Journal of Crohn's and Colitis (2014) 8, 927–935

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REVIEW ARTICLE

Treating beyond symptoms with a view to improving patient outcomes in inflammatory bowel diseases☆

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Received 26 November 2013; received in revised form 25 February 2014; accepted 26 February 2014

KEYWORDS
Algorithms;
Early diagnosis;
Inflammatory bowel diseases;
Outcome assessment;
Prognosis

Abstract

Background and aims: Treatment goals in inflammatory bowel diseases are evolving beyond the control of symptoms towards the tight control of objectively-measured gastrointestinal inflammation. This review discusses the progress and challenges in adopting a treat-to-target approach in inflammatory bowel diseases.
Methods: Evidence from the literature that highlights current thinking in terms of treating-to-target in patients with inflammatory bowel diseases is discussed.
Results: Monitoring for objective evidence of inflammation using endoscopy, cross-sectional imaging or laboratory biomarkers may be a useful approach in inflammatory bowel diseases; however, setting the appropriate treatment goal remains a challenge. Deep remission (a composite of symptom control and mucosal healing) may now be a realistic target in Crohn's disease; however, it remains to be proven that achieving deep remission will modify the long-term disease course. Assessing prognosis at an early stage of the disease course is essential for the development of an appropriate management plan, with the rationale of adapting treatment to disease severity. An algorithm has been proposed for

Abbreviations: CDI, colour doppler imaging; CEUS, contrast-enhanced ultrasound; CRP, C-reactive protein.

☆ This manuscript summarises presentations made during the 'Leading Change in IBD' meeting held in Madrid on 18–19 January 2013 and sponsored by AbbVie.

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http://dx.doi.org/10.1016/j.crohns.2014.02.021

the treatment of early Crohn's disease that involves early treatment with immunosuppressants and tumour necrosis factor antagonists, in the hope of preventing structural bowel damage.
Conclusions: Treating beyond symptoms will require a clear management plan influenced by disease severity at presentation, clinical and biological prognostic factors, achievement and maintenance of clinical and biological remission and pharmacoeconomics.

Contents

1. Introduction

Early and optimised treatment to meet specific targets is key to preventing tissue damage and ultimately physical disability in a number of chronic and progressive diseases including hypertension, type 2 diabetes mellitus and rheumatoid arthritis.[1–3] This treat-to-target approach has been facilitated by the development of algorithms based on therapeutic targets (which are modified to be more or less stringent in high-risk patient groups); adoption of a frequent monitoring policy where treatment is continually optimised until the target is reached; and recognition of early disease states.[2,4,5] In inflammatory bowel diseases (IBD), current therapeutic goals focus on induction and maintenance of clinical remission and prevention of complications of both the disease and the treatment. However, it is increasingly recognised that inflammatory activity persists even in the absence of gastrointestinal symptoms, leading to progressive accumulation of bowel damage including fistulae, abscesses and strictures in Crohn's disease (CD),[6,7] and fibrosis, dysmotility and colorectal neoplasm in ulcerative colitis (UC).[8–10] Treatment goals in IBD are therefore evolving beyond the control of symptoms alone towards the sustained control of gastrointestinal inflammation, measured objectively by endoscopic, radiologic and laboratory parameters.

2. Setting appropriate treatment goals in IBD

The ideal treatment goal in any chronic disease is one that is clearly defined, achievable with medical or surgical therapy, predictive of long-term outcomes, affordable, non-invasive and relevant across disease subtypes, with a low test-to-test variability.

In most current clinical practice, the primary goal of IBD treatment is to induce and maintain clinical remission, with therapeutic decision-making driven by the presence or absence of clinical symptoms.[11–13] However, achieving this goal does not necessarily determine the clinical course of the disease nor prevent long-term disease sequelae. Monitoring for objective evidence of inflammation using endoscopy, cross-sectional imaging or laboratory biomarkers may be a more useful approach; however, setting the appropriate goal remains a challenge (Table 1).

Biomarkers, such as C-reactive protein (CRP) and faecal calprotectin, may be useful for measuring disease activity and guiding therapeutic decisions.[14–17] However, test-to-test variability, relevance across subtypes of IBD and ability to predict long-term outcomes need to be more fully evaluated. Achieving mucosal (endoscopic) healing is an important prognostic feature of IBD treatment[18,19] and prospective studies are required to determine whether this outcome is a feasible and necessary treatment goal. While a validated definition of mucosal healing in IBD is still lacking, working definitions are beginning to evolve. Laboratory markers may also provide a surrogate measure of mucosal healing, although more work is required to validate this approach.

With the advent of biologic therapies, it has become apparent that deep remission (a composite of symptom control and mucosal healing) may now be a realistic target in CD.[20–22] The definition of deep remission should include considerations for both early and late disease,[19] with early disease including more stringent criteria. Patients diagnosed late in the course of CD, those who already have pre-existing disease complications or those who have required surgical treatment may not be capable of achieving an absence of clinical symptoms as a result of irreversible structural damage inflicted by the CD itself or by surgical resection.

Table 1 Characteristics of potential treatment goals in inflammatory bowel diseases.

	Endoscopy	C-reactive protein	Faecal calprotectin	Magnetic resonance imaging
GOAL	No mucosal lesions	Normalisation	?	?
Clearly defined goal	✓	✓	✗	✗
Goal is achievable with medical or surgical therapy	✓	✓	✓	✓
Achieving goal predicts long-term outcomes	✓	?	?	?
Goal is relevant across IBD subtypes	✓	✗	?	✗
Measurement tool is affordable	✗	✓	✓	✗
Measurement tool is non-invasive	✗	✓	✓	✓
Tool has low test-to-test variability	✓	✗	✗	?

In contrast, higher deep remission rates may be able to be achieved in patients with early disease, as defined by time from diagnosis and the absence of irreversible transmural disease (strictures or fistula).[19] While it remains to be proven that treating to the point of deep or biologic remission will affect the "natural course" of the disease, it is intuitive that therapies providing greater levels of mucosal healing and resolution of clinical symptoms may eventually modify the disease course.[23]

3. Evidence for treating to target in IBD

While there is a plethora of evidence to support treating UC and CD patients until they achieve clinical remission,[24–32] there are limited data available for the efficacy of current treatments in achieving other goals[21,33–36] and what the long-term outcomes of achieving such goals actually are (summarized in Table 2). The potential risks of aiming for tight disease control must also be considered, such as increased toxicity, cost, increasingly complex treatment algorithms and immunogenicity, as well as the modest risk and patient discomfort associated with the increased use of endoscopic or invasive procedures.

Another challenge of treating to target in IBD is that acceptance of these treatment goals is not universal across stakeholders; although many IBD specialists aim to treat beyond the symptoms based on biomarkers and presence of lesions, clinical remission is still an accepted goal for other gastroenterologists, surgeons, non-specialist physicians, patients and the authorities.

4. The importance of an accurate prognosis

Assessing prognosis at an early stage of the disease course in IBD is essential for the development of an appropriate management plan, with the rationale of adapting treatment to disease severity. CD and UC are heterogeneous diseases with some patients following a mild course and others experiencing early and aggressive disease progression.[37–39] Factors identified as potential predictors of an aggressive disease course in CD include: age < 40 years at diagnosis, presence of perianal lesions, the early need for steroids and severe endoscopic lesions.[40–43] In UC, potential negative predictors include young age at diagnosis, extensive colitis, the presence of primary sclerosing cholangitis, non-smoker status, need for early corticosteroids, intravenous corticosteroids and initial hospitalisation.[43–45] A number of factors have been identified that predict greater risk of requiring surgery; these include non-colonic disease, penetrating disease, smoking, male gender, early steroid use, severe endoscopic lesions and some genetic loci in CD; and high stool frequency, steroid use, severe endoscopic lesions, histological inflammation, high CRP and multiple single nucleotide polymorphism scores in UC.[41,43,46–52] In the future, it may be possible to predict response to therapy using biomarkers[16] or genetic profiling[53–56]; however, more studies are needed to validate these findings.

At present, there is a lack of specific and validated serological and genetic markers for disease progression in IBD and it is essential that prospective studies are conducted to explore the use of combinations of predictive factors to help us establish the prognosis for our patients. In the meantime, it remains important to rely on our clinical experience, using our knowledge of clinical characteristics, endoscopy, imaging findings and laboratory biomarkers, to make rational clinical decisions that aim to modify the disease course and delay progression as far as possible.

5. Using imaging to tailor management of IBD

There are limitations in using clinical assessment of CD for predicting the presence of active disease as it may have low sensitivity and specificity to predict endoscopic lesions.[57] Endoscopy is currently the gold standard for assessing gastrointestinal inflammatory activity. The recent Post Operative Crohn's Endoscopic Recurrence (POCER) study evaluated the utility of step-up therapy based on endoscopic targets rather than clinical assessment in CD patients who had undergone resection and were at high risk of recurrence.[58] While this study showed that tailoring therapy based on endoscopic findings is superior to current standards of care, the impact of this strategy on clinical recurrence, disease progression and disability has yet been to be fully ascertained. Furthermore, one of the potential limitations of using endoscopy to tailor treatment is that it is a relatively invasive procedure. Therefore, it is important to assess if non-invasive imaging techniques, such as magnetic resonance imaging (MRI) and ultrasound, may be of value to assess the disease course in IBD.

5.1. Magnetic resonance imaging

The sensitivity and specificity of MRI for the detection of active disease and correlation with segmental endoscopic disease severity and detection of complications are high, with more than 80% sensitivity and more than 90% specificity.[59] MRI has also been shown to be a valuable tool in the assessment of response to therapy; pathological improvements in MRI scans related to disease activity are responsive and reliable indicators of endoscopic healing.[60] Furthermore, in patients with ileal CD treated with infliximab, severity of transmural and peri-enteric lesions as measured by magnetic resonance enteroclysis has been shown to correlate well with clinical response.[61] Colonoscopy and MRI have similar value in evaluating disease activity, but MRI has greater success at identifying penetrating complications.[62] This may lead to more timely initiation of more potent therapeutic options or surgery.

5.2. Ultrasound

Ultrasound is useful for disease monitoring in CD.[63] It is a cost-effective and well-tolerated imaging technique in CD that does not require the use of ionizing radiation. A meta-analysis suggests that ultrasound may be a valid alternative to CT and MRI for the evaluation of CD.[64]

In patients with inflammatory diseases in general, the inflammation induces neoangiogenesis, which is a similar phenomenon to that which occurs in neoplasia. This is a key area of interest for ultrasound with colour Doppler imaging (CDI) and contrast-enhanced ultrasound (CEUS), allowing for subjective and quantitative evaluation of blood flow. CEUS provides greater sensitivity for the detection of disease activity compared with CDI alone.[65]

6. Algorithms for different patient types

All of the information gathered about a patient as they present with IBD can be used to determine the most appropriate management of that individual patient, including which targets should be aimed for. However, it is still unclear as to whether we should classify the patients according to symptoms, course of disease, phenotype, complications, extra-intestinal manifestations or a response or lack of response to therapy. A combination of all these factors is used currently as a basis for decisions. Several management approaches have been developed for CD (Fig. 1). All require the balancing of risks and benefits within the different treatment strategies.[66] The conventional step-up care and accelerated step-up care strategies are associated with lower efficacy, disease progression, a potentially higher risk of infections and mortality associated with repeated corticosteroid use. They are not likely to reduce the need for surgery and there is a high risk of disease progression. The benefit of these approaches is lower cost; moreover, many patients will achieve and maintain remission in traditional step-up care and accelerated step-up care approaches.

By comparison, early top-down therapy provides the benefits of higher efficacy, a lower rate of disease-related complications, higher rates of mucosal healing and, decreased rates of surgery and hospitalisation. However, downsides include a higher risk of drug-related serious infections and higher costs. The elements needed to develop optimal treatment strategies include patient profiling using prognostic factors, establishing measurable treatment goals with an acceptable benefit/risk profile and the early use of therapy to achieve optimal patient outcomes, such as mucosal healing. Several studies have shown significant treatment gains in treating disease early.[67,68]

An algorithm has been proposed for the treatment of early CD in patients with a disease duration of <2 years with no previous use of immunomodulator therapy or TNF antagonists and the absence of pre-existing transmural complications (Fig. 2).[66] The current challenge is to establish methods for profiling patients and accepting that a patient's risk profile is likely to change over time.

7. Summary and conclusions

Treating IBD beyond symptoms will require a clear management plan influenced by disease severity at presentation, clinical and biological prognostic factors, achievement and maintenance of clinical and biological remission and pharmacoeconomics. Prospective studies are required to confirm prognostic factors, the relevance of individual disease targets, the benefits and risk of treating-to-target on long-term outcomes and the pharmacoeconomic value of a targeted approach. Endoscopy, as well as cross-sectional imaging techniques such as MRI and (in some instances) ultrasound,

Table 2 Evidence distribution for the different therapies across the short- and long-term goals in inflammatory bowel disease. Note that this is not an exhaustive summary of evidence evaluating the efficacy of therapy in achieving treatment goals.

Goal	5-ASA	Steroids	AZA	MTX	Anti-TNF
Short-term endpoints					
Clinical remission	UC[69]	UC, CD[24]	UC?, CD?[25,70]	CD[26]	UC, CD[27]
Steroid-free clinical remission	?	N/A	CD[28]	CD[26]	UC + CD[29–32]
Clinical and endoscopic remission (deep remission)	UC[33,34]	UC[35]	UC[36]	?	UC, CD[21]
Treating beyond clinical and endoscopic remission	?	?	?	?	?
Long-term disease modification					
Reduction of surgical risk	?	?	Conflicting[71]	?	UC, CD[72]
Reduction of disability	?	?	?	?	?
Reduction of 'damage'	?	?	?	?	?

5-ASA, 5-aminosalicylic acid; AZA, azathioprine.

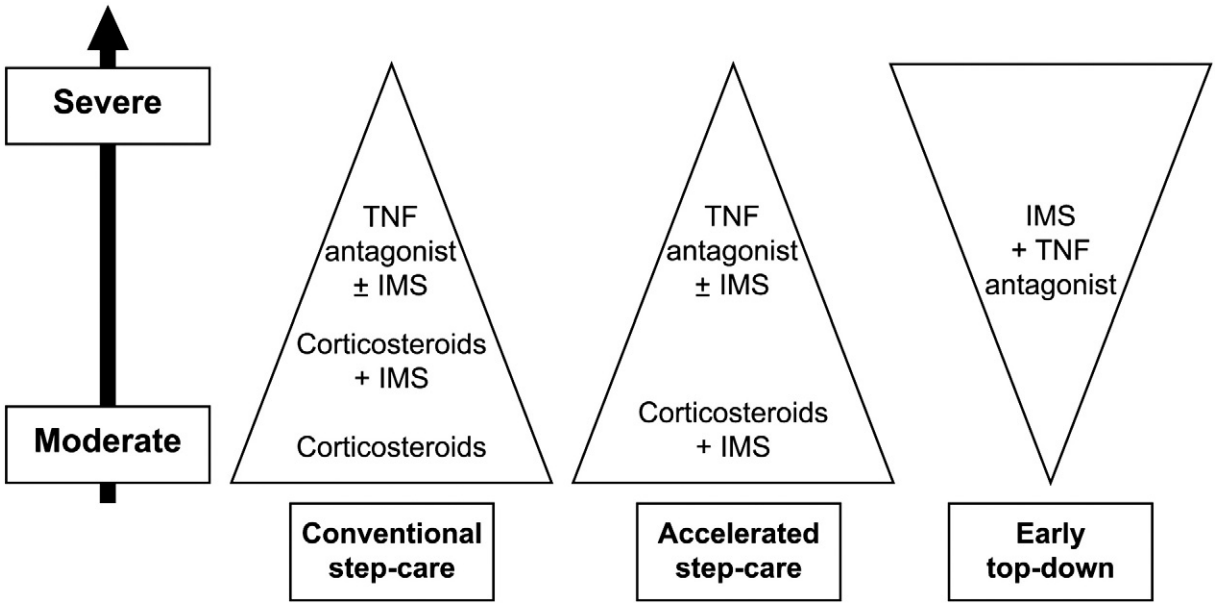

Figure 1 Conventional and evolving treatment strategies for Crohn's disease. In a conventional step-care regimen, corticosteroids and immunosuppressants (IMS) are prescribed additively and sequentially as symptoms become more severe, with tumour-necrosis factor (TNF) antagonists reserved for patients with refractory disease or intolerance to conventional therapies. In an accelerated step-care regimen, IMS are introduced in patients with newly-diagnosed disease rather than waiting until patients become steroid-dependent. As in the conventional regimen, TNF antagonists are reserved for patients with refractory disease or intolerance to conventional therapies. In the early top-down regimen, patients with high risk of disease progression receive first-line combined immunosuppression with IMS and a TNF antagonist in order to prevent irreversible bowel damage. The benefits of combined treatment need to be balanced against the risk of serious infection and lymphoma, together with pharmacoeconomic considerations. Figure adapted and reproduced from Ordás et al,[66] *with permission from BMJ Publishing Group. ©2011.*

should be utilized to strengthen the accuracy of clinical decision-making and disease management. Algorithms in IBD require improved patient profiling, identifying and validating predictors of the disease course, prognosis and drug response. There needs to be agreement concerning the treatment targets and systematic monitoring required to ensure that targets are met. In the future, it may also be of benefit to consider the creation of a risk score that will allow the stratification of patients at diagnosis and various points along their disease course.

Conflict of interest

Financial arrangements of the authors with companies whose products may be related to the present report are listed below, as declared by the authors.

Professor Sandborn has received consulting fees from AbbVie, ActoGeniX NV, AGI Therapeutics, Alaven Pharmaceuticals, Alba Therapeutics, Albireo, Alfa Wasserman, Amgen, AM-Pharma BV, Anaphore, Astellas Pharma, Athersys, Atlantic Healthcare, Axcan Pharma, BioBalance, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Celek Pharmaceuticals, Cellerix SL, Centocor, Cerimon Pharmaceuticals, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado Biosciences, Cytokine Pharmasciences, Eagle Pharmaceuticals, Eisai Medical Research, ELAN, EnGene, Eli Lilly, Enteromedics, Exagen Diagnostics, Ferring, Flexion Therapeutics, Funxional Therapeutics, Genzyme, Genentech, Gilead Sciences, Given Imaging, GlaxoSmithKline, Human Genome Sciences, Ironwood Pharmaceuticals, KaloBios Pharmaceuticals, Lexicon Pharmaceuticals, Lycera, Merck Research Laboratories, MerckSerono, Millennium, Nisshin Kyorin Pharmaceuticals, Novo Nordisk, NPS Pharmaceuticals, Optimer Pharmaceuticals, Orexigen Therapeutics, PDL Biopharma, Pfizer, Procter and Gamble, Prometheus Laboratories, ProtAb Limited, Purgenesis Technologies, Receptos, Relypsa Inc, Salient Pharmaceuticals, Salix Pharmaceuticals, Santarus, Schering-Plough, Shire Pharmaceuticals, Sigmoid Pharma, Sirtris Pharmaceuticals, SLA Pharma (UK), Targacept, Teva Pharmaceuticals, Therakos, Tillotts Pharma AG, TxCell SA, UCB Pharma, Viamet Pharmaceuticals, Vascular Biogenics, Warner Chilcott and Wyeth. He has received lecture fees from AbbVie, Bristol-Myers Squibb and Janssen. He has received research support from AbbVie, Bristol-Myers Squibb, Genentech, GlaxoSmithKline, Janssen Biotech, Millennium Pharmaceuticals, Novartis, Pfizer, Procter & Gamble, Shire Pharmaceuticals, and UCB Pharma.

Professor Hanauer has served as a consultant or on an advisory board for AbbVie, Baxter, ELAN/Biogen, Ferring, Hospira, Janssen, Pfizer, Prometheus, Shire Pharmaceuticals, Takeda, UCB Pharma and Warner Chilcott; and has received speaker/lecture fees from AbbVie, Ferring and Janssen.

Dr Van Assche has received consultancy and/or lecture fees from Abbvie, Aptalis, Bristol-Myers Squibb, Ferring, Janssen, MSD, Novartis, Takeda, UCB Pharma and Warner

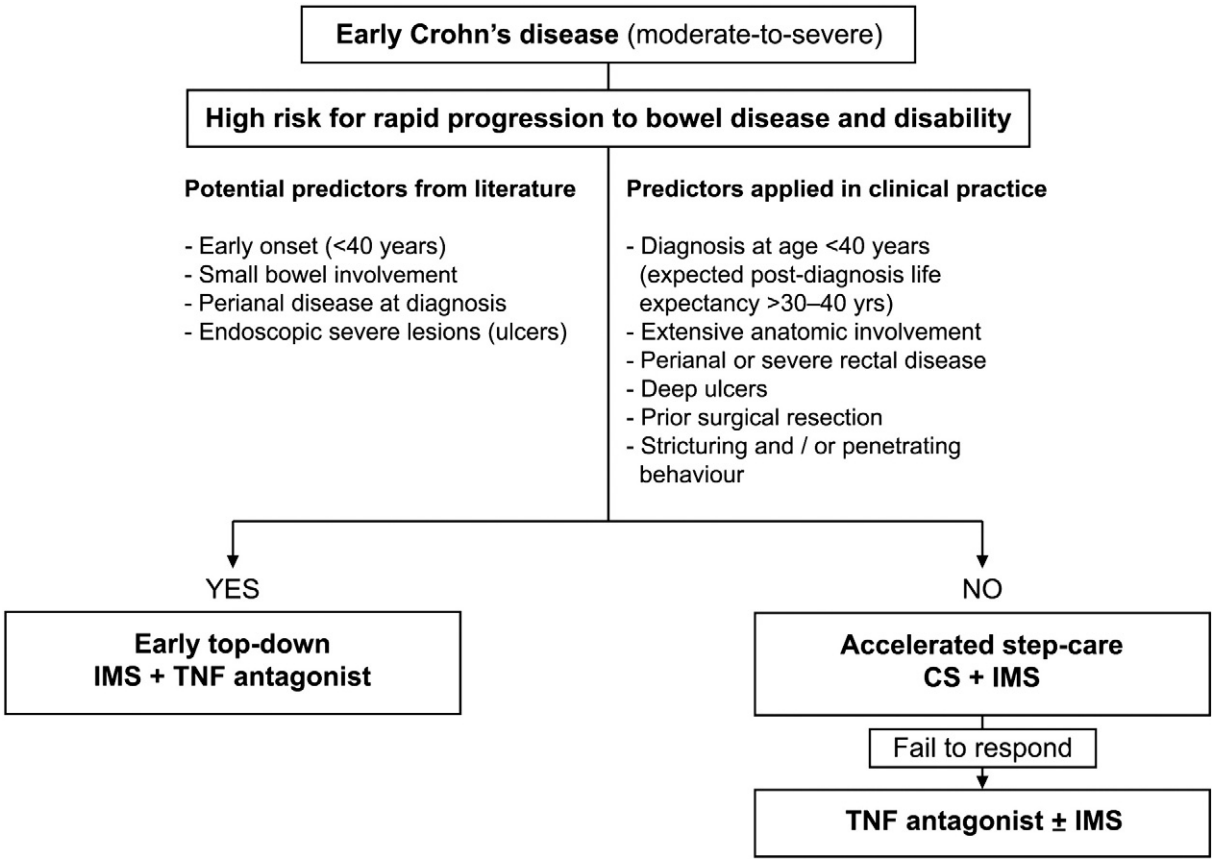

Figure 2 Proposed algorithm for treatment of early Crohn's disease (disease duration < 2 years and no previous use of immunomodulators or TNF antagonists). In this algorithm, patients with high risk for rapid progression to bowel damage and disability should be treated with front-line combined immunosuppression with immunosuppressants (IMS) and a tumour necrosis factor (TNF) antagonist.
Figure adapted and reproduced from Ordás et al,[66] *with permission from BMJ Publishing Group. ©2011.*

Chilcott. Research support to the University of Leuven has also been received from Abbvie, MSD and Zealand Pharma.

Dr Panés has received speaker fees from AbbVie, MSD, Pfizer, Shire Pharmaceuticals and UCB Pharma; acted as a scientific consultant for AbbVie, Bristol-Myers Squibb, Ferring, MSD, Novartis, Pfizer, Shire Pharmaceuticals, Tygenics and UCB Pharma; and received research grants from AbbVie and MSD.

Dr Wilson has been a consultant for Lantheus Medical Imaging and has received research grants from AbbVie, Janssen and Lantheus.

Dr Petersson is an employee of and shareholder in AbbVie.

Professor Panaccione has received consultant and/or lecture fees from AbbVie, Amgen, AstraZeneca, Axcan Pharma, Biogen Idec, Bristol-Myers Squibb, Centocor, ChemoCentryx, Eisai Medical Research, ELAN, Ferring, Genentech, GlaxoSmithKline, Janssen, MSD, Millennium, Ocera Therapeutics, Otsuka America Pharmaceuticals, Pfizer, Shire Pharmaceuticals, Prometheus, Schering Plough, Synta Pharmaceuticals, Teva, UCB Pharma and Warner Chilcott.

Acknowledgements

Contributorship

This manuscript summarises presentations made by Stephen Hanauer, Tine Jess (Statens Serum Institute, Copenhagen, Denmark), Gert Van Assche, Julián Panés, Stephanie Wilson, and Remo Panaccione at the Leading Change in IBD meeting, held in Madrid on 18–19 January 2013, which was sponsored by AbbVie. AbbVie provided funding to Lucid, Burleighfield House, Buckinghamshire, UK, to manage the Leading Change in IBD meeting, for which AbbVie provided topic ideas and participated in development of the meeting content. AbbVie paid consultancy fees to William Sandborn, Stephen Hanauer, Tine Jess, Gert Van Assche, Julián Panés, Stephanie Wilson, and Remo Panaccione for their participation in the meeting, and travel to and from the meeting was reimbursed. This manuscript reflects the opinions of the authors and each author reviewed the manuscript at all stages of development to ensure that it accurately reflects the content of their presentation. Joel Petersson, an employee of AbbVie, is an author of this manuscript and was involved in the development and review of the manuscript with the authors and the medical writer. The authors determined final content, and all authors read and approved the final manuscript. The authors maintained complete control over the content of the paper. No payments were made to the authors for the writing of this manuscript.

Sian Kneller, Dorothy Grindlay and Juliette Allport of Leading Edge (part of the Lucid Group), Burleighfield House, Buckinghamshire, UK provided medical writing and editorial support to the authors in the development of this manuscript. From slides provided by the authors and the audio

recording from the meeting, Leading Edge prepared draft outline manuscripts for author comment and approval. Leading Edge subsequently supported incorporation of comments into final drafts for author approval, and editorial styling required by the journal. Financial support to Leading Edge for medical writing and editorial assistance was provided by AbbVie.

Dr Tine Jess provided the original content for her presentation at the meeting, which was used in the development of the manuscript.

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