment of UC instead of other biologics such as adalimumab (approval: October 2016), vedolizumab (October 2017) and infliximab (August 2018).[10] Reported experiences with other biological agents are short comprehensive studies. More clinical data are available for golimumab than for other biologics.

The administration of golimumab as induction (200 mg) and maintenance (100 mg) therapies resulted in significant clinical improvements. Our study found response rates much higher than those reported in the PURSUIT trials (100% vs. 51% at week 6, 95.7% vs. 49.7% at week 54). The Mayo scores also indicated improvements in symptoms and signs. Compared with other observational trials in short term efficacy,[11-13] Detrez et al.'s study of 21 Belgian patients reported a 14% response rate at week 14 after receiving golimumab, but only 48% of them were TNF-α inhibitor naïve. Only one patient received another TNF-α inhibitor prior to our report. Nearly 96% of our patients were TNF-α inhibitor naïve, which is comparable to those enrolled in the PURSUIT trial. Bosca-Watts et al. prospectively followed 33 Spanish patients with moderate to severe UC who were treated with golimumab in several medical centers, and they reported a clinical response rate of 70% at week 14. O'Connell et al. evaluated 72 Irish patients who received golimumab, and found a response rate of 55% at week 12. None of their patients reached clinical remission (0% vs. 27.8% at week 54). Five patients experienced re-challenge with good responses; they discontinued treatment because their UC was stable and government applications for treatment were denied. The intermediate period ranges from 4 months to 8 months (mean 208 days [29.8 weeks]). The injection volume was limited by National Health Insurance regulations, and re-application of medications was considered if patients had worsening disease. Thus, further long-term follow-ups need to be conducted.

Our study showed a much higher mucosal healing rate (86.3% at week 14) than those in the literature (e.g., 19% in Detrez et al.'s trial and 42.3% in the PURSUIT trial). Endoscopy is an observer-dependent diagnostic method, with inevitable inter- and intra-observer variations.[14] Hence, it is not easy to determine the efficacy of mucosal healing using endoscopic scores. Our study also supported the efficacy of corticosteroid tapering. Corticosteroid withdrawal rates in our cohort were higher than that in the PURSUIT trial[15] (38.9% at week 52 vs. 30.5% at week 54). Our results are similar to those in the studies by Bosca et al. (29.2%, 33 patients at week 14) and Samaan et al.[16] (30%, 44 patients at week 12).

Commonly cited adverse effects associated with long-term corticosteroid exposure include hypertension; bone fracture; cataract (1%-3%); nausea, vomiting, and other gastro-intestinal conditions; and metabolic issues (eg, weight gain, hyperglycemia, and type

2 diabetes).[17] Increased risk of surgical site infection/dehiscence and postoperative mortality has also ben reported.[18] Adverse effects were limited and mild in our patients. In contrast, infections, malignancies, and tuberculosis were long-term adverse effects in the PURSUIT trial. Our evidence supports the safety of golimumab in treating UC. However, more studies are needed to confirm our results.

No review article is available on the choice of biologics after surgery to treat medically refractory UC. The current controversy regarding TNF-α inhibitor use is that it is associated with the risk of post operative peri-pouch sepsis after patients undergo ileal pouch anal anastomosis.[19] More postoperative complications and poor long-term pouch function are found in patients who undergo total colectomy and pouch reconstruction at the same time. Delayed proctectomy with pouch reconstruction appears to be better in terms of pouch function and the survival rate in the setting of preoperative TNF-α inhibitor use.

Limitations of our study are as follows. First, our study lacked data for showing a relationship between the serum golimumab concentration (SGA) and clinical response, whereas the PURSUIT trial showed a positive SGA-efficacy relationship in *post hoc* analysis.[20] Second, our study did not include the clinical response of non-TNF-α inhibitor naïve patients. Loss of response could be due to the presence of the anti-drug antibody (ADA), a mechanism well discussed in another study.[21] In the future, we will optimize dosages to treat patients based on their levels of SGA and ADA. Finally, data from a prospective comparative trial with placebo patients and intention-to-treat patients are more convincible than findings from our present retrospective non-comparative study.

Conclusions

Patients with UC are rare in Asia, although the incidence of UC has been increasing over the last 10 years. Multiple biological regimens can be used to treat patients with moderate to severe UC. Golimumab therapy is effective for inducing and maintaining a patient's clinical response.

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原　著

抗腫瘤壞死因子 α 在中重度潰瘍性大腸炎的臨床使用：從一家醫學中心的經驗

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潰瘍性大腸炎是一種特發性的腸道發炎疾病。近幾年在台灣的發病率已逐步上升，其中絕大部分為 30 歲至 40 歲的中壯族群。這些病人常因為需要藥物控制，甚至需服用長期類固醇，造成長期的併發症，進而影響工作。新型生物制劑的問世以來，一些觀察型研究顯示出有不錯的成效，但是台灣還尚未有完整的發表。因此我們蒐集院內中重度潰瘍性大腸炎的病人，評估使用抗腫瘤壞死因子 α (golimumab) 的臨床經驗，在追蹤 38 周的期間，達到有效的臨床反應，且減少使用類固醇的比例。

關鍵詞　潰瘍性大腸炎、抗腫瘤壞死因子 α、生物製劑。