HOSPITAL CHRONICLES 2020, 15(1): 24–30

ORIGINAL ARTICLE

Efficacy of Infliximab after Failure of Subcutaneous Anti-TNF Agents in Patients with Moderate to Severe Ulcerative Colitis

Nikos Viazis[1], Christos Pontas[1], George Karampekos[1], Emmanouela Tsoukali[1], Olga Giouleme[2], George Theocharis[3], Maria Tzouvala[4], Anastasia Katsoula[2], Maria Kalafateli[3], Eirini Zacharopoulou[4], Emmanouil Archavlis[1], Angeliki Christidou[1], Anastasios Manolakis[1], Gerasimos J. Mantzaris[1]

[1]Gastroenterology Department, General Hospital of Athens 'Evangelismos-Ophthalmiatreion Athinon-Polykliniki', Athens, Greece
[2]Gastroenterology – Hepatology Department, 2nd Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, Hippokrateion Hospital, Thessaloniki, Greece
[3]Gastroenterology Department, University Hospital of Patras, Greece
[4]Gastroenterology Department, Nikaia General Hospital, Athens, Greece

KEY WORDS: *ulcerative colitis; anti-TNF agents; infliximab*

Abbreviation List:
ADL: Adalimumab
Anti-TNF: anti-Tumor Necrosis Factor
GLM: Golimumab
IBD: Inflammatory Bowel Disease
IFX: Infliximab
UC: Ulcerative Colitis

Correspondence to:
Nikos Viazis MD,
31st street, number 11, 16777 Elliniko,
Athens, Greece
Tel.: +302132041609
Fax: +302132041634
E-mail: nikos.viazis@gmail.com

Manuscript received January 12, 2020;
Revised manuscript received June 02, 2020;
Accepted September 22, 2020

ABSTRACT

AIM: To assess the efficacy of infliximab in ulcerative colitis (UC) patients who had failed therapy with adalimumab or golimumab.

METHODS: Retrospective analysis of prospectively acquired data of all anti-TNF naive patients with moderate to severe UC who received adalimumab or golimumab in 4 tertiary referral centres. Patients with primary non response or secondary loss of response to adalimumab or golimumab received therapy with infliximab. Clinical response and remission rates were assessed at week 14 and 54 after initiation of infliximab.

RESULTS: Between September 2015 and September 2017, 29 of 58 (50%) anti-TNF naive patients with moderate to severe UC failed therapy with adalimumab (n=38) or golimumab (n=20). Twenty one of 29 (72.4%) patients were primary non responders and 8 (27.6%) patients lost response to adalimumab or golimumab. All these 29 patients received infliximab, while 15 (51.7%) were on concomitant azathioprine therapy. Eighteen (62.1%) and 10 (34.5%) patients showed clinical response and clinical remission at week 14 respectively, while 14 (48.3%) patients were on clinical remission at week 54 after initiation of infliximab. Azathioprine co-administration at the start of infliximab was associated with a greater proportion of patients achieving clinical remission at week 54 (10 of 15 patients on combination therapy vs 4 of 14 patients on infliximab monotherapy, p=0.04).

CONCLUSIONS: A significant proportion of anti-TNF naive patients with moderate to severe UC who have failed 1st course therapy with subcutaneous anti-TNF agents can achieve clinical response and/or remission with 2nd course therapy with infliximab.

Conflict of Interest: None declared

INTRODUCTION

Biologics against tumor necrosis factor (anti-TNF) have revolutionized the management of moderate-to-severe ulcerative colitis (UC), by inducing and maintaining clinical response and remission and decreasing the rates of complications, hospitalizations and colectomy.[1-3] In European Union countries, 3 anti-TNF agents are commercially available for the treatment of moderate-to-severe UC, namely infliximab (IFX), which is administered intravenously and adalimumab (ADL) and golimumab (GLM), which are administered subcutaneously. In randomized controlled trials and observational studies all these agents have shown efficacy in achieving remission in moderate-to-severe UC, but only IFX has been studied and proved efficacious in acute severe i.v. steroid-refractory UC, respectively.[4-9]

Despite proven efficacy, approximately one third of the patients with active UC do not respond to induction treatment with anti-TNF agents (primary non responders), whereas another one third of initial responders lose response over time (secondary loss of response).[10] Although failure to respond to 1st course anti-TNF agent does not imply a class failure, it decreases significantly the effectiveness of the 2nd course anti-TNF agents.[11] Thus, selection of and appropriate use of the most effective anti-TNF agent for the "first hit" is important. Indeed, tradition and experience have established the role of IFX as the most appropriate 1st course anti-TNF agent in UC.[12-16] However, in the absence of head-to-head, randomized, controlled trials, the selection of the appropriate anti-TNF agent for the treatment of moderate-to-severe UC in real life relies also upon patients' preferences and convenience and the necessity to reduce the workload of infusion units. This has led to an increased use of sc administered anti-TNF agents for 1st course anti-TNF treatment in ambulatory UC patients with moderate to severe disease. Whether primary non-response or secondary loss of response to ADL or GLM can be effectively re-captured with second course anti-TNF therapy with IFX has not been adequately studied. We, therefore, aimed at assessing the effectiveness of IFX as second course anti-TNF treatment in patients with moderate-to-severe UC, who did not respond primarily or developed secondary loss of response to ADL or GLM.

METHODS

This is a multicentre retrospective study which analysed prospectively acquired data on consecutive anti-TNF naove patients with moderate-to-severe UC, who were treated with ADL or GLM as first course anti-TNF therapy. Eligible were patients older than 18 years, with moderate-to-severe UC, diagnosed according to standard criteria,[17] with disease duration of at least 6 months prior to treatment, naive to anti-TNFs. Patients were not included in the study if they had active infection, latent or active tuberculosis, a history of previous demyelinating disorders or malignancies, severe heart failure, previous colectomy or any poorly controlled co-morbidity. Pregnant or breast feeding female patients were also excluded.

The study was conducted in 4 major tertiary referral IBD centres covering a large geographical area in Greece. UC was defined as extensive, left-sided or proctitis according to the Montreal classification,[18] while severity was graded according to the total Mayo score.[19] Eligible patients had active UC with a Mayo score of 6 to 9 points and more than 1 point in each of the 4 sub-scores (scores can range from 0 to 12, with higher scores indicating more severe disease activity). Previous and current use of corticosteroids and any immunosuppressive agent was recorded.

Reasons for ADL or GLM discontinuation included primary non response and secondary loss of response. Primary non response was defined as a failure to achieve a decrease from baseline in the total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the sub-score for rectal bleeding of at least 1 point or an absolute sub-score for rectal bleeding of 1. Secondary loss of response was defined as reappearance of symptoms of active UC in association with elevation of CRP at any time period between week 14 and 54 of ADL or GLM maintenance therapy, in the absence of any infection, such as clostridium difficile or cytomegalovirus.

Patients with primary non response or secondary loss of response to ADL or GLM received the classical IFX induction and maintenance therapy, i.e. 5 mg/Kg at weeks 0, 2 and 6 and then every 8 weeks until week 54. During this period, patients were assessed at each IFX infusion with physical examination, laboratory tests, partial Mayo score and a check for adverse events. Extra visits were arranged at any time recurrence of symptoms suggested a relapse of UC. Endoscopic assessment was performed at baseline, at weeks 14 and 54, and at any time recurrence of symptoms suggested a flare of disease.

Clinical response to IFX induction was assessed with the total Mayo score at week 14 and defined as a decrease from baseline of at least 3 points and at least 30% percent from baseline, with an accompanying decrease in the sub-score for rectal bleeding of at least 1 point or an absolute sub-score for rectal bleeding of 1. Clinical remission to IFX was assessed at week 14 and 54 of IFX treatment and was defined as a Mayo score of ≤ 2 with no individual sub-score >1.

STATISTICAL ANALYSIS

Statistical analysis of initial response and remission rates was limited to descriptive statistics. The X^2 test or Fisher's exact test were used for comparing qualitative variables and results were reported as numbers and percentages. Analyses were performed using SPSS software version 17.0 (Chicago, Illinois, USA) and a two-tailed p-value of <0.05 was considered statistically significant.

The study was approved by the Ethics committee of the participating Institutions; all patients gave written informed consent.

RESULTS

Between 1st September 2015 and 30th September 2017, 58 anti-TNF naive UC patients with moderate-to-severe disease were treated with ADL (n=38) or GLM (n=20) in the participating centres. The baseline characteristics of the patients are summarised in table 1. All patients had received corticosteroids at some point in time. At initiation of anti-TNF treatment, all patients were receiving oral and/or rectal mesalazine, 12 (20.7%) patients were receiving oral corticosteroids and 36 (62.1%) patients were receiving thiopurines (35 azathioprine and 1 mercaptopurine).

Overall, 21 of 58 (36.2%) patients showed primary non-response to ADL (n=13, 61.9%) or GLM (n=8, 38.1%) and another 8 patients (13.8%) developed secondary loss of response to ADL (n=7, 87.5%) or GLM (n=1, 12.5%). Among the 7 patients with secondary loss of response to ADL, ineffective dose escalation to 40mg every week had been performed in 4 patients prior to cessation of therapy.

Thus, 29 patients were started on IFX. The baseline characteristics of these patients are summarised in table 2. None of the patients was receiving corticosteroids at the time of IFX initiation, while all 29 were receiving oral and/or rectal mesalazine and 15 (51.7%) patients were also receiving azathioprine.

TABLE 1. Baseline characteristics of patients receiving subcutaneous anti-TNF

Males/females, n (%)	31 (53.4%)/27 (46.5%)
Adalimumab/Golimumab, n (%)	38 (65.5%)/20 (34.5%)
Age (years), median (range)	40.6 (19-78)
Disease extent, n (%)	E1 = 1 (1.7%) E2 = 32 (56.1%) E3 = 25 (43.1%)
Disease duration (months), median (range)	38.6 (6-72)
Smokers/non-smokers, n (%)	19 (32.7%)/39 (67.2%)
Corticosteroids, n (%)	12 (20.7%)
5-ASA, n (%)	Per os = 58 (100%) Per rectum = 44 (75.8%)
Immunosuppressants, n (%)	Azathioprine = 35 (60.3%) 6-mercaptopurine = 1 (1.7%)

TABLE 2. Baseline characteristics of patients receiving Infliximab

Males/females, n (%)	16 (55.2%) /13 (44.8%)
Age (years), median (range)	38.9 (21-69)
Disease extent, n (%)	E2 = 18 (62.1%) E3 = 11 (37.9%)
Disease duration (months), median (range)	34.8 (6-67)
Smokers/non-smokers, n (%)	8 (27.5%) /21 (72.4%)
Corticosteroids, n (%)	0 (0%)
5-ASA, n (%)	Per os = 29 (100%) Per rectum = 19 (65.5%)
Immunosuppressants, n (%)	Azathioprine = 15 (51.7%)

Eighteen (62.1%) patients were responders to IFX induction therapy at week 14, while 10 (34,5%) and 14 (48.3%) patients were in clinical remission at week 14 and 54 respectively (Fig. 1). The median full Mayo score at baseline was 9 (Interquantile range 2, Fig. 2) versus 5 (Interquantile range 5, Fig. 3) at week 14 and 3 (Interquantile range 3.5, Fig. 4) at week 54. At baseline, 26 (89.6%) patients had an elevated C-reactive protein (CRP >5mg/L), while the number of patients presenting with CRP >5mg/L at weeks 14 and 54 were 13 (44.8%) and 7 (24.1%) respectively.

The proportion of patients who were either non-responders (11 out of 21, 52.4%) or lost response to ADL or GLM (3 out of 8, 37.5%) and achieved clinical remission after 2nd course anti-TNF therapy with IFX, at week 54, was not significant

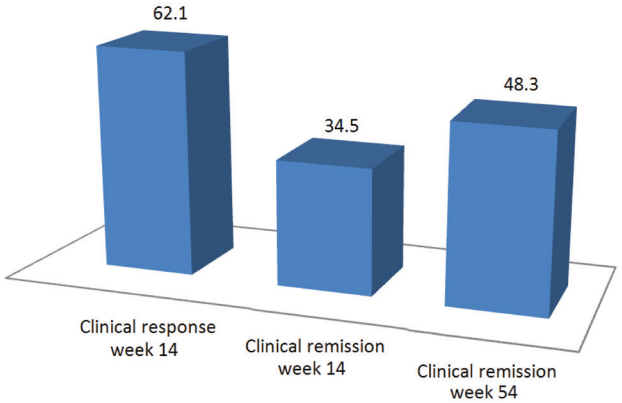

FIGURE 1. Proportion of patients treated with Infliximab achieving clinical response at week 14 and clinical remission at weeks 14 and 54.

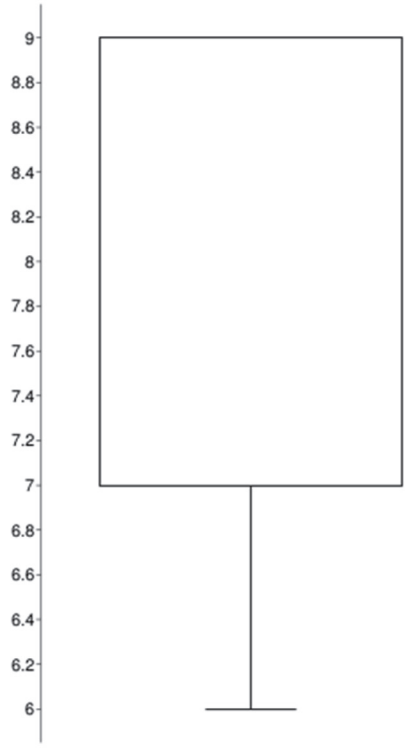

FIGURE 2. Median full Mayo score and interquantile range at baseline for patients receiving Infliximab.

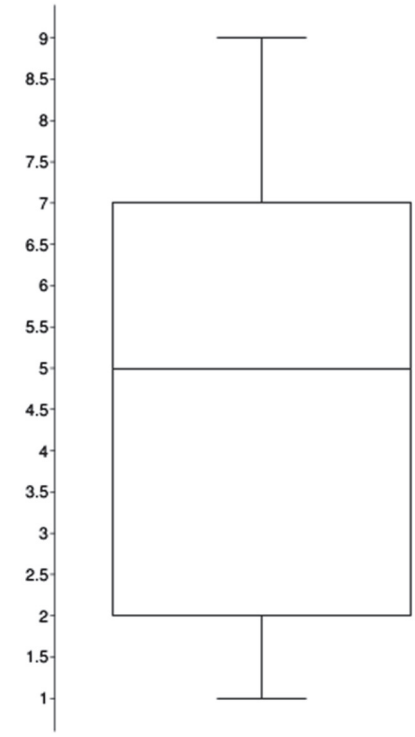

FIGURE 3. Median full Mayo score and interquantile range at week 14 for patients receiving Infliximab.

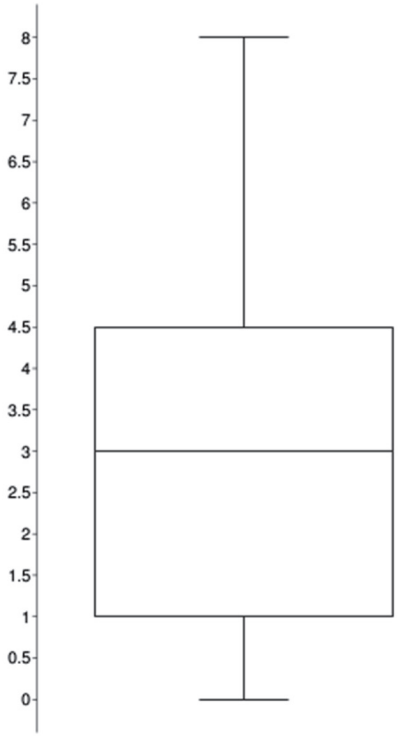

FIGURE 4. Median full Mayo score and interquantile range at week 54 for patients receiving Infliximab.

(p=0.47). However, concomitant treatment with azathioprine at initiation of IFX was associated with a greater proportion of clinical remission at week 54 (10 of 15 patients receiving azathioprine achieved clinical remission vs 4 of 14 patients on IFX monotherapy, p=0.04).

Seven of the 11 (37.9%) patients who did not show a satisfactory clinical response to IFX at week 14, received a dose escalation (10mg/Kg every 8 weeks) for maintenance; 4 patients responded to dose intensification, but 2 patients were switched to vedolizumab and 1 patient opted to colectomy.

IFX administration was safe and no serious adverse reactions were seen. One patient developed a psoriasiform rash at his palms, which responded to local treatment and IFX administration was not discontinued.

DISCUSSION

In this study, anti-TNF naive patients with UC of moderate-to-severe activity who failed 1st course treatment with the subcutaneously administered anti-TNF agents ADL and GLM could be successfully recaptured with 2nd course therapy with IFX. Indeed, among the 29 patients who developed primary non response or secondary loss of response to ADL or GLM, 18 (62.1%) and 10 (34.5%) patients showed clinical response

and clinical remission at week 14 respectively, while 14 (48.3%) patients were on clinical remission at week 54 after initiation of IFX. Continuing azathioprine at initiation of IFX was associated with a significantly greater proportion of patients achieving clinical remission at week 54.

Confusion regarding the position of biologics in treatment algorithms for moderate-to-severe UC has increased due to the advent of additional anti-TNF molecules, biologics which target non anti-TNF inflammatory pathways, the approval of biosimilars to anti-TNF originators and approval of small molecules.[20] Studies based on propensity score matching of patients treated with different class biologics cannot deliver a robust proposal for selecting one class of biologic over the other and until prospective, randomized, head-to-head studies are available the selection of the most appropriate treatment for the individual patient relies on rather arbitrary criteria, such as physician experience and preferences, patient preferences and cost of treatment. However, it has been quite clear that inappropriate selection and use of the first biologic agent for the individual patient undermines the future course of disease and the response to subsequent biologics.[11-16]

Accumulated data from randomized controlled trials, real-life studies and data from meta-analyses provide the best long term evidence that all approved anti-TNF agents are effective in inducing and maintaining corticosteroid free remission and mucosal healing in patients with moderate-to-severe UC.[20-22] In the ACT 1 and ACT 2, IFX achieved significantly higher rates of clinical remission over placebo at week 8 of treatment (35% and 31% vs 15% and 6% in ACT 1 and ACT 2 studies, respectively) and sustained remission was achieved during the entire study period in 20% of patients on IFX vs 5% of patients on placebo.[4] Real life data from major referral centres have confirmed the results of randomized, controlled trials.[23,24] In the ULTRA 1 and 2 randomized, controlled trials the classical dosing regimen of ADL (160/80mg subcutaneously at weeks 0 and 2, followed by 40mg subcutaneously every 2 weeks) achieved and maintained significantly higher annual rates of remission over placebo (17% vs 9%, respectively).[6,7] Difference in remission rates was even higher for biologic naive patients (22% vs 10% for ADL and placebo treated patients, respectively). Finally, in the PURSUIT trials, GLM resulted in a greater proportion of patients achieving clinical remission at week 6, following induction therapy with 200/100mg or 400/200mg compared to placebo (51% and 55% vs 30% respectively).[8] In the PURSUIT-M, 464 patients with moderate-to-severe UC, who had responded favourably to GLM in the induction trial demonstrated greater efficacy over placebo at maintaining clinical remission at week 54 (42% vs 27% respectively).[9] However, with the exception of the dominant role of IFX as rescue therapy for iv corticosteroid refractory UC,[25] the crucial selection of the most appropriate of the available anti-TNF agents for the first treatment of ambulatory patients with moderate-to-severe UC remains, as said before, arbitrary.[26,27]

A recent meta-analysis of eight randomized controlled trials in IBD patients who have failed first line biologic therapy with an anti-TNF agent stratified response to second-line biologic by reason for discontinuing anti-TNF therapy [primary non-response vs. secondary loss of response vs. intolerance].[12] This study revealed that patients with primary non-response to atni-TNF therapy were 24% (RR, 0.76 [0.61– 0.96]) and 27% (RR, 0.73 [0.56–0.97]) less likely to achieve remission with second-line biologics compared to patients who discontinued anti-TNF for intolerance or secondary loss of response to first line anti-TNF, respectively. Another systematic review with meta-analysis focusing on the efficacy of a second anti-TNF in IBD patients, whose previous anti-TNF treatment has failed, identified only six studies in UC, in which all patients had received IFX and switched to ADL, with remission rates varying from 0 to 50%.[11] Thus, we think that our study is the first in the literature to report on the clinical response and remission rates of patients with moderate-to-severe UC receiving IFX after failure of ADL or GLM. According to our results, IFX appears to be effective in this setting, independent of the reason for failure of ADL or GLM (primary non response or secondary loss of response).

In our study azathioprine co-administration at the initiation of treatment with IFX was associated with a greater proportion of patients achieving clinical remission at week 54. This effect may be due to a higher synergistic effect of azathioprine with IFX than with ADL or GLM, but also to interference of azathioprine in pharmocodynamics and pharmacokinetics of IFX, such as preventing anti-drug antibodies by down-regulating the immunogenic effect of IFX (a chimeric antibody of proven higher immunogenicity than ADL or GLM), decreasing the metabolism of IFX, increasing the recycling rates of IFX via the neonatal FCn receptor, by reducing the production of endogenous IgG, etc.[28] Higher rates of efficacy of the combination therapy with IFX and azathioprine have been documented in the SONIC trial in biologic naive patients with Crohn's disease,[29] as well as in the UC-SUCCESS trial in patients with UC.[30] Following these results, in many centres therapy is initiated with both combined thiopurine and anti-TNF administration, while thiopurines are then discontinued after 6 months in the setting of clinical and biochemical remission, a strategy which has been supported in the literature mainly for patients with Crohn's disease.[31] Although it could be argued that adding an anti-TNF biologic to pre-existing treatment with azathioprine does not increase the short term efficacy of the anti-TNF agent, as was shown in several post-hoc analyses of randomized controlled trials with IFX, ADL or GLM,[32] this scenario is entirely different from what we have observed in this study, in which IFX has replaced a failing first line subcutaneously administered anti-TNF agent. On the other hand we cannot exclude a chance observation due to the small number of patients on combination IFX plus azathioprine therapy.

Our study has several limitations, mainly its retrospective design and lack therapeutic drug monitoring. However, we think that there are also strong points, since all data were acquired prospectively, treatment in the participating centres followed strict evidence-based rules, the study population was homogenous as regards ethnicity, social class and residence, while the total Mayo score with colonoscopy was used to document response to therapy.

In conclusion, a significant proportion of anti-TNF naive patients with moderate to severe UC who have failed 1st course therapy with subcutaneous anti-TNF agents can achieve clinical response and/or remission with 2nd course therapy with IFX.

REFERENCES

1. Nielsen OH, Ainsworth MA. Tumor necrosis factor inhibitors for inflammatory bowel disease. *N Engl J Med* 2013;369:754–62.
2. Sandborn WJ, Rutgeerts P, Feagan BG, et al. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. *Gastroenterology* 2009;137:1250–1260.
3. Gisbert JP, Gonzalez-Lama Y, Maté J. Systematic review: infliximab therapy in ulcerative colitis. *Aliment Pharmacol Ther* 2007;25:19–37.
4. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;353:2462-2476.
5. Laharie D, Bourreille A, Branche J, et al. Long term outcome of patients with steroid-refractory acute severe UC treated with ciclosporin or infliximab. *Gut* 2018;67:237-243.
6. 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; 142:257-265.
7. 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;109:1771-1780.
8. Sandborn WJ, Feagan BG, Marano C, et al; PURSUIT-SC Study Group. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014;146:85-95.
9. Sandborn WJ, Feagan BG, Marano C, et al; PURSUIT-Maintenance Study Group. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014;146:96-109.
10. Papamichael K, Gils A, Rutgeerts P, et al. Role for therapeutic drug monitoring during induction therapy with TNF antagonists in IBD: evolution in the definition and management of primary non-response. *Inflamm Bowel Dis* 2015;21:182–197.
11. Gisbert JP, Marin AC, McNicholl AG, Chaparro M. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. *Aliment Pharmacol Ther* 2015;41:613–623.
12. Singh S, George J, Boland B, Vande Casteele N, Sandborn WJ. Primary Non-Response to Tumor Necrosis Factor Antagonists is Associated with Inferior Response to Second-line Biologics in Patients with Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis. *Journal of Crohn's and Colitis* 2018;12:635–643.
13. Peyrin-Biroulet L, Laclotte C, Roblin X, Bigard MA. Adalimumab induction therapy for ulcerative colitis with intolerance or lost response to infliximab: an openlabel study. *World J Gastroenterol* 2007;13:2328–2332.
14. Oussalah A, Laclotte C, Chevaux JB, et al. Long-term outcome of adalimumab for ulcerative colitis with intolerance or lost response to infliximab: a single-centre experience. *Aliment Pharmacol Ther* 2008;28:966–972.
15. Taxonera C, Estelle´s J, Fernandez-Blanco I, et al. Adalimumab induction and maintenance therapy for patients with ulcerative colitis previously treated with infliximab. *Aliment Pharmacol Ther* 2011;33:340–348
16. Olivera P, Danese S, Pouillon L, Bonovas S, Peyrin-Biroulet L. Effectiveness of golimumab in ulcerative colitis: A review of the real world evidence. *Dig Liver Dis* 2019;51:327-334.
17. Magro F, Gionchetti P, Eliakim R, et al. 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;11:649–670.
18. Silverberg M, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Ulcerative colitis clinical classification. *Can J Gastroenterol* 2005;19(Suppl. A):9A–13A.
19. D'Haens G, Sandborn WJ, Feagan BG, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology* 2007;132:763–786.
20. Reinglas J, Gonczi L, Kurt Z, Bessissow T, Lakatos P. Positioning of old and new biologicals and small molecules in the treatment of inflammatory bowel diseases. *World J Gastroenterol* 2018;24:3567-3582.
21. Vickers A, Ainsworth C, Mody R, et al. Systematic Review with Network Meta-Analysis: Comparative Efficacy of Biologics in the Treatment of Moderately to Severely Active Ulcerative Colitis. *PLoS One* 2016; DOI:10.1371/journal.pone.0165435 October 24.
22. Danese S, Fiorino G, Peyrin-Biroulet L, et al. Biological agents for moderately to severely active ulcerative colitis: a systematic review and network meta-analysis. *Ann Intern Med* 2014;160:704-711.
23. Reinisch W, Van Assche G, Befrits R, et al. Recommendations for the treatment of ulcerative colitis with infiximab: a gastroenterology expert group consensus. *J Crohns Colitis* 2012;6:248-258.
24. Beigel F, Deml M, Schnitzler F, et al. Rate and predictors

of mucosal healing in patients with inflammatory bowel disease treated with anti-TNF-alpha antibodies. *PLoS One* 2014;9:e99293.
25. Järnerot G, Hertervig E, Friis-Liby I, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo controlled study. *Gastroenterology* 2005;128:1805-1811.
26. Bressler B, Marshall J, Bernstein C, et al. Toronto Ulcerative Colitis Consensus Group. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. *Gastroenterology* 2015;148:1035-1058.
27. Feuerstein J, Nguyen G, Kupfer S, Falck-Ytter Y, Singh S; American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute guideline on therapeutic drug monitoring in inflammatory bowel disease. *Gastroenterology* 2017;153:827–834.
28. Mantzaris GJ. Thiopurines and methotrexate use in IBD patients in a Biologic Era. *Curr Treat Options Gastroenterol* 2017;15:84-104.
29. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine or combination therapy for Crohn's disease. *N Engl J Med* 2010;362:1383-1395.
30. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology 2014;146:392-400.
31. Drobne D, Bossuyt P, Breynaert C, et al. Withdrawal of immunomodulators after co-treatment does not reduce trough level of infliximab in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2015;13:514-521.
32. Mao E, Hazlewood G, Kaplan G, Peyrin-Biroulet L, Ananthakrishnan A. Systematic review with meta-analysis: comparative efficacy of immunosuppressants and biologics for reducing hospitalisation and surgery in Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther* 2017;45:3-13.