Short Report

Rapid Changes in Laboratory Parameters and Early Response to Adalimumab: A Pooled Analysis From Patients With Ulcerative Colitis in Two Clinical Trials

Stephen Hanauer, a William J. Sandborn, b Jean-Frederic Colombel, c Severine Vermeire, d Joel Petersson, e Kristina Kligys, e Qian Zhou, e Andreas Lazar, f Walter Reinisch g

aNorthwestern University, Digestive Health Centre, Chicago, IL, USA bUniversity of California San Diego, Division of Gastroenterology, La Jolla, CA, USA cIcahn School of Medicine at Mount Sinai, Gastroenterology, New York, NY, USA dUniversity Hospital Leuven, Gastroenterology, Leuven, Belgium eAbbVie Inc., Global Pharmaceutical Research & Development, North Chicago, IL, USA fAbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany gMedical University of Vienna, Department for Gastroenterology and Hepatology, Vienna, Austria

Corresponding author: Stephen Hanauer, MD, Northwestern University Feinberg School of Medicine, NMH/Arkes Family Pavilion, Suite 1400, 676 N Saint Clair Street, Chicago, IL 60611, USA. Tel.: 312-695-8952; Email: shanauer@northwestern.edu

Abstract

Background and Aims: The efficacy and safety of adalimumab for induction and maintenance of clinical remission in patients with moderately to severely active ulcerative colitis were demonstrated in the ULTRA 1 and 2 clinical trials. This post-hoc, pooled analysis evaluated early changes in laboratory parameters, Mayo subscores, mucosal healing, and health-related quality of life.

Methods: Mean changes in laboratory parameters including albumin, high-sensitivity C-reactive protein, total protein, haematocrit, haemoglobin, red blood cell and platelet counts, Inflammatory Bowel Disease Questionnaire, and Short Form 36 Health Survey were evaluated from baseline to Weeks 4 and 8. Mean changes in Mayo subscores of rectal bleeding and stool frequency were evaluated from baseline to Weeks 2, 4, 6, and 8. Mucosal healing was assessed with endoscopy at baseline and Week 8. Categorical variables were evaluated with the Cochran-Mantel-Haenszel test; continuous variables were evaluated with analysis of covariance and considered significant if \( p < 0.05 \).

Results: Treatment with adalimumab significantly improved laboratory and quality-of-life measures at Weeks 4 and 8 compared with placebo \( p < 0.05 \) and \( p < 0.001 \). Mean reductions from baseline in rectal bleeding and stool frequency were significantly larger in patients receiving adalimumab compared with placebo at Week 2 and sustained through Week 8 \( p < 0.01 \). Normal mucosa at Week 8 was achieved by 13% of patients receiving adalimumab compared with 6% of those receiving placebo \( p < 0.001 \).

Conclusions: Adalimumab resulted in rapid improvements in laboratory markers and early reductions in rectal bleeding and stool frequency. Early improvement in quality-of-life scores correlated with the clinical and laboratory findings.

Key Words: Biomarkers; endoscopy; quality of life
1. Introduction

Ulcerative colitis [UC] is a chronic inflammatory bowel disease [IBD] characterised by mucosal inflammation and ulceration.\textsuperscript{1,2} Recommended treatment targets include both symptomatic and endoscopic improvement, including resolution of rectal bleeding and normalisation of bowel habits, discontinuation of steroid use, endoscopic remission, histological improvement, and avoidance of hospitalisation and colectomy.\textsuperscript{3-5} Rapid achievement of clinical response is associated with improved quality of life, and may also influence long-term outcomes.\textsuperscript{6,7} Signs of early response may appear before mucosal healing and can be used to guide clinical treatment decisions during initial weeks of therapy.\textsuperscript{8,9} Laboratory measures of inflammation, such as haemoglobin and C-reactive protein [CRP], and surrogate markers of endoscopic activity, such as rectal bleeding, can provide information on early response to treatment.\textsuperscript{10} These parameters often correlate with disease activity, and assessment of early changes can provide insight into UC treatment efficacy.

Biologic therapies, such as tumour necrosis factor α [TNF-α] monoclonal antibodies, have been shown to be effective in treating UC.\textsuperscript{11,12} The European Crohn's and Colitis Organisation guidelines recommend anti-TNF or vedolizumab as first-line biologic therapy for treatment of active UC.\textsuperscript{3} The efficacy and safety of adalimumab [anti–TNF-α] for induction and maintenance of clinical remission in adult patients with moderately to severely active UC were demonstrated in two randomized, placebo-controlled clinical trials, ULTRA 1 and 2.\textsuperscript{14,15} This post-hoc analysis evaluated early changes in laboratory parameters, Mayo subscores, and health-related quality of life in patients from ULTRA 1 and 2.

2. Methods

ULTRA 1 and 2 were phase 3, multicentre, randomised, double-blind, placebo-controlled trials that have been previously described.\textsuperscript{14,15} Briefly, adults with moderately to severely active UC, confirmed by colonoscopy with biopsy or flexible sigmoidoscopy with biopsy during screening; and a Mayo score of 6–12 with an endoscopy subscore of ≥2 despite concurrent and stable treatment with oral corticosteroids and/or immunomodulators, were randomised to receive double-blind placebo or adalimumab [160 mg at Week 0, 80 mg at Week 2, followed by 40 mg every other week]. Following a protocol amendment, ULTRA 1 had an additional adalimumab induction group of 80/40 mg at Week 0/2, but data from those patients were not included in this pooled analysis. Previous anti-TNF exposure was only allowed in ULTRA 2. Concomitant steroid use was permitted with no dosage adjustments during the first 8 weeks of the study. Primary safety and efficacy data from ULTRA 1 and 2 were reported.\textsuperscript{14,15}

Data from patients receiving placebo or adalimumab 160/80 mg induction dosing in ULTRA 1 or 2 were analysed to evaluate changes in laboratory, clinical, and quality-of-life measures. Albumin, high-sensitivity C-reactive protein [hs-CRP], total protein, haematocrit, haemoglobin, red blood cell and platelet counts, Inflammatory Bowel Disease Questionnaire [IBDQ],\textsuperscript{16} and Short Form 36 Health Survey [SF-36]\textsuperscript{17} scores were evaluated at baseline and Weeks 4 and 8.
The IBDQ was used to evaluate bowel disease-related quality of life, whereas the SF-36 was used to assess general mental and physical health. Mayo subscores of rectal bleeding [RBS] and stool frequency [SFS] were determined using the worst diary entry from the 3 days before each study visit and evaluated at baseline and Weeks 2, 4, 6, and 8. Mucosal healing, defined as Mayo endoscopy subscore [ES] of ≤1, was assessed by the site investigator at baseline and Week 8.

Figure 1. Mean change from baseline in [A] haematocrit fraction, [B] red blood cell count, [C] haemoglobin, [D] platelet count, [E] total protein, [F] albumin, and [G] hs-CRP at Weeks 4 and 8. Error bars show standard error of mean; p-values were determined using analysis of covariance with factors for treatment and baseline score. hs-CRP, high-sensitivity C-reactive protein.
Figure 2. Mayo subscore mean change [LOCF] from baseline for [A] rectal bleeding and [B] stool frequency. NRI for proportion of patients with [C] RBS ≤1, [D] SFS ≤1, [E] RBS = 0, [F] SFS = 0, and [G] ES ≤1 or 0 at Week 8. ES, endoscopy subscore; LOCF, last observation carried forward for non-missing, post-baseline values; NRI, non-responder imputation; RBS, rectal bleeding subscore; SFS, stool frequency subscore. Error bars show standard error of mean; *p-values for mean changes from baseline were determined using analysis of covariance with treatment as factor, stratification level as cofactor, and baseline value as covariate; **p-values for NRI data were determined using the Cochran-Mantel-Haenszel test. ***p < 0.001.
Changes from baseline in laboratory parameters, Mayo subscores, IBDQ, and SF-36 were compared using an analysis of covariance model. The proportions of patients achieving RBS = 0, RBS ≤1, SFS = 0, SFS ≤1, ES = 0, and ES ≤1 were compared using the chi square test. Last observation carried forward was used for missing assessments of continuous variables, and non-responder imputation was used for categorical endpoints.

3. Results

A total of 938 patients [placebo, n = 468; adalimumab, n = 470] were included in the analyses. Overall, baseline characteristics were similar between the placebo and adalimumab groups [Table 1]. Median duration of UC was 5.9 and 6.2 years for the placebo and adalimumab groups, respectively. Significant improvements from baseline in all laboratory parameters were observed at Weeks 4 and 8 with adalimumab treatment compared with placebo [Figure 1]. Significant differences in mean changes from baseline in RBS and SFS were observed in patients receiving adalimumab versus placebo as early as Week 2 [p < 0.001], and were sustained through Week 8 [Figure 2A, B]. Additionally, significantly more patients receiving adalimumab achieved RBS ≤1 or reported no blood in stool [RBS = 0] at Week 2 compared with placebo [p < 0.001; Figure 2C, E]. Significantly more patients receiving adalimumab achieved SFS ≤1 at Week 2 compared with placebo [p < 0.001], with 7% reporting a normal number of stools per day [SFS = 0]. By Week 8, 10% of patients receiving adalimumab had a normal number of stools per day compared with 5% of patients receiving placebo [Figure 2D, F]. At Week 8, significantly more patients receiving adalimumab achieved mucosal healing, as defined as ES ≤1 or ES = 0, compared with patients receiving placebo [ES ≤1, p = 0.002; ES = 0, p < 0.001; Figure 2G]. Normal mucosa [ES = 0] was achieved at Week 8 by 13% of patients receiving adalimumab versus 6% of patients receiving placebo.

Improvements from baseline in IBDQ and SF-36 physical component scores at Weeks 4 and 8 were significantly greater for the adalimumab versus the placebo group [p < 0.001; Figure 3]. Improvement from baseline in the SF-36 mental component score was significantly greater at Week 4 [p = 0.005], and numerically greater at Week 8 [p = 0.052], for the adalimumab versus the placebo group.

4. Discussion

Primary results from the ULTRA studies demonstrated that adalimumab was effective in inducing and maintaining clinical response, remission, and mucosal healing in patients with moderately to severely active UC. In this pooled, post-hoc analysis of ULTRA 1 and 2, early, significant, and clinically meaningful improvements in symptoms and changes in laboratory markers for haematological and inflammatory status were observed in patients receiving adalimumab compared with those receiving placebo. In addition, a significantly greater proportion of patients in the adalimumab group [43%] versus the placebo group [33%] achieved mucosal healing at Week 8, with 13% of patients receiving adalimumab achieving normal mucosa at Week 8.

With the increasing number of approved therapies for the treatment of UC, rapidity of response and improvements in markers of inflammation are becoming important factors when choosing a treatment option. Previous studies have shown that response to anti–TNF-α treatment after 6 to 8 weeks of induction therapy can predict long-term outcomes for patients with active disease.

![Figure 3. Mean change from baseline in (A) IBDQ score (LOCF) and (B) SF-36 physical and mental component summary scores at Weeks 4 and 8. IBDQ, Inflammatory Bowel Disease Questionnaire; LOCF, last observation carried forward; SF-36, Short Form 36 Health Survey. Error bars show standard error of mean; p-values were determined using analysis of covariance with treatment as factor, stratification level as cofactor, and baseline value as covariate.](image-url)

Because the burden of disease is high in patients with active UC, rapid changes [within days or weeks] in rectal bleeding or decreases in stool frequency are important therapeutic goals. Post-hoc analyses from the OCTAVE 1 and 2 trials demonstrated significant improvements in partial Mayo score with 10 mg tofacitinib compared with placebo starting at Week 2, and reduction from baseline in stool frequency of ≥1 by Day 3. In GEMINI I, patients with UC...
receiving vedolizumab demonstrated significant response [SFS ≤1 or RBS = 0] compared with placebo at Week 6 and as early as Week 2 in anti-TNF-naive patients. Our analysis included patients naive to ULTRA 1 and those with ULTRA 2 previous anti-TNF exposure, and demonstrated that even in this mixed population, response to adalimumab was observed as early as Week 2. The rapid decrease in rectal bleeding may be a particularly important finding, as a recent meta-analysis demonstrated endoscopic remission in patients with normal rectal bleeding subscores.

This analysis also investigated the effect of adalimumab on early changes in haematological markers at Week 4, the first assessment after therapy initiation. Anaemia is prevalent among patients with IBD, occurring in 68% of patients with IBD-associated hospitalisations. Furthermore, elevated platelet counts are observed in IBD, and a link between inflammation and coagulation in UC and Crohn’s disease was shown. Our results agree with previous studies demonstrating significant improvements in haemoglobin levels with anti-TNF therapy in patients with Crohn’s disease and other chronic inflammatory diseases. Because anaemia is correlated with disease activity, haematological parameters can be monitored with rectal bleeding and stool frequency to provide key information about therapeutic effectiveness in healing the underlying IBD.

Although these results demonstrate that adalimumab therapy in patients with UC led to early changes in patient-reported outcomes and laboratory parameters, there were limitations of the analysis. Evaluation of early mucosal improvement could not be assessed as endoscopy was only performed starting at Week 8 in ULTRA 1 and 2. Central reading was not performed, which may explain the high number of patients with mucosal healing in the placebo group; however, the placebo response in UC and/or improvements from concomitant treatment such as corticosteroids may also have contributed to this finding. Despite these limitations, consistent improvement was observed between RBS and endoscopy subscores. Early changes in laboratory biomarkers for mucosal health [e.g., faecal calprotectin and serum CRP] should be assessed in future studies. Additionally, the study design of ULTRA 1 included only 8 weeks of double-blind treatment, and therefore the long-term benefit of early response in this pooled, placebo-controlled population could not be assessed in the present study. However, subgroup analyses from ULTRA 2 demonstrated that response to adalimumab at Week 8 was predictive of positive patient outcomes at 12 months.

In summary, this analysis demonstrated that adalimumab treatment leads to early changes in inflammatory markers and laboratory parameters that correspond with early clinical and quality-of-life measures in patients with UC. These results suggest that early response may be used to guide treatment decisions in a clinical setting.

Funding
This work was supported by AbbVie Inc. The ULTRA 1 and 2 studies were funded by AbbVie Inc. The writing of this manuscript was funded by AbbVie Inc. Writing support was provided by Catherine DeBrosse, PhD, of Complete Publication Solutions, LLC [North Wales, PA, USA]. AbbVie reviewed and approved the publication.

Data Sharing
AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised, individual- and trial-level data [analysis datasets], as well as other information [e.g., protocols and clinical study reports], as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and statistical analysis plan [SAP] and execution of a data sharing agreement [DSA]. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: [https://www.abbvie.com/our-science/clinical-trials/data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html].

Conflict of Interest
SH: consulting fees from AbbVie, Actavis, Allergan, Amgen, Arena, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Celltrion, Ferring, Genentech, Gilead, GSK, Hospira, Janssen, Lilly, Merck, Nestle, Novartis, Pfizer, Prometheus, Receptos, Sanofi, Samsung Bioepis, Sanofi-Avantis, Seres Health, Shire, Takeda, Therakos; research support [Institution] from AbbVie, Allergan, Amgen, Celgene, Genentech, GSK, Janssen, Lilly, Novartis, Pfizer, Prometheus, Receptos, Sanofi-Avantis; received speaker fees from AbbVie, Janssen, Takeda. WJS: consulting fees from AbbVie, Akros Pharma, Allergan, Ambrx Inc., Amgen, Ardeleyx, Arena Pharmaceuticals, Atlantic Pharmaceuticals, Avaxia, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Conatus, Cosmo Technologies, Escalier Biosciences, Ferring, Ferring Research Institute, Forward Pharma, Galapagos, Genentech, Gilead Sciences, Immune Pharmaceuticals, Index Pharmaceuticals, Janssen, Kyowa Hakko Kirin Pharma, Lilly, MedImmune, Mesoblast, Miraca Life Sciences, Nivalis Therapeutics, Novartis, Nutrition Science Partners, Oppilan Pharma, Otsuka, Palatin, Paul Hastings, Pfizer, Precision IBD, Progenity, Prometheus Laboratories, Qu Biologics, Regeneron, Ritter Pharmaceuticals, Robarts Clinical Trials [owned by Health Academic Research Trust or HART], Salix, Seattle Genetics, Seres Therapeutics, Shire, Sigmodi Biotechnologies, Takeda, Theradag, Theravance, Tigenex, Tillotts Pharma, UCB Pharma, VCB Pharma, Vascular Biogenics, Vivelrix; research grants from Atlantic Healthcare, Amgen, Genentech, Gilead Sciences, AbbVie, Janssen, Takeda, Lilly, Genentech/Receptos; payments for lectures/speakers bureau from AbbVie, Janssen, Takeda; and holds stock/stock options in Escalier Biosciences, Oppilan Pharma, Precision IBD, Progenity, Ritter Pharmaceuticals. J-FC: consultant, advisory board member, or speaker for AbbVie, Bristol-Myers Squibb, Ferring Pharmaceuticals, Genentech, Giuliani SPA, Given Imaging, Merck, Millennium Pharmaceuticals, Pfizer, Prometheus Laboratories, Sanofi, Schering-Plough Corporation, Takeda, Teva Pharmaceuticals, UCB Pharma [formerly Cellectec Therapeutics]. SW: grant support from AbbVie, MSD, Pfizer, J&J, Takeda; speaker fees from AbbVie, MSD, Takeda, Ferring, Dr. Falk Pharma, Hospira, Pfizer, Tillotts; and served as a consultant for AbbVie, MS, Takeda, Ferring, Genentech/Roche, Shire, Pfizer, Galapagos, Mundipharma, Hospira, Celgene, Second Genome, Janssen, JP, KK, QZ, and AL are employees of AbbVie Inc., and may own AbbVie stock options. WR: lecture fees from AbbVie, Actelion, Alphawassermer, Astra Zeneca, Cellaxis, Cellerix, Cosmo Pharmaceuticals, Ferring, Genentech, Grunenthal, Johnson & Johnson, Millennium, Merck, Novo Nordisk, Nycomed, Pfizer, Pharmacosmos, Schering-Plough, Salix, Takeda, UCB Pharma, Vifor; consultant for AbbVie, Actelion, Alphawassermer, AstraZeneca, Cellerix, Cosmo Pharmaceuticals, Ferring, Genentech, Grunenthal, Johnson & Johnson, Millennium, Merck, Novo Nordisk, Nycomed, Pfizer, Pharmacosmos, Schering-Plough, Salix, Takeda, UCB Pharma, Vifor; advisory board member for AbbVie, Actelion, Alphawassermer, AstraZeneca, Cellerix, Cosmo Pharmaceuticals, Ferring, Genentech, Grunenthal, Johnson & Johnson, Millennium, Merck, Novo Nordisk, Nycomed, Pfizer, Pharmacosmos, Schering-Plough, Salix, Takeda, UCB Pharma, Vifor.

Author Contributions
All authors contributed to the interpretation of data and critical review and revision of each draft of the manuscript. All authors had access to the data and approved the final version of the article for submission, including the authorship list.
References
1. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet* 2007;369:1641–37.
2. Magro F, Gionchetti P, Eliakim R, et al.; European Crohn’s and Colitis Organisation [ECCO]. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. *J Crohns Colitis* 2017;11:649–70.
3. Harbord M, Eliakim R, Bettenworth D, et al.; European Crohn’s and Colitis Organisation. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. *J Crohns Colitis* 2017;11:769–84.
4. Magro F, Langner C, Driessen A, et al.; European Society of Pathology [ESP]; European Crohn’s and Colitis Organisation [ECCO]. European consensus on the histopathology of inflammatory bowel disease. *J Crohns Colitis* 2013;7:827–51.
5. Peyrin-Biroulet L, Sandborn W, Sands BE, et al.; Selecting Therapeutic Targets in Inflammatory Bowel Disease [STRIDE]: determining therapeutic goals for treat-to-target. *Am J Gastroenterol* 2015;110:1324–38.
6. Reinisch W, Sandborn WJ, Bala M, et al. Response and remission are associated with improved quality of life, employment and disability status, hours worked, and productivity of patients with ulcerative colitis. *Inflamm Bowel Dis* 2007;13:1135–40.
7. Ferrante M, Vermeire S, Fidder H, et al. Long-term outcome after infliximab for refractory ulcerative colitis. *J Crohns Colitis* 2008;2:219–25.
8. Feagan BG, Sandborn WJ, Lazar A, et al. Adalimumab therapy is associated with reduced risk of hospitalization in patients with ulcerative colitis. *Gastroenterology* 2014;146:110–8 e113.
9. Colombel JF, Sandborn WJ, Ghosh S, et al. Four-year maintenance treatment with adalimumab in patients with moderately to severely active ulcerative colitis: Data from ULTRA 1, 2, and 3. *Am J Gastroenterol* 2014;109:1771–80.
10. Sandborn WJ, Colombel JF, D’Haens G, et al. One-year maintenance outcomes among patients with moderately-to-severely active ulcerative colitis who responded to induction therapy with adalimumab: subgroup analyses from ULTRA 2. *Aliment Pharmacol Ther* 2013;37:204–13.
11. Narula N, Alshahrani AA, Yuan Y, Reinisch W, Colombel JF. Patient-reported outcomes and endoscopic appearance of ulcerative colitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2019;17:411–9.e3.
12. Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn’s disease. Crohn’s Disease cA2 Study Group. *N Engl J Med* 1997;337:1029–35.
13. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;353:2462–76.
14. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut* 2011;60:780–7.
15. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012;142:237–65.e1–3.
16. Guyatt G, Mitchell A, Irvine EJ, et al. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology* 1989;96:804–10.
17. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–83.
18. Murthy SK, Greenberg GR, Croitoru K, Nguyen GC, Silverberg MS, Steinhart AH. Extent of early clinical response to infliximab predicts long-term treatment success in active ulcerative colitis. *Inflamm Bowel Dis* 2015;21:2090–6.
19. Sandborn WJ, Su C, Sands BE, et al.; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2017;376:1723–36.
20. Feagan BG, Lasch K, Lissoos T, et al. Rapid response to vedolizumab therapy in biologic-naive patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2018;17:1308.
21. Gomollón F, Gisbert JP. Anemia and inflammatory bowel diseases. *World J Gastroenterol* 2009;15:4659–65.
22. Voudoukis E, Karmiris K, Kourtoulakis IE. Multipotent role of platelets in inflammatory bowel diseases: a clinical approach. *World J Gastroenterol* 2014;20:3180–90.
23. Bergamaschi G, Di Sabatino A, Albertini R, et al. Prevalence and pathogenesis of anemia in inflammatory bowel disease. Influence of anti-tumor necrosis factor-alpha treatment. *Haematologica* 2010;95:199–205.
24. Bes C, Yazici A, Soy M. Monoclonal anti-TNF antibodies can elevate hemoglobin level in patients with ankylosing spondylitis. *Rheumatol Int* 2013;33:1415–8.
25. Davis D, Charles PJ, Potter A, Feldmann M, Maini RN, Elliott MJ. Anaemia of chronic disease in rheumatoid arthritis: in vivo effects of tumour necrosis factor alpha blockade. *Br J Rheumatol* 1997;36:930–6.
26. Gnarud S, Brown A, Chefetz A, Levitan EB, Kelly CP. Meta-analysis of the placebo response in ulcerative colitis. *Dig Dis Sci* 2008;53:873–91.