THE FULL PICTURE OF ULCERATIVE COLITIS: THE BURDEN, THE PATIENT, THE TREATMENT

This symposium took place on 26th October 2015 as part of United European Gastroenterology (UEG) Week 2015 in Barcelona, Spain

Chairperson

Julián Panés[1,2]

Speakers

Edouard Louis,[3] Paul Rutgeerts[4]

1. Department of Medicine, University of Barcelona, Barcelona, Spain
2. International Clinical Observation Programs in the Inflammatory Bowel Diseases Unit, Hospital Clínic Barcelona, Barcelona, Spain
3. University of Liege, Liege, Belgium
4. University of Leuven, Leuven, Belgium

Disclosure: Julián Panés has received grants/research support from Abbott Laboratories and Merck Sharp & Dohme Corp.; consulting/speaker fees from AbbVie, Abbott Laboratories, Boehringer Ingelheim, Ferring, Galapagos, Genentech, Janssen Biologics, Merck Sharp & Dohme Corp., Millennium (Takeda), MSD, Pfizer, Roche, Shire, Schering-Plough, Takeda, Tigenix, and TxCell. Edouard Louis has received educational grants from MSD and Abbvie; speaker fees from Abbvie, Ferring, MSD, Chiesi, Mitsubishi Pharma, Hospira, and Janssen; and has served on advisory boards for Abbvie, Ferring, MSD, Takeda, Mitsubishi Pharma, and Celltrion.
Acknowledgements: Writing assistance was provided by Dr Allan Johnson, Medical Writing Limited.
Support: The symposium was jointly organised and funded by Abbvie. All authors received honoraria for preparation and delivery of their presentations. The publication of this article was funded by Abbvie. This article is an interpretation of the views of the speakers, but is not written by them. The views and opinions expressed are those of the authors and not necessarily those of Abbvie.
Citation: EMJ Gastroenterol. 2015;4(1):58-65.

MEETING SUMMARY

Ulcerative colitis (UC) carries a significant, progressive disease burden that is often underestimated or misinterpreted by healthcare providers. Adverse outcomes have a major impact on patient quality of life, with a significant burden of symptoms both during and between inflammation flares. Chronic, uncontrolled disease leads to epithelial fibrosis and 'lead pipe' colon, dysplasia, and potential colonic cancer. Healthcare providers and patients share similar treatment goals, even if these are not verbalised in the same way, and clinicians need to fully understand the issues most important to patients. Understanding and collaboration can improve identification of meaningful treatment goals and overall disease management. In real-world practice, patients should be categorised according to disease characteristics and prognosis, and managed with appropriate, optimised therapies. Early, top-down management should be implemented in high-risk patients and all patient-centric therapeutic decisions made within the context of a full benefit/risk assessment.

The Burden: Global and Personal Perspectives

Professor Julián Panés

The global burden of UC is considerable and continues to rise, even in western countries where historical prevalence was already high.[1] The natural history of UC suggests that in the years following diagnosis, only half of all patients achieve remission, with the remainder continuing to experience disease burden; this results in an increasing proportion requiring colectomy. After 10 years of treatment,

over one-third of patients still have active disease and 20% will undergo colectomy.[2]

Even for patients who initially present with a limited extent of disease, such as those with proctitis or proctosigmoiditis, UC will progress to a greater extent of disease extension in about one-third of patients, with 10–20% developing extensive colitis.[3]

A case–control study by Etchevers et al.[4] suggests that UC acquires a particularly severe and refractory course when disease extension occurs. Inflammatory markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate, are higher in progressing patients compared with patients with extensive but stable disease. Pharmacological and inpatient requirements are greater, and the number needing surgical intervention increased from 5% to 19%. In paediatric patients, the situation is even more concerning: approximately 10% of adult patients have experienced colectomy within 10 years of diagnosis,[5] while 20% of children have undergone colectomy after only 5 years.[6]

The patient perception of disease burden was investigated by the IMPACT study, an online survey of inflammatory bowel disease (IBD) patients conducted by the European Patient Association, with almost 5,000 patients (63% with Crohn's disease [CD], 33% with UC) from 24 countries participating.[7] Results suggest that the impact of disease on everyday working behaviour is similar between UC and CD patients. Almost two-thirds of patients feel stressed or pressured about 'sick leave', whilst 30% consider themselves quieter at meetings. Participation in social activities and general motivation is reduced compared with their colleagues, and irritability is increased.[7] In terms of quality of life, over half of patients consider that UC 'controls their lives', a greater proportion than reported for patients with asthma or rheumatoid arthritis,[8] with even mild symptoms having an impact on Inflammatory Bowel Disease Questionnaire (IBDQ) scores.[9]

Direct assessment of UC disease burden will be measured in the international, 2-year observational ICONIC study, which will use a variety of instruments to measure the multi-faceted burden of disease in recently diagnosed UC patients. The ICONIC study will recruit 1,800 patients and will use the innovative Pictorial Representation of Illness and Self Measure (PRISM) tool to define individual disease burden[10] and highlight any differences in perception of disease burden between patients and physicians.

In patients undergoing surgery, colectomy does not necessarily lead to a restoration of 'normal life'. One-third of patients experience postoperative complications, with approximately 11–44% reporting short-term complications (e.g. infections or pouch-related) and 19–55% reporting long-term complications (e.g. pouchitis, CD of the pouch, infertility, faecal incontinence). The psychological burden of procedure-associated infertility should not be underestimated.[11]

Recognising the burden of UC is key to understanding the need for intervention, either medical or surgical. However, the impact of current and appropriate treatment on disease burden and progression should be considered carefully. When assessing the risk of developing colon cancer in patients with IBD, data suggest that UC patients still have an elevated incidence compared with the general population. However, the risk of colon cancer is not greater than the general population for CD patients.[12]

A recent investigation of a Danish patient cohort (n=35,782) suggests that UC patients have experienced a progressive and significant decline in the cumulative probability of colectomy over time: a reduction of almost 50% since 1979–1986.[13] However, findings from a separate study analysing the rate of colectomy between 1998 and 2011 suggest that the rate has not changed over the last 20 years.[14]

Whilst contradictory, it is important to note that even recent, well-designed studies do not investigate whether there have been changes in the time from diagnosis to surgery, or if there is a delay in the time from diagnosis to initiation of immunomodulators (IMMs) or biological therapies (which could be identified by evaluating cumulative exposure to corticosteroids). Therefore, it is hard to determine if appropriate therapies, initiated earlier, might be able to alter the disease course.

Suggestions that IMMs and biological therapies are introduced too late are based on comparisons between UC and CD. In patients with CD, where IMMs and biological therapies are used more extensively and are initiated earlier in the course of disease, there have been marked reductions in the rates of surgery. This finding is not observed in UC patients, where penetration of these drugs is lower and initiation is later in the disease course (Figure 1).[15]

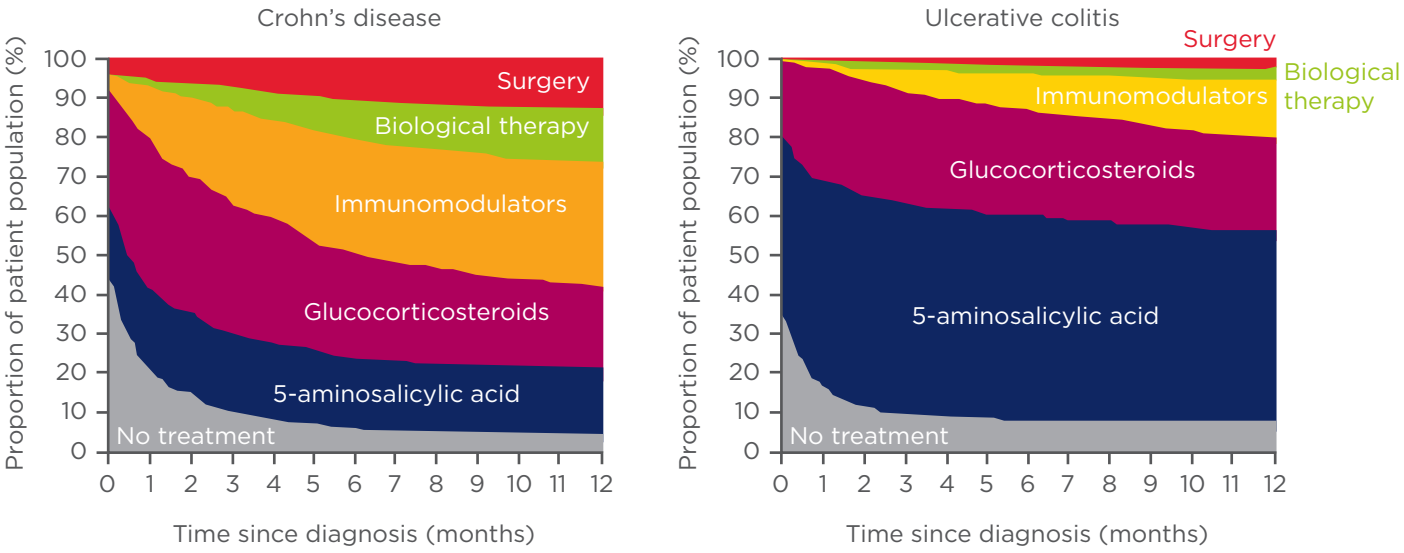

Figure 1: Change in treatment strategy with earlier and more frequent use of immunomodulators and biologicals in Crohn's disease has been associated with reduced surgery rates.[15]

While it is often considered less serious than CD, UC is increasingly recognised as a disease that has a major impact on patient quality of life. Understanding patient issues is important, as is awareness of the impact of symptoms both during and between the flares, to establish meaningful patient-centred management goals and treat each patient appropriately and effectively.

The Patient: Aligning Clinical Management with Patient Needs

Professor Edouard Louis

Patient satisfaction with their IBD care is lower than expected. Only half of patients consider the IBD care that they receive to be 'excellent' or 'very good',[16] and a perception gap exists between clinicians and patients over the impact of UC on everyday life. While most clinicians may consider that patients have symptomatic control, the majority of patients consider their symptoms to be incompletely controlled and causing them difficulties in daily life.[17] Furthermore, when investigating which symptoms are most bothersome, there are discrepancies between healthcare providers and patients. While urgency, number of stools, and blood in stools are concerning for both patients and clinicians, physicians and nurses underestimate the impact of pain and pill burden on patients.[18]

The levels of acceptable risk for a specific clinical outcome can also vary between clinician and patient. Clinicians may consider that patients would accept a relatively high risk of infection, progressive multifocal leukoencephalopathy, or lymphoma to reduce disease severity from severe to moderate levels, whereas patients are willing to accept the most risk for moderate disease going into remission.[19]

Although verbalised differently, the main treatment goals of patients and clinicians are similar: clinicians focus on induction of remission, maintaining steroid-free remission, and preventing complications, while patients focus on fast symptom relief, sustained symptom control with minimal side effects, and avoiding hospitalisation and surgery.

Recognising shared goals facilitates discussion regarding treatment plans focussed on addressing these requirements. The CYSIF study demonstrated that fast symptom relief in the presence of acute severe colitis is possible with use of infliximab or ciclosporin.[20] With moderate-to-severe disease, anti-tumour necrosis factor agents (anti-TNFs), such as subcutaneous adalimumab, provide significant decreases in stool frequency and incidence of blood in stools within 2 weeks of treatment initiation;[21,22] these symptoms are important to patients and translate into improvement in Mayo score responses for the clinician.[21]

The ULTRA studies of adalimumab demonstrate that sustained symptom relief with minimal side

effects is a realistic treatment goal. Remission and mucosal healing rates were achieved early (data showed this from Week 8) and maintained through 4 years of treatment. In addition, in patients who used corticosteroids at baseline, the proportion of patients who discontinued corticosteroids increased over time from Week 16 to Week 208 of adalimumab treatment.[23]

The tolerability profiles for biologics are well characterised and major side effects are rare. When considering adalimumab, analysis of all adult UC clinical trials, comprising over 3,000 patient-years of follow-up, demonstrates reassuring safety outcomes with no increase in mortality rates compared with the general population. Side effects of particular concern for patients, such as serious infections, malignancy, and demyelinating disorders, have event rates per 100 patient-years that are quite low: 3.4, 0.9, and <0.1, respectively.[24]

In terms of avoiding complications such as hospitalisation and surgery, a recent meta-analysis evaluating infliximab and adalimumab studies determined that both of these treatments demonstrate reductions in the risk of hospitalisation in UC patients compared with placebo, with a significant favourable overall treatment effect (risk ratio [RR]: 0.71, 95% confidence interval [CI]: 0.56–0.90; p=0.004).[25]

The ability to understand patient concerns and offer appropriate, effective treatment enables clinicians and patients to work together towards improving outcomes. However, it is critical to understand and discuss the concerns of the patient, especially as patient belief in their therapy is a key aspect of long-term treatment adherence and disease management. This is particularly true in chronic treatment, where necessity beliefs (personal judgement on the need for medication) may decrease and concerns about potential side effects may increase, thus potentially increasing the risk of noncompliance.[26]

The ALIGN study was designed to assess the correlation between patients' necessity beliefs and concerns regarding their therapies with long-term treatment adherence. Overall results from ALIGN indicate that UC patients have similar concerns regarding anti-TNFs and IMMs, both of which are greater than those for 5-aminosalicylic acid (5-ASA). However, they believe that anti-TNF agents are more necessary to control their disease than either 5-ASAs or IMMs. Therefore, although patients may have some concerns about anti-TNF therapy, their belief that it is necessary to control their disease outweighs their concerns, resulting in high medication adherence.[27]

The next step in engaging patients regarding their care is complete involvement in the disease management process. In a study performed in Denmark and Ireland, UC patients (n=333) were randomised to receive treatment with either 'standard care' or a web-based interaction with the clinical team to permit self-treatment. After 12 months, 88% of patients preferred web-based management, and adherence to 4 weeks of acute treatment increased by 30–40%, compared with standard care. In addition, patients receiving web-based management had reductions in the median duration of relapse: 18 days (95% CI: 10–21) in the web-based management group compared with 77 days (95% CI: 46–108) in the standard care group. There were also fewer medical visits associated with web-based patients, with cost savings estimated at €189/patient/year.[28]

Disease burden in UC is often underestimated and sometimes misinterpreted by clinicians. Nonetheless, healthcare providers and patients often have similar treatment goals and therefore a structured collaboration between patients and clinicians may help to improve therapeutic adherence and overall IBD management.

The Treatment: Optimising Strategies to Improve Outcomes

Professor Paul Rutgeerts

Treatment goals for patients include complete resolution of symptoms with limited or manageable side effects and a normalised quality of life. From the perspective of the clinician, disease remission (especially with mucosal healing), eliminating steroids from the therapeutic regimen, and avoiding therapy escalation are key for long-term management. Improved outcomes result in fewer complications, hospitalisations, and surgeries, and lower mortality, thus decreasing societal and financial costs.

Current issues in the treatment of UC include early identification of patients with predicted poor outcome, use of appropriate therapies earlier in the disease course, and optimising such therapies to improve patient outcomes. Such issues may provide

opportunities to implement top-down management approaches in UC patients.

Identifying aggressive disease is complex in patients with UC, but may be associated with young age at presentation, a requirement for steroids as part of initial therapy, extent of disease at time of treatment, and extension of disease course over time. Biological signs of inflammation are also important in predicting aggressive disease, with mucosal ulceration[29] and high CRP[30] as signatures of severe and aggressive outcomes.

UC appears to be a progressive disease. In long-term UC, chronic inflammation can lead to epithelial fibrosis and 'lead pipe' colon,[31] resulting in colon shortening and chronic watery diarrhoea, with associated difficulties for patient continence.[32] The long-term duration of disease may also result in development of dysplasia, the precursor to colonic cancer; the incidence of colon cancer is reported as 18% at 30 years.[33] Finally, regeneration of mucosa characteristic of UC leads to extensive pseudopolyps, which hinder surveillance.[32]

UC patients may be categorised into four groups: (1) patients responding to 5-ASAs or steroids with sustained remission or occasional flares; (2) patients with chronically active disease who are never completely controlled on 'standard' therapies (including steroid-dependent or refractory patients); (3) patients with acute severe UC; and (4) candidates for colectomy. Patients responding to 5-ASAs or steroids with sustained remission have a favourable prognosis and are straightforward to manage with appropriate therapies. In the presence of occasional flares, use of oral or topical steroids should be considered and maintenance therapy can remain unchanged (Figure 2). Patients experiencing more than one flare per year require a reassessment of treatment.

Chronic active disease is never completely controlled with conventional therapy. However, there is often a disconnect between the perceptions of clinicians and patients in this category. While the clinician considers the patient to be adequately managed, there is an inadequate or incomplete response to conventional therapy. The patient is functioning and non-hospitalised, but is under-treated and has persistent symptoms with an ongoing impact on daily quality of life; ineffective low doses of steroid are often still included in the treatment regimen. Such patients require a change in therapy as IMMs are ineffective. For patients with more challenging steroid-dependent or refractory disease, anti-TNF and azathioprine combination therapy (or anti-migration therapy) should be initiated early (Figure 2); oral 5-ASAs could potentially be stopped. The goal of treatment should be mucosal healing, which significantly reduces rates of colectomy at 1 year compared with patients with inflammatory activity: 19% versus 81%, respectively (RR: 0.22, 95% CI: 0.06–0.79; p=0.02).[34]

Patients with acute severe colitis are key candidates for top-down therapy, which provides a reduced time to disease remission and mucosal healing with the potential benefits of steroid and immunosuppressant avoidance. Other patient categories may also benefit from top-down approaches. Patients with extensive colitis and CRP elevation who demonstrate resistance to optimal-dose 5-ASA treatment should be considered, as should those with persistent, even low-grade, active inflammation despite conventional therapy. With the decreasing costs and an extensive range of anti-TNF therapies and anti-migration therapies, maintained remission and the avoidance of dysplasia and surgery enable improved management as treatment approaches become more cost-effective.

Optimisation of therapies can improve patient outcomes. The UC SUCCESS study demonstrates that combination therapy with infliximab and azathioprine significantly increases both clinical remission rates and mucosal healing after 16 weeks compared with either treatment alone. Mucosal healing results are reported as 37% for azathioprine, 55% for infliximab monotherapy, and 63% for combination therapy.[35]

There is an apparent correlation between therapeutic concentration and remission rates. This can be seen for adalimumab, where UC or CD patients with lower serum concentrations are less likely to achieve remission;[36] lower trough levels are also associated with reduced mucosal healing rates.[37] Investigation of serum level optimisation in the TAXIT infliximab study (n=260) suggests that, following stable clinical and biological remission at 1 year, only 43% of patients had optimal infliximab trough levels (3–7 µg/mL). In total, 26% of patients had infliximab trough levels >7 µg/mL, 22% had low levels (<3 µg/mL), and 9% had undetectable trough levels; most of these patients also had anti-infliximab antibodies.[38]

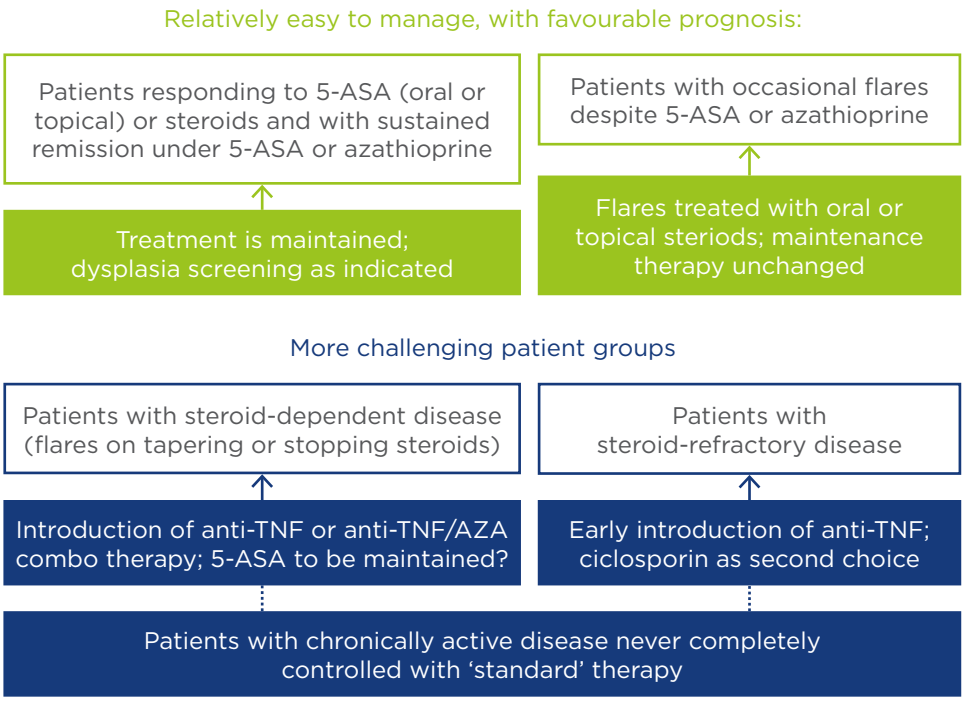

Figure 2: Selection of therapy in the clinical practice of Professor Paul Rutgeerts.
5-ASA: 5-aminosalicylic acid; anti-TNF: anti-tumour necrosis factor; AZA: azathioprine.

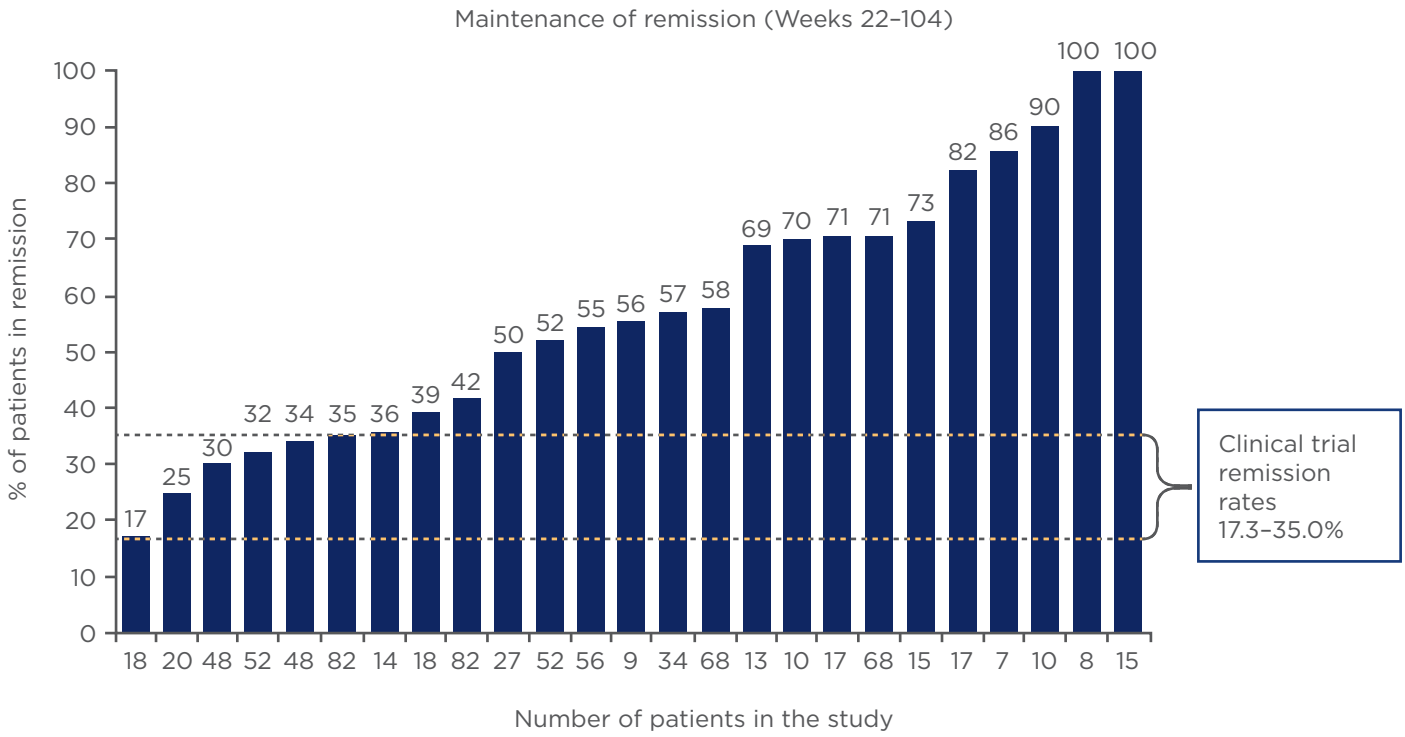

Figure 3: Anti-TNFs: real-world effectiveness.[40-50]
Anti-TNF: anti-tumour necrosis factor.

The ongoing SERENE UC study will investigate the efficacy of a higher adalimumab induction dosing strategy to induce clinical remission, and evaluates different maintenance dosing strategies, including therapeutic drug monitoring, to determine the optimal dosing required to maintain remission through 1 year.[39]

There is an important gap between results from clinical trials and real-world clinical practice.

Compared with controlled clinical trials, patients in clinical practice are more heterogeneous and physicians are able to exercise variable treatment regimens, including dose optimisation, to obtain maximal clinical benefit. Maintenance of remission rates in clinical trials of anti-TNF agents range from 17–35%. In contrast, most real-world cohorts report remission rates higher than those observed in clinical trials (Figure 3).[40-50]

Conventional step-up care has not altered the natural history of IBD. To reduce the burden of UC in clinical practice, management goals should be set in collaboration with the patient, who is categorised according to disease characteristics and prognosis. To optimise outcomes, effective therapies must be implemented early in the disease course in high-risk patients, who should be considered for top-down management. There should be a time-bound, monitored approach to reach treatment goals, and all therapeutic decisions must be made within the context of a full benefit/risk assessment.

Conclusion

UC has a major impact on quality of life, and clinicians need to fully understand the issues most important to patients. As part of a patient-centric approach, close collaboration is required to identify meaningful management goals and optimise treatment outcomes. Clinical management approaches should categorise patients according to disease characteristics and prognosis, and initiate early, effective treatment in high-risk patients.

REFERENCES

1. Molodecky NA et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142:46-64.

2. Langholz E et al. Course of ulcerative colitis: analysis of changes in disease activity over years. Gastroenterology. 1994;107:3-11.

3. Henriksen M et al. Ulcerative colitis and clinical course: results of a 5-year population-based follow-up study (the IBSEN study). Inflamm Bowel Dis. 2006;12(7):543-50.

4. Etchevers J et al. Risk factors and characteristics of extent progression in ulcerative colitis. Inflamm Bowel Dis. 2009;15:1320-5.

5. 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;44:431-40.

6. Gower-Rousseau C et al. The natural history of pediatric ulcerative colitis: a population-based cohort study. Am J Gastroenterol. 2009;104:2080-8.

7. EFCCA IMPACT survey. Available at: http://efcca-solutions.net/european.php. Last accessed: 24 November 2015.

8. Rubin DT et al. The impact of ulcerative colitis on patients' lives compared to other chronic diseases: a patient survey. Dig Dis Sci. 2010;55:1044-52.

9. Panés J et al. Randomized trial of tofacitinib in active ulcerative colitis: analysis of efficacy based on patient-reported outcomes. BMC Gastroenterol. 2015;15:14.

10. Büchi S et al. Preliminary validation of PRISM (Pictorial Representation of Illness and Self Measure) - a brief method to assess suffering. Psychother Psychosom. 2002;71:333-41.

11. Peyrin-Biroulet L et al. Colectomy is not a cure for ulcerative colitis: A systematic review. J Crohns Colitis. 2015;9:S280-1.

12. Jess T et al. Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. Gastroenterology. 2012;143:375-81.

13. Rungoe C et al. Changes in medical treatment and surgery rates in inflammatory bowel disease: a nationwide cohort study 1979-2011. Gut. 2014;63:1607-16.

14. Banerjee I et al. No Difference in Ulcerative Colitis Colectomy Rate in Pre and Post Biologic Era. Gastroenterology. 2015;suppl 1 148.4:S5.

15. Burisch J. The epidemiology of inflammatory bowel disease. Scand J Gastroenterol. 2015;50:942-51.

16. IBD2020 Meeting report, Oct 2013. Available at: http://ibd2020.org/wp-content/themes/ibd2020/pdf/IBD2020_REPORT_2013_LOWRES-11.pdf. Last accessed: 24 November 2015.

17. Schreiber S et al. Perception gaps between patients with ulcerative colitis and healthcare professionals: an online survey. BMC Gastroenterol. 2012;12:108.

18. Schreiber S et al. National differences in ulcerative colitis experience and management among patients from five European countries and Canada: an online survey. J Crohns Colitis. 2013;7:497-509.

19. Johnson FR et al. Crohn's disease patients' risk-benefit preferences: serious adverse event risks versus treatment efficacy. Gastroenterology. 2007;133(3):769-79.

20. 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;380:1909-15.

21. Sandborn W 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.

22. Hanauer SL et al. Rapid Changes in Laboratory Parameters and Early Response to Adalimumab: Pooled Analysis from ULTRA 1 and ULTRA 2. J Crohns Colitis. 2015;9(Suppl 1):S289-90.

23. Colombel JF 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.

24. Colombel JF et al. Long-Term Safety of Adalimumab in Clinical Trials in Adult Patients With Crohn's Disease or Ulcerative Colitis. Abstract 3730. UEG Week 2015, Barcelona, Spain, 24–28 October, 2015.

25. Lopez A et al. Efficacy of tumour necrosis factor antagonists on remission, colectomy and hospitalisations in ulcerative colitis: Meta-analysis of placebo-controlled trials. Dig Liv Dis. 2015;47:356-64.

26. Horne R. The art of adherence:

optimising patient outcomes in rheumatoid arthritis and psoriasis. 2011.

27. Michetti P et al. Medication adherence in IBD in the global ALIGN study: Impact of concerns and perceived necessity of immunosuppressants, aminosalicylates and TNF inhibitors. Oral presentation. UEG Week 2015, Barcelona, Spain, 24–28 October, 2015.

28. Elkjaer M et al. E-health empowers patients with ulcerative colitis: a randomised controlled trial of the web-guided 'Constant-care' approach. Gut. 2010;59:1652-61.

29. Colombel JF et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology. 2011;141:1194-201.

30. Blonski W et al. Clinical predictors of aggressive/disabling disease: ulcerative colitis and crohn disease. Gastroenterol Clin North Am. 2012;41(2):443-62.

31. Torres J et al. Ulcerative colitis as a sole mucosal disease: another misunderstanding? Gut. 2012;61:633.

32. Wang C et al. Clinical, laboratory, endoscopical and histological characteristics predict severe ulcerative colitis. Hepatogastroenterology. 2013; 60:318-23.

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

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

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

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

37. Roblin X et al. Association between pharmacokinetics of adalimumab and mucosal healing in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2014;12:80-4.

38. Vande Casteele N et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology. 2015;148: 1320-9.

39. AbbVie. Study to Evaluate the Safety and Efficacy of Two Drug Regimens in Subjects With Moderate to Severe Ulcerative Colitis. NCT02065622. https://clinicaltrials.gov/ct2/show/NCT02065622.

40. Gisbert JP et al. Systematic review: infliximab therapy in ulcerative colitis. Aliment Pharmacol Ther. 2007;25(1):19-37.

41. Afif W et al. Open-label study of adalimumab in patients with ulcerative colitis including those with prior loss of response or intolerance to infliximab. Inflamm Bowel Dis. 2009;15:1302-7.

42. Garcia-Bosch O et al. Observational study on the efficacy of adalimumab for the treatment of ulcerative colitis and predictors of outcome. J Crohns Colitis. 2013;7:717-22.

43. Armuzzi A et al. Adalimumab in active ulcerative colitis: A "real-life" observational study. Dig Liv Dis. 2013; 45:738-43.

44. Szepes Z et al. Short and medium term efficacy of adalimumab in ulcerative colitis-a multicentre, prospective observational study. J Crohns Colitis. 2014;8(Supplement 1):S208.

45. Busquets D, Aldeguer X. Clinical experience with adalimumab in anti-TNF-naïve patients with ulcerative colitis. J Crohns Colitis. 2013;7:e195.

46. Ignacio FHJ et al. Adalimumab achieves mucosal and histological healing in adult patients with moderate to severe ulcerative colitis naive to anti-TNFα treatment. Inflamm Bowel Dis. 2014; 20:S53.

47. Lequoy M et al. Efficacy of adalimumab in refractory ulcerative colitis in clinical practice. Gastroenterology. 2013;144(5):S203.

48. Lorente R et al. Adalimumab as first-line anti-TNF treatment in ulcerative colitis. A "real-life" observational study. Journal of Crohns & Colitis. 2015;9:S280.

49. Tursi A et al. Effectiveness of adalimumab for ambulatory ulcerative colitis patients after failure of infliximab treatment: a first 'real-life' experience in primary gastroenterology centers in Italy. Ann Gastroenterol. 2014;27:369-73.

50. Hussey M et al. Long Term Assessment of Clinical Response to Adalimumab Therapy in Refractory Ulcerative Colitis. Eur J Gastroenterol Hepatol. 2015. [Epub ahead of print].