MANAGEMENT OF ULCERATIVE COLITIS: PUTTING PATIENTS AT THE CENTRE

Summary of presentations from the Takeda-sponsored symposium at the 11th Congress of the European Crohn's and Colitis Organisation, held in Amsterdam, Netherlands on 18th March 2016

Chairperson

Iris Dotan[1]

Speakers

Peter Irving,[2] David T. Rubin[3]

1. Tel Aviv Sourasky Medical Center and the Sackler School of Medicine, Tel Aviv, Israel
2. Guy's and St Thomas' NHS Foundation Trust, London, UK
3. Section of Gastroenterology, Hepatology and Nutrition, University of Chicago Medicine Chicago, Illinois, USA

Disclosure: Iris Dotan has been a consultant for and received grant support from AbbVie, Janssen, Takeda, Pfizer, Genentech, Rafa Laboratories, Protalix, Ferring, and Given Imaging. She has undertaken speaking and teaching engagements for AbbVie, Janssen, Takeda, Genentech, Ferring, Falk Pharma, Merck Sharp & Dohme, and Given Imaging. Peter Irving has received grant support from Merck Sharp & Dohme and Takeda, and has been a consultant for AbbVie, Merck Sharp & Dohme, Takeda, Warner Chilcott, Vifor Pharma, Pharmacosmos, Topivert, Genentech, Hospira, Tillotts, and Symprove. He has taken part in Speaker Bureau activities for AbbVie, Falk Pharma, Ferring, Merck Sharp & Dohme, Takeda, Warner Chilcott, Johnson and Johnson, and Shire. David Rubin has been a consultant for AbbVie, Amgen, Celgene, Janssen, Pfizer, Prometheus, Takeda, and UCB. He has been a board member of the ACG Board of Trustees and is the VP of Cornerstones Health Incorporated, a non-profit medical education organisation.
Acknowledgements: Writing assistance was provided by Stephanie Gibson, PhD, Ashfield Healthcare Communications Ltd.
Support: The publication of this article was funded by Takeda. The views and opinions expressed are those of the speakers and not necessarily of Takeda.
Citation: EMJ Gastroenterol. 2016;5[Suppl 6]:12-19.

MEETING SUMMARY

The treatment landscape of ulcerative colitis (UC) is changing, with new treatment options becoming available and insights into disease management demonstrating the importance of a patient-centric approach. Induction and maintenance of long-term remission are important treatment goals. However, some of the current treatment options often have limited efficacy, which may be coupled with an unfavourable safety profile, such as an increased risk of infection. A multiphase approach to disease management, which includes induction and maintenance of remission through close monitoring, is a viable clinical strategy. Selecting an appropriate first-line therapy is a crucial part of this strategy, as options are sometimes limited for patients who have failed anti-tumour necrosis factor (TNF) therapy. The integrin antagonist, vedolizumab, has demonstrated effective induction and maintenance of clinical remission in both anti-TNF-naïve and anti-TNF-failure patients, with no increase in infection risks. Therefore, vedolizumab should be considered for inducing and maintaining remission as part of a patient-centric disease management programme. The development of simplified monitoring systems that provide an indication of endoscopic activity will also aid patients in taking charge of their disease management. In conclusion, putting our patients at the centre of a proactive model of disease management can help prevent complications in the long-term, and selecting suitable first-line therapies is an important step in this process.

Introduction

Doctor Iris Dotan

Management of UC is changing. Until 2013, mesalazine (5-aminosalicyclic acid) and steroids were the most commonly used treatments.[1] However, the advent of new treatments, advances in surgical procedures, and new approaches to disease management including the use of multidisciplinary teams, means that we now have a broader range of options for our patients. This meeting explored methods of implementing these strategies into a framework that will benefit patients and involve them in their disease management.

Partnering with Patients to Optimise Treatment Outcomes in Ulcerative Colitis

Doctor Peter Irving

There have been rapid advances in the management of inflammatory bowel disease (IBD) in the past 15 years. This has been partly driven by the development of new treatments and firmer remission endpoints being defined. However, an unmet need remains for the management of active UC. Many patients have ongoing disease activity, and approximately 50% of UC patients will have an unfavourable disease course.[2] With current medical treatment, 50% of patients relapse within the first year after diagnosis, and after 3–7 years 18% of patients experience a relapse every year.[3] These relapses cause significant disruption in the lives of patients with UC, with a recent survey indicating that ~45% of patients spend more time at home and ~40% cut back on their social life or change their work life to compensate for UC.[4] Considering the impact on the patient is crucial, as physicians often underestimate the effect of UC on individuals' lives and mental wellbeing.[5]

Several options are currently available for the treatment of UC. While steroids are effective induction agents, they are inappropriate for maintenance therapy.[1] This class of drug is associated with side effects such as acne, osteoporosis, and Cushing's syndrome, and as a result steroids are disliked by both patients and physicians.[1] In contrast, thiopurines have been shown to be inefficient as induction agents.[6] A meta-analysis of seven studies indicated that thiopurines were beneficial in maintaining clinical remission with an odds ratio (OR) of 2.56 (95% confidence interval [CI]: 1.51–4.34) showing that treatment favours azathioprine plus mercaptopurine versus placebo or mesalazine.[6] However, this class of drug demonstrated no benefit in induction of remission versus placebo.[6]

Current treatment regimens using therapies such as thiopurines or TNF antagonists have been associated with limited efficacy. The randomised, double-blind, UC SUCCESS trial evaluated the efficacy of 16 weeks of treatment with the TNF antagonist; infliximab; the thiopurine, azathioprine; or a combination of the two drugs. The study included both patients who had failed previous anti-TNF therapy, and anti-TNF-naïve patients. Overall, 40% of patients treated with infliximab and azathioprine achieved steroid-free remission at Week 16, compared with 24% of patients treated with azathioprine (p=0.032) and placebo, and 22% of patients treated with infliximab and placebo (p=0.017).[7] In the randomised, multicentre, double-blind, placebo-controlled, Phase III ULTRA 2 study, anti-TNF-naïve and anti-TNF-failure patients were treated with adalimumab or placebo. The proportion of patients treated with adalimumab who were in clinical remission at Week 8, defined as a Mayo score of ≤2 with no individual subscore of ≥1, was 9.2% in anti-TNF-failure patients and 21.3% in anti-TNF-naïve patients.[8] At Week 52, 10.2% of anti-TNF-failure patients and 22.0% of anti-TNF-naïve patients were in clinical remission.[8] While response rates were low, they were significantly greater than placebo in anti-TNF-failure patients at Week 52, and in naïve patients at both Week 8 and Week 52.[8] The TNF antagonist, golimumab, was investigated as a maintenance therapy in the PURSUIT study versus placebo.[9] The results of this Phase III, double-blind study show that golimumab maintenance therapy at 50 mg and 100 mg doses produced significantly greater rates of durable clinical remission (23.2% and 27.8%, respectively), compared with patients treated with placebo (15.6%, p<0.05).[9] However, the overall rates of response to therapy were still low.[9]

Along with limited efficacy, some of the current therapies have been associated with safety and tolerability issues. The TREAT Registry indicates that patients with Crohn's disease treated with prednisone therapy (hazard ratio [HR]: 1.57; 95% CI: 1.17–2.10, p=0.002) or narcotic analgesic treatment (HR: 1.98; 95% CI: 1.44–2.73, p<0.001) had an increased risk of developing a serious infection.[10]

TNF antagonists have also been shown to double the risk of developing an infection. A meta-analysis of 22 randomised controlled studies found that the relative risk of developing an opportunistic infection with an anti-TNF drug was 2.05 (95% CI: 1.10–3.85) compared with placebo.[11] Safety issues associated with thiopurines include an increased risk of developing skin cancer and lymphoma. A prospective, observational study in 19,486 IBD patients found that treatment with azathioprine increased the risk of developing lymphoma with a yearly incidence rate of 5.41 per 1,000 patient/years of lymphoma in patients >65 years who are on continuing therapy.[12] An increased risk of non-melanoma skin cancer was also associated with thiopurine therapy, with a yearly incidence rate in patients >65 years of 4.04 per 1,000 patient/years in those on therapy and 5.70 per 1,000 patient/years in patients who discontinued therapy.[13]

UC is a progressive disease and it is important to not only treat patients, but to treat beyond the symptoms despite the limited efficacy and unfavourable safety profiles of some therapeutic options. As UC progresses, the risk of developing colorectal cancer increases.[14] Increases in the colonoscopic inflammation score or histological inflammation score are significantly associated with an increased risk of colorectal cancer.[15] Additionally, physicians need to be aware that early treatment outcomes can be predictive of the long-term course of the disease.[16] A multivariate analysis of a cohort of patients with moderate-to-severe, newly-diagnosed UC found that patients with a complete response to treatment at Month 3 had a significantly lower likelihood of hospitalisation (p=0.033) or immunosuppression therapy (p=0.0029) at 5-year follow-up, compared with patients who had partial or no response at Month 3.[16] A cohort of patients in Norway also demonstrated that long-term mucosal healing can significantly reduce the numbers of colectomies and resections in UC patients at 1 year (p=0.02).[17] Therefore, patients who are in remission earlier are more likely to have favourable outcomes in later years.[16,17]

Aiding patients in monitoring their disease themselves can be beneficial in ensuring that therapeutic intervention occurs in a timely fashion. For example, utilising non-invasive disease markers can be a useful strategy for self-monitoring. The biomarker faecal calprotectin has 91% sensitivity and 90% specificity for endoscopic activity. Analysis of faecal calprotectin levels can be carried out by patients at home, allowing them to actively participate in their disease management.[18]

In conclusion, UC is an active disease with a substantial impact on patients' quality of life. While the treatment landscape is changing with more therapies becoming available, issues with the efficacy and safety of current treatments remain. Despite the current unmet needs regarding treatment of UC, it is important to manage active disease in patients to reduce the risk of later complications.

Biologic Therapy Options for Ulcerative Colitis in a Patient-Centric Treatment Paradigm

Professor David T. Rubin

Currently, not all patients achieve the preferred treatment outcomes. This could be due to therapy being initiated too late, the limited efficacy of therapies, therapies not being optimised, an incorrect diagnosis, or the patient simply being satisfied with an improvement in symptoms. It is important to realise that treatment for UC is not 'one size fits all'. In addition, current treatment algorithms require patients to either fail treatment or experience adverse events before switching. This stepwise approach to treatment has been shown to be inadequate and unhelpful for patients. Treatment algorithms for UC are now evolving to reflect this, and shifting towards treat-to-target with less emphasis on systemic treatment and more on targeted therapies.[19-21] When initiating therapy, it is important to analyse the risks and benefits of a therapy, optimise treatment, and to avoid ignoring active inflammation. A five phase management system can be used to help control chronic diseases such as UC: pre-treatment assessment, induction, maintenance, monitoring, and cessation.[22]

PRE-TREATMENT ASSESSMENT

Early aggressive therapy should be considered in patients with UC who display predictors of poor medical response. These predictors can be broadly separated into two categories: quantifiable predictors and symptomatic indicators. Quantifiable predictors of poor medical response include low serum albumin, erythrocyte

sedimentation rate >30 mm/hour, heart rate >90 bpm, and increased C-reactive protein.[23,24] In addition, prolonged flare, active infections, severe endoscopic lesions, and a high percentage of bloody stools can be symptomatic predictors of poor medical response.[23,24]

INDUCTION AND MAINTENANCE

An appropriate treatment should be selected and initiated based on the patients' needs. Several treatment options are available including steroids, TNF-antagonists, cyclosporine, and integrin antagonists. As discussed in the previous presentation, certain treatment options are more appropriate for the induction of remission or for its maintenance. These treatment goals need to be considered alongside a patient's treatment history when initiating a new therapy.

In patients with steroid-refractory UC, treatment options are more limited. The use of cyclosporine or the anti-TNF therapy, infliximab, in patients with severe UC that had been unsuccessfully treated with steroids showed similar efficacy.[25] Data from the CYSIF study demonstrated that the 1-year, colectomy-free survival rates were similar for cyclosporine (71%) and infliximab (70%).[26] This similarity was maintained for the 5-year, colectomy-free survival rates of 62% versus 65%, respectively.[26]

An alternative treatment for patients with moderate-to-severe UC is anti-α4 integrins. Vedolizumab is a monoclonal antibody that targets the α4β7 integrin in the gut-tropic T cell and prevents migration of the lymphocyte into the gut mucosa.[27] In the Phase III, randomised, double-blind, placebo-controlled GEMINI I study, patients received either vedolizumab 300 mg or placebo intravenously at Weeks 0 and 2 in cohort 1, and a second cohort (cohort 2) received open-label vedolizumab at Weeks 0 and 2, with disease evaluation at Week 6.[28] Patients in either cohort who responded to vedolizumab were randomised to receive either vedolizumab or placebo every 8 or 4 weeks for up to 52 weeks. A response was defined as a reduction in Mayo Clinic score of ≥3 and a reduction from baseline of ≥30%, in addition to an accompanying reduction in rectal bleeding subscore of ≥1 or an absolute rectal bleeding subscore of 0 or 1.

Both anti-TNF-naïve and anti-TNF-failure patients were enrolled in the study. Vedolizumab met the primary induction endpoint of the study as it demonstrated significant improvement in clinical response at Week 6 in both anti-TNF-naïve and anti-TNF-failure patients compared with placebo (47.1% versus 25.5%, p<0.001; Figure 1).[28] Secondary induction endpoints of clinical remission (16.9% versus 5.4%, p=0.01) and mucosal healing (40.9% versus 24.8%, p=0.001) were also met (Figure 1).[28] Maintenance data from the same study indicated that at Week 52, 4-weekly vedolizumab significantly improved Mayo Clinic scores and glucocorticoid use in patients, compared with placebo (p<0.001).[28] Data from the long-term safety study, where patients were treated with 4-weekly vedolizumab, indicated that at Week 52, 65.8% of patients who completed the GEMINI I study were in clinical remission.[29] This proportion increased to 77.1% at Week 80, and at Week 104 72.7% of patients remained in clinical remission.[29] The proportion of patients who had failed previous anti-TNF therapy in remission (65.3%) was slightly lower compared with anti-TNF-naïve patients (76.7%).[29]

A meta-analysis of seven studies of several treatments including TNF antagonists and vedolizumab indicated that therapy favours vedolizumab over placebo as both first-line induction therapy (OR: 4.5) and first-line maintenance therapy (OR: 3.6; Figure 2).[30] However, the differences in study designs and patient characteristics means it is not possible to make a direct comparison between post-approval studies, limiting the usefulness of the meta-analysis.

Following licensing in Europe and the USA in 2014, increasing amounts of data on the post-approval experience with vedolizumab are now available. There is a variation in response rates, but overall the data from the real-world studies resemble the outcomes of the clinical trial (Table 1). Response rates varied from 15% at Week 12 in a US consortium to 57% at Week 14 in a multicentre study in France.[31,32]

When selecting a first-line therapy, any safety concerns associated with treatment should also be considered. An integrated safety summary of six studies of vedolizumab with up to 5 years of follow-up indicated that this treatment did not result in an increased risk of infection or serious infection versus placebo, with a median exposure range of 1–1,977 days.[33] No reports of progressive multifocal leukoencephalopathy were observed with vedolizumab treatment.[33]

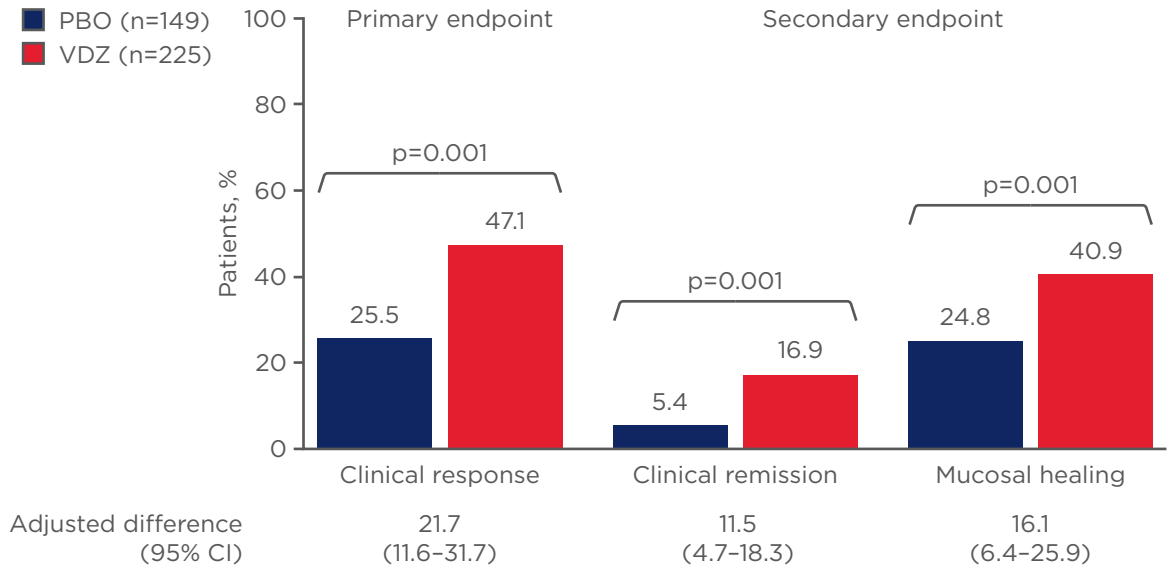

Figure 1: Rates of clinical response, clinical remission, and mucosal healing at Week 6 in the Phase III GEMINI I study of vedolizumab in ulcerative colitis.[28]

PBO: placebo; VDZ: vedolizumab; CI: confidence interval.

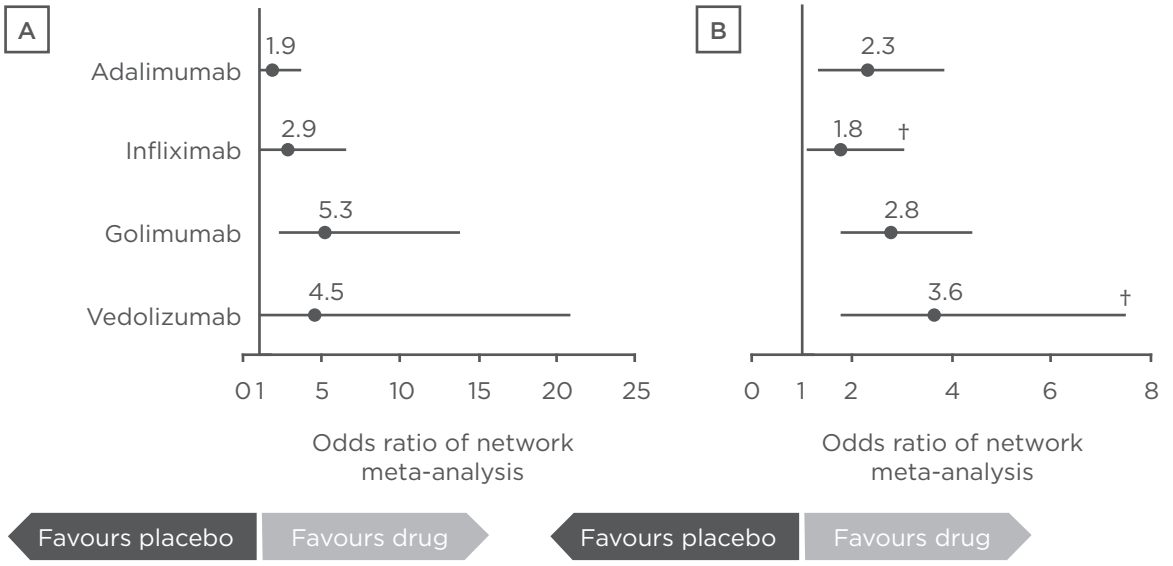

Figure 2: Results of a meta-analysis of seven studies of induction and maintenance therapy in ulcerative colitis: odds ratio of the network meta-analysis.

A) Induction therapy: clinical remission compared with placebo; B) maintenance therapy: clinical remission compared with placebo.

†The study design in the golimumab and vedolizumab trials differed from the adalimumab and infliximab trials; the maintenance therapy phases included only patients who responded to induction therapy.

Optimising therapy is a key component of obtaining and maintaining favourable outcomes for our patients. Optimisation could involve combining treatments, or adjusting the dose or frequency of therapy.[34] Additionally, monitoring of early responses to treatment can be useful in predicting longer term outcomes and aid in swapping or cycling treatments.[35,36] One proposed algorithm is to increase doses of TNF antagonists or reduce dose intervals in patients with a poor response and undetectable or low levels of anti-TNF who do not have anti-drug antibodies. Conversely, patients with a poor response with high anti-TNF levels and who have anti-drug antibodies should be switched to another class of drug.[37]

Table 1: Post-approval experience with vedolizumab.

Study	N	Number of UC patients (%)	Response rate		
			Week 6	Week 14	Week 30
University of Chicago[41]	130 (69)*	39		CD: 58% UC: 50%	CD: 60% UC: 52.9%
Cedars-Sinai Medical Center[42]	66	26	IBD: 49%	IBD: 42%	IBD: 33
Swedish IBD Registry[43]	100	33		At FU (median 10 weeks) CD: 33% UC: 40%	
Boston Experience (MGH & BWH)[30]	172	34		CD: 48.9% UC: 53.5%	
French Multicentre Experience (GETAID)[44]	294	41	CD: 57% UC: 41%	CD: 64% UC: 57%	
Washington University[45]	51	41	CD HBI score: 8.9 (BL 9.3) UC partial Mayo score: 2.9 (BL 5.5)	CD HBI score: 6.9 UC partial Mayo score: 2.6	
Boston University[46]	30	33	CD HBI score: 5.4 UC SCCAI score: 4.4		
US Consortium[31]	141	42		Week 12 CD: 5% UC: 16%	Week 30 CD: 35% UC: 73%

CD: Crohn's disease; UC: ulcerative colitis; IBD: inflammatory bowel disease; FU: follow-up; HBI: Harvey–Bradshaw Index; SCCAI: Simple Clinical Colitis Activity Index; BL: baseline; MGH: Massachusetts General Hospital; BWH: Brigham and Women's Hospital.
*130 patients started vedolizumab; 69 reached the 14-week time point at abstract submission.

Serial adjustments in therapy in patients with persistent endoscopic activity have been associated with mucosal and histological healing, highlighting the need for consistent control of IBD.[38] A study by Bougen et al.[38] in 60 patients who received any adjustment in medical therapy with at least two consecutive endoscopic assessments, found that 60% of patients with baseline endoscopic activity and 50% of patients with histological disease at baseline achieved mucosal healing. These data indicate that treat-to-target is a feasible clinical strategy for UC.[38]

MONITORING AND REGAINING CONTROL

It is important to understand why patients do not respond to certain therapies to ensure that they are switched to an appropriate alternative. Once a patient reaches target, close monitoring is essential to identify potential subclinical relapse and to identify possible disease progression. Smartphone applications that are able to read the results of faecal calprotectin levels are in development and could aid patients in managing their disease.[39]

CESSATION

Monitoring strategies are not only needed for disease progression but are also useful in planning for potential de-escalation of treatment. However, there are currently few data available on de-escalation in UC.[40] Prior to de-escalation, deep remission of UC must be confirmed and patients should be aware of the risks of reducing their treatment doses or dose intervals, including the potential for relapse or the possibility that there will be a loss of response to their current therapy.[40] In addition to a monitoring strategy, physicians must also have a 'rescue' strategy planned to prevent any disease progression that may result from a change of therapy.[40]

Conclusion

Employing a patient-centric chronic disease management model is key to ensuring that disease targets are not only achieved but also maintained. Treatments should be tailored to the needs of individual patients with well-defined response targets from the outset. In addition, understanding disease prognosis is an important aspect of selecting an appropriate therapy.

The anti-α4 integrins are a novel therapy and offer an alternative option for patients. The integrin antagonist, vedolizumab, is a monoclonal antibody that targets α4β7 integrin in the gut-tropic T cell, preventing migration of lymphocytes to the gut mucosa. Vedolizumab has proven efficacy in both induction and maintenance therapy along with a favourable safety profile, which has been demonstrated in both clinical trials and real-life studies.

REFERENCES

1. Dignass A et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis. 2012;6(10):991-1030.

2. Solberg IC et al. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). Scand J Gastroenterol. 2009;44(4):431-40.

3. Langholz E et al. Course of ulcerative colitis: analysis of changes in disease activity over years. Gastroenterol. 1994;107(1):3-11.

4. Loftus EV et al. A practical perspective on ulcerative colitis: patients' needs from aminosalicylate therapies. Inflamm Bowel Dis. 2006;12(12):1107-13.

5. Rubin D et al. Impact of ulcerative colitis from patients' and physicians' perspectives: Results from the UC: NORMAL survey. Inflamm Bowel Dis. 2009;15(4):581-8.

6. Gisbert JP et al. Meta-analysis: the efficacy of azathioprine and mercaptopurine in ulcerative colitis. Aliment Pharmacol Ther. 2009;30(2): 126-37.

7. Panaccione R et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology. 2014;146(2):392-400.

8. Sandborn WJ et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012;142(2):257-65.

9. Sandborn WJ. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014; 146(1):96-109.

10. Lichenstein GR et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. Am J Gastroenterol. 2012;107(9):1409-22.

11. Ford AC, Peyrin-Biroulet L. Opportunistic Infections With Anti-Tumor Necrosis Factor-α Therapy in Inflammatory Bowel Disease: Meta-Analysis of Randomized Controlled Trials. Am J Gastroenterol. 2013;108(8):1268-76.

12. Beaugerie L et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet. 2009;374(9701):1617-25.

13. Peyrin-Biroulet L et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. Gastroenterology. 2011; 141(5):1621-6.

14. Eaden JA et al. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut. 2001;48(4):526-35.

15. Rutter M et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology. 2004;126(2):451.

16. Ardizzone et al. Mucosal healing predicts late outcomes after the first course of corticosteroids for newly diagnosed ulcerative colitis. Clin Gastroenterol Hepatol. 2011;9(6):483-89.

17. Frøslie KF et al. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology. 2007;133(2):412-22.

18. Schoepfer A et al. Fecal calprotectin more accurately reflects endoscopic activity of ulcerative colitis than the Lichtiger Index, C-reactive protein, platelets, hemoglobin, and blood leukocytes. Inflamm Bowel Dis. 2013; 19(2):332-41.

19. Carbonnel F et al. Colonoscopy of acute colitis. A safe and reliable tool for assessment of severity. Dig Dis Sci. 1994;39(7):1550-7.

20. Hamedani R et al. Review article: Drug development in inflammatory bowel disease: budesonide--a model of targeted therapy. Aliment Pharmacol Ther. 1997;11(suppl 3):98-107.

21. Jovani M et al. Vedolizumab for the treatment of IBD: a selective therapeutic approach targeting pathogenic a4b7 cells. Curr Drug Targets. 2013;14(12): 1433-43.

22. Glasziou P et al. Monitoring in chronic disease: a rational approach. Br Med J. 2005;330(7492):644-8.

23. Lindgren SC et al. Early predictors of glucocorticosteroid treatment failure in severe and moderately severe attacks of ulcerative colitis. Eur J Gastroenterol Hepatol. 1998;10(10):831-5.

24. Gonzalez-Lama Y et al. Open-label infliximab therapy in ulcerative colitis: a multicenter survey of results and predictors of response. Hepatogastroenterology. 2008;55(86-87):1609-14.

25. Laharie D et al. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. Lancet. 2012;380(9857):1909-15.

26. Laharie D et al. Long-term outcomes in a cohort of patients with acute severe ulcerative colitis refractory to intravenous steroids treated with cyclosporine or infliximab. Gastroenterology. 2015;148:S-163. Abstract 829. European Crohn's and Colitis Organisation Congress, Barcelona, Spain, 18-21 February 2015.

27. von Andrian UH, Engelhardt B. Alpha4 integrins as therapeutic targets in autoimmune disease. N Engl J Med. 2003;348(1):68-72.

28. Feagan BG et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369(8):699-710.

29. Feagan BG et al. Long-Term Efficacy of Vedolizumab Therapy for Patients With Ulcerative Colitis. Abstract 1616. Annual Scientific Meeting of the American College of Gastroenterology, Philadelphia, PA, USA, 17-22 October 2014.

30. Danese S et al. Biological agents for moderately to severely active ulcerative colitis: a systematic review and network meta-analysis. Ann Intern Med. 2014;160(10):704-11.

31. Shelton E et al. Efficacy of Vedolizumab

as Induction Therapy in Refractory IBD Patients: A Multicenter Cohort. Inflamm Bowel Dis. 2015;21(12):2879-85.

32. Dulai PS et al. Vedolizumab for Moderate to Severely Active Inflammatory Bowel Disease: A Multicenter U.S. Consortium. Abstract 1904. Annual Scientific Meeting of the American College of Gastroenterology, Honolulu, Hawaii, USA, 16-21 October 2015.

33. Colombel JF et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. Gut. 2016. [Epub ahead of print].

34. Panaccione R et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology. 2014;146(2):392-400.

35. Adedokun OJ et al. Association Between Serum Concentration of Infliximab and Efficacy in Adult Patients With Ulcerative Colitis. Gastroenterology. 2014;147(6):1296-307.

36. Vaughn BP et al. Proactive therapeutic concentration monitoring of infliximab may improve outcomes for patients with inflammatory bowel disease: results from a pilot observational study. Inflamm Bowel Dis. 2014;20(11):1996-2003.

37. Colombel JF et al. Therapeutic drug monitoring of biologics for inflammatory bowel disease. Inflamm Bowel Dis. 2012; 18(2):349-58.

38. Bouguen G et al. Feasibility of endoscopic assessment and treating to target to achieve mucosal healing in ulcerative colitis. Inflamm Bowel Dis. 2014;20(2):231-9.

39. Vinding KK et al. Fecal Calprotectin Measured By Patients at Home Using Smartphones-A New Clinical Tool in Monitoring Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis. 2016;22(2):336-44.

40. Torres J et al. Systematic Review of Effects of Withdrawal of Immunomodulators or Biologic Agents From Patients With Inflammatory Bowel Disease. Gastroenterology. 2015; 149(7):1716-30.

41. Christensen B et al. Vedolizumab in the treatment of IBD: the University of Chicago experience. Gastroenterology. Abstract Tu1350. Digestive Diseases Week, Washington D.C., USA, 16-19 May 2015.

42. Morganstern B et al. Single-center experience of vedolizumab in patients with inflammatory bowel disease: does age matter? Abstract Sa1182. Digestive Diseases Week, Washington D.C., USA, 16-19 May 2015.

43. Eriksson C et al. Vedolizumab in inflammatory bowel disease, the first experience from the Swedish IBD Registry (SWIBREG). Abstract Tu1368. Digestive Diseases Week, Washington D.C., USA, 16-19 May 2015.

44. Amiot A et al. Effectiveness and Safety of Vedolizumab Induction Therapy for Patients With Inflammatory Bowel Disease. Clin Gastroenterol Hepatol. 2016. In press.

45. Vivio EE et al. Vedolizumab Effectiveness and Safety Over the First Year of Use in an IBD Clinical Practice. J Crohns Colitis. 2015;10(4):402-9.

46. Oppenheim S et al. A retrospective review of response rates and risk of complications among inflammatory bowel diseases patients treated with vedolizumab. Abstract Tu1371. Digestive Diseases Week, Washington D.C., USA, 16-19 May 2015.