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Novel concepts in inflammatory bowel disease

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Abstract

Introduction: Clinical management in inflammatory bowel disease (IBD) is constantly changing. Although improvement in symptoms is of paramount importance, using this as the only surrogate marker of disease activity might underestimate disease burden.

Sources of data: New data from randomized clinical trials are now available. Treatment paradigms are constantly changing leading to an evolution in the therapeutic approach in routine IBD practice.

Areas of agreement: Patients with an aggressive disease phenotype should be identified at the onset and treated more intensely in order to achieve long-lasting mucosal remission.

Areas of controversy: Patients who have mild and indolent disease need to be identified and not over treated.

Growing points: The primary endpoint in IBD management should ideally be mucosal healing. Ample data are now available that correlates mucosal healing with surgical-free outcomes with minimal intestinal damage and patient disability. However, the exact degree of mucosal healing that will lead to improved long-term remission, decreased hospital and surgical rates remains unknown.

Areas timely for developing research: Clinical translational work is needed to identify novel pathways in IBD pathogenesis that sub-select patients who would benefit by specific-cytokine pathway modulation.

Key words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, anti-TNF drugs, mucosal healing, remission

Introduction

Inflammatory bowel disease (IBD) consists of Crohn's disease (CD) and ulcerative colitis (UC), which are chronic relapsing and remitting inflammatory diseases of the intestinal tract. In the case of UC the inflammatory process is usually located superficially within the mucosa, whereas in CD the inflammation is often transmural. These changes lead to an array of symptoms and numerous extra-intestinal manifestations that disrupt the quality of life.[1]

Historically, gastroenterologists worldwide treated patients with IBD according to their reported symptoms or signs and relied on the premise that these reflected disease activity. It is now well recognized that the presence of inflammation at the intestinal level may not be correlated with patient reported symptoms. This review will focus on novel concepts in IBD, concentrating on the importance of monitoring and treating toclinical endpoints that more accurately reflect disease activity. The evolving role of drug management will be discussed, focusing mainly on new and more effective treatment paradigms of available pharmacotherapy and introducing drug therapies that have promise for the future.

The long-term importance of mucosal healing

Recently, the concept of mucosal healing has been brought forward as a tangible primary endpoint in clinical care.[2] Presently, there is no valid definition of what constitutes mucosal healing in IBD. The International Organization for the study of IBD suggested that in UC this would constitute the absence of blood, friability, erosions and ulcerations,[3] while in CD this generally constitutes an absence of mucosal ulceration.[4] A wealth of prospective and retrospective data is available showing that this endpoint correlates significantly with hard and easily measurable outcomes such as surgery and hospitalization rates. Moreover, endoscopic lesion severity correlates with the severity of surgical outcomes. Mucosal healing and a reduction in endoscopic disease burden should be the novel clinical outcome to which the IBD-practicing gastroenterologist should strive. Despite these positive conclusions, there are still some limitations in using mucosal healing as an endpoint in clinical practice. The diagnosis of mucosal healing depends heavily on the skill and opinion of the endoscopist and is thus operator dependent and is strongly affected by inter-individual variability. Moreover, recent advances in novel technological imaging techniques are starting to revolutionize our understanding of the inflammatory process in IBD and could thus re-define what we mean with mucosal healing.[5] A better endoscopic appreciation of the inflammatory burden will eventually get us closer to a complete absence of mucosal inflammation and histological remission which could eventually be the ultimate goal in IBD.[6,7] Till international consensus is obtained on the degree and definition of mucosal healing needed as a clinical endpoint, clinical judgement by the IBD clinician should be used.

Crohn's disease

In a Norwegian population study, 458 patients with IBD were assessed endoscopically at 1 and 5 years.[8] Patients in endoscopic remission at 1 year had significantly lower surgical resection rates (11 vs. 20%) at 5-year follow-up. In a follow-up study of the same cohort at 10 years, results were similarly maintained, highlighting the importance of mucosal healing as a more effective endpoint of clinical care in CD.[9]

In a retrospective study aimed at identifying predictive factors of colectomy-free survival, 102 subjects with CD who had an index colonoscopy at the start of follow-up were recruited. Of these, 53 subjects had severe colonic lesions, defined as deep ulcerations involving >10% of the specific colonic segment studied. Probabilities of colectomy in patients with and without endoscopic lesions were 31 and 6% at 1 year, 42 and 8% at 3 years and 62 and 18% at 8 years, respectively. The presence of deep ulceration at the index colonoscopy was associated with complicated disease ($P = 0.003$) and a higher risk of surgery [OR: 6.72, 95% confidence interval (CI) 2.26–20.03].[10]

In a retrospective single-centre study, 214 patients out of a total of 614 patients had available endoscopic data on mucosal remission after infliximab therapy.[11]

Mucosal healing was observed in 124 (67.4%) out of the original 183 who initially responded, with 22.4% of the patients showing partial mucosal healing. Concomitant steroid usage had a negative effect on mucosal healing [37.9% in patients with corticosteroids versus 63.2% in patients without corticosteroids; $P = 0.021$, odds ratio (OR) 0.36, 95% CI: 0.16–0.80]. Mucosal healing was associated with significantly less major abdominal surgery (14.1% with mucosal healing vs. 38.4% without mucosal healing; $P < 0.0001$). Of note, no significant difference in the incidence of abdominal surgery was noted between subjects achieving complete or partial mucosal healing, highlighting the importance of exploring more stringent cut-off definitions.

Perhaps the best study demonstrating the importance of achieving mucosal healing is the 'step-up' 'top-down' study.[12] One hundred and thirty-three patients were originally randomized to two arms: either conventional therapy with steroids and then azathioprine if clinically indicated. Episodic infliximab therapy was instituted only if patients failed azathioprine. In the second arm of the study, patients were treated with combination therapy of three infusions of infliximab and concomitant azathioprine. Further infliximab was prescribed if needed. At Week 104, no colonic ulcers were seen in 73.1% of patients assigned to the combined immunosuppression group, compared with 30.4% in the conventional group ($P = 0.0028$) with respective endoscopy scores of 0.7 (standard deviation 1.5) and 3.1 (2.9) ($P < 0.001$). A subset of 49 patients initially randomized underwent repeat ileocolonoscopy after 2 years.[13] Complete mucosal healing (i.e. SES-CD score of 0) at the 2-year endoscopy predicted sustained steroid-free remission at 3 and 4 years after therapy was initiated. Seventeen out of the 24 (70.8%) patients achieving mucosal remission after 2 years of instituting treatment were in steroid-free remission as opposed to 27.3% of patients who did not ($P = 0036$; OR = 4.352; 95% CI: 1.10–17.220). Steroid-free remission without anti-TNF therapy was observed in 62.5% of patients in the endoscopic remission group, but in only 18.2% of patients with evidence of endoscopic disease ($P = 0.032$; OR = 4.883; 95% CI: 1.144–20.844). Of the patients deemed to be in clinical remission as per Crohn's disease activity index (CDAI), only 52% had achieved mucosal healing. Mucosal healing and not a normal CDAI predicted steroid-free remission in this group, once again highlighting the danger of solely relying on symptoms when clinically judging disease activity. Finally, patients with mucosal healing at the end of the 2-year follow-up had significantly less active perianal disease and disease relapses with no witnessed change in hospitalization and abdominal surgery when compared with the cohort without mucosal healing. Only 7/24 (33%) of the group showing mucosal healing at 2 years needed further infliximab therapy as opposed to 64% of the patients who still had active disease at the start of follow-up.

In a later sub-study[14] of the original ACCENT I trial,[15] patients achieving long-term mucosal healing (as rated by two follow-up visits at Weeks 10 and 52) needed less CD-related hospitalizations (0.0%) compared with those achieving short-term mucosal healing (18.8%) or no healing at all (28.0%).

Ulcerative colitis

In a Norwegian population, only 2% of the UC patients who showed mucosal healing at 1 year needed a colectomy as opposed to 7% who did not.[9] In a French study, 23% of patients without deep ulceration had undergone surgery when compared with 93% with ulceration.[16] A Japanese study in steroid-refractory UC patients rescued with cyclosporine identified that mucosal improvement at 14 days was associated with significantly lower rates of colectomy at 1 years ($P < 0.01$), though this effect did not translate into good long-term outcomes.[17] In a similar patient population, the presence of severe endoscopic lesions was identified as an independent predictive factor of colectomy [adjusted hazard ratio (HR) = 2.38, 95% CI: 1.80–3.14]. Short-term clinical response and mucosal healing were identified as independent predictive factors for colectomy-free survival even in infliximab rescued steroid-refractory patients. This patient cohort had a relatively long-term median follow-up of 33 months (IQR = 17.0–49.8), indicating

that mucosal healing in the short term is probably indicative of a long-term surgery-free survival.[18]

In a prospective study 157 patients with UC from an inception cohort were followed up in a tertiary centre for 5 years.[19] After follow-up, there were significant differences between complete and partial responders in the rates of hospitalization, immunosuppression therapy, colectomy and their combination. After multivariate analysis, lack of mucosal healing was the only factor associated with negative outcomes at 5 years (immunosuppressors: HR = 10.581; 95% CI: 2.193–51.039; $P = 0.0033$; hospitalization: HR = 3.634; 95% CI: 1.556–8.485; $P = 0.0029$ and colectomy: HR = 8.397; 95% CI: 1.278–55.186; $P = 0.0268$).

Finally, in a sub-analysis of the ACT I and II trials,[20] 48.3% of the patients who had achieved mucosal healing at 8 weeks were in clinical remission at 30 weeks as opposed to 9.5% of the patients who were not.

These retrospective and prospective data from studies and clinical trials in both CD and UC highlight the fact that mucosal healing should be the primary endpoint for modern clinical practice in IBD. The fact that it has been used in a non-clinical trial setting especially in retrospective and single centre prospective studies indicates that this outcome is an achievable measure in routine clinical practice.

A measure of disease burden

Mucosal healing

Control of intestinal inflammation needs to be the cornerstone of therapy. Unchecked inflammatory activity leads to a progression of the disease. In CD, the disease likely progresses from uncomplicated inflammatory phenotypes to complicated phenotypes such as stricturing and penetrating phenotypes as described by the Montreal classification.[21] The development of these more advanced phenotypes or complications is often associated with the need for surgery. Following a resection, this cycle repeats itself unless modified by timely medical management.

In UC, colorectal cancer risk increases with disease activity and disease history.[22]

Disease phenotype was retrospectively mapped over time in a cohort of 297 CD patients. Whereas disease location remained stable in 84% of CD patients, change in disease behaviour was observed more commonly. Over 10 years, 46% of CD patients with an inflammatory phenotype experienced a change in disease behaviour (i.e. fibrostenotic or penetrating).[23] In a separate study, Cosnes *et al.*[24] demonstrated that within 20 years of diagnosis 88% of CD patients experienced a stricturing (18%) or penetrating (70%) complication. These studies were later confirmed with population-based data.[25] Collectively, these data suggest that the therapeutic target in IBD has changed to prevention of progression to structural bowel damage.

Novel clinical scores

Recently, in CD, a score that accounts for cumulative bowel damage and disease activity has been introduced: the Lémann score.[26] The Lémann score proposes to (i) measure cumulative bowel damage at a specific time in a patient's history; (ii) measure the progression of bowel damage over time; (iii) identify high-risk patients and (iv) compare the effects of treatment on disease progression.

The damage score will be based on a comprehensive evidence of bowel damage including features of complicated disease and surgical resection. The Lémann score aims to differentiate patients with similar clinical activity but different disease prognosis in order to alter the paradigm of the treatment strategies in CD. However, before the Lémann score can be used in clinical practice, prospective studies validating the score and randomized controlled trials demonstrating that outcomes change are needed. Furthermore, a similar score in UC is lacking.

Disability and quality of life

Treatment strategies should achieve prevention of IBD-related disability and impaired quality of life. Several factors have been associated with these qualitative outcomes. Quality of life is often assessed by the 36-item version (or shorter validated versions) of the IBD questionnaire (IBDQ), which also correlates with increased disability. In one study, independent

predictors of a low IBDQ included females, hospitalizations for disease flare, symptomatic activity, disease recurrence and a low education level.[1] Other studies have identified surgical intervention,[27] perianal disease, persistently active disease, other chronic diseases and the presence of a stoma as significant factors for disabling disease.[28]

The World Health Organization assesses disability using the integrative model of human functioning and disability in the International Classification of Functioning, Disability and Health (ICF). The ICF possesses four levels of details that include over 1400 categories and is not IBD specific. In a recent consensus conference and after four preparatory studies (systematic literature reviews, qualitative studies, expert surveys and cross-sectional studies), the 'IBD disability index' was developed. This index has 19 ICF core set categories: seven on body functions, two on body structures, five on activities and participation and five on environmental factors. The IBD disability index will require validation prior to utilization by clinicians and clinical trialists.[29]

In an attempt to specifically quantify work-related disability, the CD-perceived work disability questionnaire [30] has now been validated as a reliable tool for measuring subjective work disability in CD through its significant correlation with impaired quality of life in CD patients as measured by the IBDQ.

Novel strategies: treatment beyond symptoms

Biological monotherapy

The treatment paradigms have now shifted in the management of IBD. The target goal of mucosal healing with the overall aim to decrease total disease burden and disability has never been as important as in recent years. Medical management of IBD patients will need to adapt to achieve these evolving endpoints.

In an endoscopic sub-study of 99 patients in the ACCENT 1 trial, 29% (13/45) of patients had achieved mucosal healing after induction at Week 10. In the subject cohort who were dosed with scheduled infliximab the rate of mucosal healing rose to 44% (16/36) after 54 weeks as opposed to 18% (4/22) among patients who received episodic treatment.[15]

In a randomized, double-blind, placebo-controlled trial (EXTEND trial), adalimumab monotherapy was assessed for the induction and maintenance of mucosal healing in 135 patients with ileocolonic CD.[31] Baseline disease activity was assessed with an index colonoscopy. All patients were induced in a standard fashion and then randomized to adalimumab 40 mg every other week or placebo from Week 4. Open-label extension was available for non-responders as from Week 8. Endoscopic mucosal healing was assessed at Week 12 and at the end of follow-up at Week 52. At Week 12, mucosal healing was witnessed in 27% of subjects in the treatment arm vs. 13% in the placebo arm ($P = 0.056$). At the end of follow-up, none of the subjects in the placebo arm achieved mucosal healing while 24% of subjects who had received scheduled adalimumab were in remission ($P = 0.001$). Similarly remission rates were significantly higher in adalimumab-treated subjects at both Weeks 12 and 52. In a subsequent sub-study of the EXTEND trial, deep remission, a composite endpoint of clinical remission and mucosal healing at 12 weeks has been shown to predict a better outcome at Week 52. Patient in deep remission at Week 12 needed less adalimumab optimizations, had less hospitalizations or CD-related surgery and a better quality of life at Week 52 than patients not in deep remission. These studies compositely point to the importance of mucosal healing as a very important endpoint.[32]

The MUSIC trial is an open-label 54-week trial designed to study the effect of certolizumab pegol on mucosal healing.[33,34] Subjects with active endoscopic disease (ulcerations in ≥2 intestinal segments with a CD Endoscopic Index of Severity [CDEIS] score ≥8 points) were treated with 400 mg of subcutaneous (s.c.) certolizumab pegol every 2 weeks for the 4 weeks and then 400 mg of s.c. certolizumab pegol every 4 weeks till 54 weeks. The primary endpoint was a change from baseline in the CDEIS score at Week 10. A total of 89 patients were enrolled with a mean CDEIS score of 14.5. The CDEIS score decreased to a mean of 8.3 in the 78 patients completing 10 weeks of treatment and a mean of 9.6 in

the 53 who completed the study. Of all the study cohort, 61.5 and 62.3% of patients showed an endoscopic response, while 42.3 and 28.3% achieved endoscopic remission and 11.5 and 18.9% achieved complete endoscopic remission at 10 and 54 weeks, respectively. Certolizumab pegol improved endoscopic lesions and induces endoscopic response and remission in CD patients with active, severe endoscopic disease.

In a logistic regression analysis of the MUSIC data, CDEIS ($P = 0.0047$) and CRP level ($P = 0.0146$) were statistically significant prognostic factors of endoscopic remission. Lower baseline CDEIS or CRP level was associated with higher remission rates, thus highlighting that following certolizumab pegol exposure, baseline disease status (CRP and CDEIS) is the best predictor of success.[33]

Similar data are available for natalizumab, a humanized monoclonal antibody to α4-integrin. In 53 patients in whom endoscopic data were available in the ENACT-1 study, 22% of the patients who showed mucosal ulcerations at study entry achieved complete mucosal healing as opposed to 8% who were exposed to placebo.[35]

Combination therapy

Although monotherapy with biologics can achieve mucosal remission, combination therapy with an immunomodulator may be more efficacious.

The importance of combination therapy was further studied by another recent pivotal study in CD —the SONIC trial.[36] This randomized double-blind study investigated the efficacy of infliximab monotherapy, azathioprine monotherapy and a combination of the two. Five-hundred and eight adult patients were recruited and were followed up to 50 weeks. All patients had early disease (<2 years). Infliximab was given at a dose of 5 mg/kg at 0, 2 and 6 weeks with 8 weekly dosing thereafter. Azathioprine was prescribed at a dose of 2.5 mg/kg.

At 26 weeks, 56.8% of patients treated with combination therapy were in corticosteroid-free remission when compared with 44.4 and 30% receiving infliximab ($P = 0.02$, when compared with the group treated with combination therapy) and azathioprine monotherapy ($P < 0.001$ for the comparison with combination therapy and $P = 0.006$ for the comparison with infliximab), respectively. Similar outcomes were reported at the end of follow-up.

At 26 weeks, 43.9% of patients treated with combination therapy achieved mucosal healing when compared with 30.1 and 16.5% receiving infliximab ($P = 0.06$, when compared with the group treated with combination therapy) and azathioprine monotherapy ($P < 0.001$ for the comparison with combination therapy and $P = 0.02$ for the comparison with infliximab), respectively. No significant differences in adverse events were noted between the groups. *Post hoc* analysis suggested that patients with evidence of inflammation (a high CRP and endoscopic evidence of mucosal ulceration) showed the best response to infliximab therapy. It is not clear how much mucosal healing is needed to ensure long-term remission. A recent sub-analysis of the SONIC trail suggested that mucosal healing at Week 26 (defined as at least a 50% reduction in the SES-CD score) is associated with corticosteroid-free remission at Week 50.[37] These studies indicate that the combination therapy with azathioprine and infliximab is superior to either therapy alone in achieving corticosteroid-free remission and mucosal healing.

In the pivotal 'step-up' 'top-down' trial,[12] 60% of patients given combined immunosuppression were in remission, compared with 35.9% of controls ($P = 0.0001$) by Week 26. At 52 weeks, 61.5% of patients in the combined immunosuppression group were in remission as opposed to 42% in the conventional management group ($P = 0.0278$). After Week 52, the proportion of patients in remission did not differ between the two treatment arms. The median time to relapse after successful induction therapy at Week 14 was longer for patients assigned to early immunosuppression than for controls. Patients in the combined immunosuppression group were less exposed to steroids but to more immunosuppression. At the end of the study the proportion of patients on infliximab was similar in both groups. Patients in the combined immunosuppression group showed a more rapid drop in disease activity as measured by Crohn's disease activity index (CDAI) ($P = 0.0184$) and C-reactive protein (CRP) ($P = 0.0244$). After

Week 10, the mean CDAI in both groups was similar. Quality of life as measured by IBDQ improved more rapidly by Week 10 in the combined immunosuppression group ($P = 0.0014$) than in the control group. After that time point, mean IBDQ scores were similar in both groups.

Though the proportion of patients achieving the primary endpoints was similar in both groups, the proportion of patients achieving mucosal remission was still significantly different in the two groups at the end of the study. Endoscopic healing did not correlate with symptomatic remission as defined by a CDAI score of <150.

Two recent randomized controlled trials in CD comparing early azathioprine therapy to conventional immunosuppression (azathioprine use in steroid-dependent disease)[38] and early azathioprine therapy to placebo[39] have failed their primary endpoints as well, thus disputing the notion of step-up therapy. These studies did not show a clear benefit in using early azathioprine in achieving sustained corticosteroid-free remission, although patients exposed to early azathioprine experienced less symptoms from active perianal disease[38] and less clinical relapses.[39]

A recent meta-analysis, investigating the efficacy and safety of combination therapy vs. anti-TNF monotherapy, has since disputed these findings.[40] Overall, combination therapy was no more effective than monotherapy for induction or maintenance of response, partial or complete fistula closure and incidence of serious adverse events. In subsequent subgroup analyses, combination therapy was more effective than monotherapy for 6-month remission in patients exposed to infliximab but not to other anti-TNFs. Specifically in this group, combination therapy was associated with fewer infusion reactions. The study concluded that when initiating infliximab, the continued use of an immunomodulator may be associated with greater clinical remission rates and fewer infusion reactions. When using other anti-TNFs, these findings do not support the use of combination therapy.

To investigate the effect of combination therapy in steroid refractory moderate-to-severe UC, Panaccione *et al.*[41] conducted a 16-week, randomized, double-blind, controlled trial in biologic- and azathioprine naïve patients (or azathioprine withdrawn ≥3 months before study entry.

Two-hundred and thirty-nine subjects were randomized to azathioprine monotherapy (2.5 mg/kg), scheduled infliximab monotherapy or combination therapy. At Week 8, non-responders (defined as failure to reduce the Mayo score by 1 point) in the azathioprine monotherapy arm were eligible for infliximab open-label treatment. The primary endpoint was steroid-free remission at Week 16 and a total Mayo score ≤2. Secondary endpoints included response (decrease in total Mayo score of ≥3 points and at least 30% lower than baseline Mayo score) and mucosal healing (Mayo endoscopy subscore of 0 or 1) at Week 16. A significantly greater proportion of patients achieved steroid-free remission at Week 16 in the combination treatment arm (44%, $P < 0.05$) when compared with the azathioprine monotherapy arm (24%). Clinical response was achieved by greater proportions of patients in both infliximab arms (77 and 69% for combination therapy and infliximab monotherapy, respectively; $P < 0.05$) when compared with the azathioprine arm (50%). Moreover, mucosal healing response was achieved by greater proportions of patients in both infliximab arms (63 and 55% for combination therapy and infliximab monotherapy, respectively; $P < 0.05$) when compared with the azathioprine arm (37%). These findings echo the ones in CD and once again support the use of combination therapy.

Withdrawal studies

Although combination therapy seems to be superior, these data apply only to patients with early disease, with evidence of inflammation and naïve to immunotherapy and infliximab therapy. The concept of deep remission defined as mucosal healing and clinical remission has been suggested as a possible useful composite outcome to identify patients in whom it might be permissible to withdraw biological therapy.

The importance of combination therapy was further investigated in a withdrawal study carried out by Van Assche *et al.*[42] Eighty patients with stable CDAI (>6 months) after the start of episodic or

scheduled maintenance infliximab (5 mg/kg) therapy and combined immunosuppression with azathioprine or subcutaneous methotrexate were recruited for this study. Patients were then randomized in 1:1 fashion to continue combination therapy or withdrawal of immunotherapy (azathioprine or methotrexate) and were followed up for 104 weeks. Primary endpoint was the proportion of patients who required a decrease in infliximab dosing interval or stopped infliximab therapy. The only significant difference noted between the two groups at the end of the study was a significantly higher trough infliximab level and lower CRP in the combination therapy group when compared with the infliximab monotherapy group. No difference in mucosal healing was noted between the two groups by the end of the study. Although this study did not meet its endpoints, the effect of combination therapy was still evident at the end of follow-up. Possibly, a longer follow-up in this study might have highlighted to a greater and more clinically significant extent the effect of combination therapy.

In a separate observational study on patients with CD in clinical remission on a combination of infliximab and azathioprine, azathioprine withdrawal was shown to be associated with a high risk of relapse in patients with a duration of combination therapy of <27 months and/or the presence of biological inflammation as evidenced by a CRP > 5 mg/l (HR = 4.79, $P = 0.008$) and platelet count > 298×10^9/l (HR = 4.75, $P = 0.02$).[43]

Subgroup analyses of other clinical trials of infliximab that included patients who were previously exposed to azathioprine but failed to respond showed no added benefit for treatment with combination therapy during a 6–12 month period when compared with infliximab monotherapy.[44]

In a separate withdrawal study (STORI),[45] 115 patients with CD treated with combination therapy of infliximab and an anti-metabolite (azathioprine, 6-MP or methotrexate) for at least 1 year and in corticosteroid-free remission for at least 6 months were recruited for this study. Infliximab was discontinued in all patients. The primary endpoint was clinical relapse defined by a CDAI >250 points or between 150 points and 250 points with a 70-point increase from baseline over 2 consecutive weeks. Patients were followed up until they relapsed with a median follow-up period of 28 months. Upon relapse the prior treatment schedule was re-introduced. Approximately 50% of patients relapsed within 1 year. Based on multivariable cox regression analysis, risk factors for relapse included male sex, no history of abdominal surgery, active disease as evidenced by a high leukocyte count, high CRP, high faecal calprotectin level and low haemoglobin. Patients with no more than two of these risk factors had a 15% risk of relapse within 1 year. Rescue treatment with infliximab was effective in the short term in the majority of patients.

In a similar study comparing the effect of combination therapy with subcutaneous methotrexate and scheduled infliximab to methotrexate monotherapy in active luminal CD induced with steroids showed no additional benefit of combination therapy in this group.[46]

These studies show that combination therapy may be superior to biological monotherapy or azathioprine monotherapy both in CD and in UC. The difference between a 'step-up' approach to a 'step-down approach' is not immediately meaningful. A 'step-up' approach does induce significantly higher rates of mucosal remission though these findings are not consistent and universal. The information presented in this section should be used with a broader picture in mind. A more stringent adherence to mucosal remission outcomes should be applied to patients with more aggressive disease. A slightly more lenient approach is permissible in cases where the disease is more indolent. Successfully classifying patients in these two categories requires experience by the gastroenterologist.

Novel drugs

Newer anti-TNF therapies

Up to now, conventional or novel therapy in IBD has been instituted with classic immunosuppressive drugs or in-label anti-TNF therapy. Golimumab (Johnson & Johnson, New Brunswick, NJ, USA), an IgG1 monoclonal antibody to TNF with greater affinity and neutralizing capacity to TNF than

adalimumab has recently been used out-of label IBD and in clinical trials. Data from a large phase 2 dose ranging followed by a phase 3 confirmatory placebo-controlled clinical trial assessing golimumab induction therapy is now available. Primary endpoint was clinical response at Week 6 in patients enrolled after dose selection. Subjects were exposed to either placebo or golimumab 100/50 mg or golimumab 200/100 mg or golimumab 400/200 mg at Weeks 0 and 2. Subjects with moderate-to-severe UC have shown a significant increase in clinical response, remission, mucosal healing rates and IBDQ scores when compared with placebo without a significant increase in adverse events at the end of the study at Week 6. All patients were ant-TNF naïve.[47]

Patients who completed the induction phase study were entered in a phase 3 double-blind trial.[48] Patients who had responded to induction therapy were randomly assigned to placebo or golimumab 50 or 100 mg through to 52 weeks. Patients who had responded to placebo in the induction study were maintained with placebo while those who did not, were treated with 100 mg of golimumab. The primary endpoint was clinical response maintained through to Week 54 and secondary endpoints were clinical remission and mucosal healing at Weeks 30 and 54.

Golimumab 100 mg achieved a significantly higher clinical response (50.6%), clinical remission (28.6%) and mucosal healing (43.5%) when compared with 50 mg or placebo. Safety data were consistent with that from other anti-TNF drugs.

In a small open-label experience study, Ben-Bassat *et al*.[49] showed promising results in CD with 56% of subjects achieving steroid-free remission at Week 12, with 78% of patients maintaining remission to Month 17.

These data show encouraging results for a fourth anti-TNF drug in IBD and further studies are needed to validate this.

Newer molecular targets

Tofacitinib (CP-690–550) (Pfizer, New York city, USA)

Tofacitinib is an oral janus kinase (JAK) inhibitor that has been investigated in both moderate-to-severe CD and UC. The JAK family is one of 10 recognized families of non-receptor tyrosine kinases. Each protein has a kinase domain and an inactive pseudokinase domain. These proteins are usually found at the cytosol but because of their interaction with cytokine receptors, they localize to the plasma membrane. Upon binding of cytokines to their receptors, JAKs are activated and phosphorylate the receptors, leading to activation of signalling transduction pathways, namely members of the signal transducer and activator of transcription (STAT) family. JAK1 inhibition leads to inactivation of receptor families with the shared subunits γc or gp130 and a downregulation of interferon (IFN). JAK2 inhibition leads to a decrease in interleukin 3 receptor families with the shared subunit gp130, IFN-γ and hormone-like cytokines (e.g. growth hormone, prolactin) signalling. Finally, JAK3 inhibition leads to inhibition of receptor families with a γc shared subunit.

Tofacitinib inhibits JAK 1, 2 and 3 with *in vivo* specificity on JAK 1 and 2 over JAK 3. Altered signalling of JAK1 and 3 will lead to modulation of γ-chain containing cytokines predominantly interleukins 2, 4, 7, 9, 15 and 21. This is thought to be beneficial in IBD.

In a multicentre, double-blind, randomized, placebo-controlled phase 2 study, in moderate-to-severe UC, 194 subjects were randomized to receive twice daily tofacitinib at doses of 0.5, 3, 10 and 15 mg and placebo. Clinical benefit was suggested by the finding of response rates at 8 weeks in 32, 48, 61, 78 and 42% of patients in each group, respectively. A dose-dependent improvement in clinical response and remission was noted in this UC cohort. The drug was once again well tolerated.[50] To this effect, tofacitinib was later shown to possess linear pharmacokinetic properties in UC patients as in normal subjects.[51] These data show encouraging results in UC with larger studies awaited

Traficet-EN (CCX-282B) (GlaxoSmithKline, Middlesex, UK)

Traficet-EN is an oral bio-available, CCR9-specific chemokine antagonist. CCR9 is a member of the beta chemokine receptor family. The specific ligand of this receptor is CCL25 and is differentially expressed by T lymphocytes of the small intestine and colon, suggesting a role in thymocyte recruitment.

In a phase 2 placebo-controlled trial,[52] 71 subjects with moderately active CD (CDAI 220–450) were randomized to receive 250 mg of CCX-282B daily or placebo in a 2:1 ratio. The primary endpoint was clinical response as measured by a 70-point drop in CDAI. No significant difference was noted between the treatment and placebo arms of the study but a subpopulation analysis (in subjects with a CDAI of 250 and a CRP of 7.5 mg/l) showed a significant difference in clinical response between the CCX-282B arm of the study (58%) vs. the placebo arm (31%). Stepwise subpopulation analyses show increasing difference between the treatment and placebo cohort in 70-point reductions in CDAI.

PROTECT-1 is a multinational, randomized, double-blind, placebo-controlled trial in 436 subjects with moderate-to-severe CD. Three doses of 250 mg QID, 250 mg BID and 500 mg QID were compared with placebo. The primary endpoint of this trial was a 70-point drop in CDAI assessed at 12 weeks. The 500 mg dose was consistently better than placebo across all efficacy endpoints. At the end of follow-up, a higher proportion of subjects treated with this dosage achieved the CDAI ≥ 70-point response (61 vs. 47%; $P = 0.039$) and the CDAI ≥ -100-point response (55 vs. 40%; $P = 0.029$). Efficacy was observed irrespective of disease location. Traficet-EN significantly decreased disease burden as shown by the increased rates of mucosal remission observed in subjects exposed to Traficet-EN 500 mg QID when compared with placebo (CDAI of severity drop −8.4 vs. −1.1; $P = 0.049$) and the median decrease in CRP of −6.7 vs. −2.9 mg/l in Traficet-EN 500 mg QD and placebo, respectively. Overall, Traficet-EN was well tolerated across all doses studied.[53]

The 241 subjects who achieved response as predefined by the primary endpoint were re-randomized to maintenance Traficet-EN 250 mg BID for 36 weeks or placebo. At the end of the study, 47% of subjects on Traficet-EN were in remission vs. 31% on placebo ($P = 0.01$), while 41% of subjects were in corticosteroid-free remission vs. 28% on placebo ($P = 0.04$). At 36 weeks, more subjects in the intention-to-treat group had a normal CRP (19 vs 9%; $P = 0.04$), and fewer subjects required corticosteroid rescue therapy (11 vs. 21%, $P = 0.04$).[53]

This study shows that this anti-chemokine is effective in the induction and maintenance of CD while being well tolerated in most subjects.

Antibodies to interleukin 12/23

Interleukin 12 and 23 have been implicated in the pathophysiology of CD, while a gene wide association study has identified a significant association between CD and a receptor subunit of interleukin 23.

Interleukin 12 is essential in the differentiation of naïve $CD4^+$ T cells into Th1 T cells, which predominantly produce interleukin 2 and IFN γ, pivotal in CD pathogenesis. Interleukin 12 is a heterodimer of p40 and p35 subunits. Interleukin 23, a heterodimer of p40 and p19 subunits is important in the differentiation of TH17 T cells. This T cell subset produces interleukin 17, interleukin 17F, interleukin 6 and TNFα to mediate cellular immunity. Inhibiting both these interleukins would have a broad and overarching effect. Monoclonal antibodies to the p40 subunit of IL12/23 are effective in treating murine colitis.

Ustekinumab (interleukin 12/23 p40 subunit monoclonal antibody) (Janssen Biotech, Pennsylvenia, USA)

A double-blind, cross-over phase 2a study investigating the clinical effects of ustekinumab in 104 patients with moderate-to-severe CD has been carried out.[54] Primary endpoint was clinical response at Week 8 after induction (25% decrease or a 70-point drop in CDAI). Clinical response rates for ustekinumab and placebo-treated subjects were 53 and 30% ($P = 0.02$), respectively, at Weeks 4 and 6, and 49 and 40% ($P = 0.34$), respectively at Week 8. In a subgroup analysis of patients who were previously non-responders to infliximab, the response rates were more significant ($P < 0.05$). After open-label extension treatment, the clinical response rates at 6 weeks were greater in the intravenous group (62%) than the subcutaneous group (36%). These data suggest a utility of ustekinumab for moderate-to-severe Crohn's disease particularly in patients with non-responsive disease to prior anti-TNF therapy.

These findings were further investigated in a phase 2b randomized, double-blind, placebo-controlled

trial in 526 CD patients who failed prior anti-TNF therapy.[55] All patients had moderate-to-severe disease with a CDAI of 220–450. Other chronic medications were allowed and patients had to be off their anti-TNF drugs for 8 weeks before enrolment. Patients had mean disease duration of 12.3 years and the majority had an ileocolonic disease location. More than a third (n = 190) of the study cohort discontinued the study before 36 weeks due to unsatisfactory therapeutic effect, loss to follow-up, failure to adherence to protocol, adverse events or worsening of the disease activity.

At Week 6, using intravenous ustekinumab at 6 mg/kg, the observed rates of clinical remission were lower when compared with placebo but showed no significant difference between the different treatment arms. A significantly greater clinical response (39.7%) was shown in the 6 mg/kg ustekinumab group when compared with placebo (23.5%, $P = 0.005$). A significant improvement was also shown across other secondary endpoints, including greater reductions in mean CRP, CDAI score and greater proportion of patients with a 70-point decline in CDAI.

Patients who showed a clinical response to induction with intravenous ustekinumab received 90 mg of ustekinumab sc at Weeks 8 and 16. There was a significantly higher clinical response (69.4 vs. 42.5%) and clinical remission (41.7 vs. 27.4%) at Week 22 in the ustekinumab group when compared with the placebo group. Sustained reduction in CDAI scores and CRP levels were achieved in subjects on maintenance ustekinumab rather than placebo. Subjects who did not show a clinical response at ustekinumab induction showed no response at Week 22 after maintenance therapy. The safety profile of ustekinumab in this phase 2b study was reassuring though more than a third of patients did not complete the study. Of note, a basal cell carcinoma was reported in a patient in the ustekinumab group. Data from the ongoing phase 3 trial are awaited to clarify the safety and drug efficacy findings observed in these two trials.

Observations from real life practice have shown encouraging efficacy data and a good safety profile for ustekinumab in CD. Ustekinumab use on a compassionate programme has been retrospectively analysed recently in a cohort of Spanish patients previously exposed to multiple immunosuppressive and anti-TNF agents.[56] Ileocolonic CD was found in the majority of patients (57.6%) with 60.6% of this cohort showing only an inflammatory behaviour. Most subjects had long-standing disease (median 10 years, range 1–34) and over half had at least one previous intestinal resection (range 1–7). A large proportion of this patient cohort had previously failed at least two immunosuppressants (66.7%) and anti-TNF agents (78.7%). The most frequent induction schedule (65.4%) was 90 mg weekly sc for 4 weeks, with 73.1% being treated with a 90 mg sc ustekinumab 8-weekly maintenance schedule. After induction, 57.7% of subjects responded while 30.3% of patients showed a response at the end of follow-up. Of all treated subjects, 26.9 and 45.5% were in remission after induction and at the end of follow-up, respectively. These data show that even out of the clinical trial setting, ustekinumab showed promising results especially in the treatment-resistant anti-TNF-refractory patient population.

Vedolizumab (humanized antibody to α4β7 integrin) (Millenium, Pennsylvenia, USA)

Lymphocytes adhere to and migrate through the vascular endothelium in response to inflammatory stimuli. Integrins are heterodimeric glycoproteins expressed on the cell surface of the lymphocyte that mediate migration of lymphocytes after interaction with their receptors on the vascular endothelium. Theoretically, blocking integrin activity would attenuate lymphocyte migration. Natalizumab is a selective adhesion molecule antagonist which blocks the interaction between the α4-integrin-containing heterodimers, α4β7 and α4β1, and their receptors on the vascular endothelium—primarily mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and to a lesser extent vascular cell adhesion molecule-1 and. In phase 3 trials, natalizumab has shown to be effective in the treatment of CD[35] and multiple sclerosis. However, three cases of progressive multifocal leucoencephalopathy (PML) had been identified in subjects exposed to natalizumab. Since then, natalizumab has been available for use in CD only through special dispensation in the USA.

The humanized monoclonal antibody MLN0002 (vedolizumab) is a highly selective adhesion molecule antagonist that targets specifically the interaction between α4β7 integrins on lymphocytes and its specific ligand MAdCAM-1 whose expression is increased in IBD. MLN0002 differs from natalizumab in that its actions are specific to the α4β7 integrins and not its monomers. Through this gut-specific action, it is postulated that vedolizumab would not pose the same PML risk as natalizumab while still possessing a significant therapeutic effect in IBD.

In a phase 2 double-blind placebo-controlled trial in CD, patients were randomized to receive MLN0002 2.0 mg/kg ($n = 65$), MLN0002 0.5 mg/kg ($n = 62$) or placebo ($n = 58$) by intravenous infusion on Days 1 and 29.[57] The primary efficacy endpoint that was clinical response (CDAI ≥ 70-point response) at Day 57 was met by 53, 49 and 41% in the MLN0002 2.0 mg/kg, MLN0002 0.5 mg/kg and placebo groups, respectively. Clinical remission rates at the same time point were 37, 30 and 21%, respectively ($P = 0.04$ for the 2.0 mg/kg vs. placebo comparison). These data suggest a dose-dependent effect of MLN0002 on clinical remission. This drug was well tolerated.

A phase 3, randomized, parallel-grouped, double-blind, placebo-controlled trial was run from December 2008 to May 2012 in adult patients with active CD.[58] In the induction trial, 368 patients were randomly assigned to receive intravenous vedolizumab therapy (300 mg) or placebo at Weeks 0 and 2 (cohort 1), while 747 patients received open-label vedolizumab at Weeks 0 and 2 (cohort 2). The co-primary endpoints for the induction trial were clinical remission (CDAI < 150) and a CDAI-100 response (>100-point decrease in CDAI). The secondary endpoint was mean change in CRP levels from baseline to 6 weeks. The patient cohort recruited for this study had considerable disease burden. Patients had a mean baseline CDAI of 324, a median CRP of 11.5 mg/l and a median faecal calprotectin level of 686 μg/g. A third of the patients had a penetrating disease phenotype with 42% of this patient cohort having had at least one intestinal resection. Half of all the patients recruited for this study had failed at least one anti-TNF drug. The primary endpoint for the maintenance trial was clinical remission at Week 52. The co-secondary endpoints in a ranked order were, CDAI-100 response, glucocorticoid-free remission (clinical remission at Week 52 in the absence of glucocorticoid therapy) and durable clinical remission (clinical remission in >80% of the visits).

The primary endpoint in the induction trial was achieved in 14.5% of patients in the vedolizumab arm in cohort 1 vs. 6.8% of patients in the placebo arm ($P = 0.02$). Only 31.4% of the vedolizumab-exposed patients achieved a CDAI-100 response when compared with 25.7% of patients exposed to placebo ($P = 0.23$). Of the patients exposed to vedolizumab in both cohorts, 39 and 36.4% of patients receiving vedolizumab every 8 and 4 weeks, respectively, achieved clinical remission at Week 52 when compared with placebo (21.6%, $P < 0.001$ and $P = 0.004$, respectively). CDAI-response and glucocorticoid-free remission were significantly more common in the vedolizumab-exposed patients but durable clinical remission was not significantly different amongst the studied groups. When compared with placebo, serious adverse events, serious or not serious infections were more likely in the patients exposed to vedolizumab.

In a short-term study in UC, blocking α4β7 activity proved to be effective.[59] In this phase 2 double-blind placebo-controlled trial, 181 patients were randomized to the same dosing regimen described in the phase 2 CD study. The primary endpoint was clinical remission at Week 6 (Mayo score of 0 or 1) after a clinical and sigmoidoscopic assessment. Clinical remission at Week 6 was seen in 33, 32 and 14% of subjects exposed to the 0.5 mg/kg, 2 mg/kg and placebo, respectively ($P = 0.03$). Correspondingly, 66, 53 and 33% of patients had a three-point drop in the Mayo score ($P = 0.002$), while 28, 12 and 8% achieved mucosal remission, respectively ($P = 0.007$). These data showed that vedolizumab may be effective in inducing clinical and mucosal healing in UC.

A phase 3 randomized, placebo-controlled double-blind multicentre trial investigated vedolizumab therapy as an induction and maintenance agent in UC.[60] The primary endpoint was clinical response at 6 weeks (a reduction in complete Mayo score of ≥3 points and ≥30% from baseline, with a decrease in rectal bleeding subscore of ≥1 point or an absolute

rectal bleeding subscore of ≤1 point). In the induction trial, 374 patients were randomly assigned to receive intravenous vedolizumab therapy (300 mg) or placebo at Weeks 0 and 2 (cohort 1), while 521 patients received open-label vedolizumab at Weeks 0 and 2 (cohort 2). In the maintenance trial, 373 patients who showed a clinical response in the induction trial were assigned to receive placebo or vedolizumab every 4 or 8 weeks till Week 52. At 6 weeks significantly greater proportion of vedolizumab-treated patients achieved clinical response (47.1 vs. 25.5%, $P < 0.001$), clinical remission (16.9 vs. 5.4%, $P = 0.0001$) and mucosal healing (40.9 vs. 24.8%, $P = 0.0001$) when compared with placebo. At 52 weeks, 41.8% of patients who received vedolizumab every 8 weeks and 44.8% of patients who were on 4-weekly treatment were in remission ($P < 0.0001$ vs. placebo). Rates of durable clinical response and remission, mucosal healing and glucocorticoid-free remission were higher in the vedolizumab exposed. No differences were observed between the two vedolizumab regimes. Concurrent treatment or previous exposure to anti-TNF agents did not significantly affect the response to vedolizumab. The incidence of adverse events was similar between the vedolizumab and placebo-treated groups. Both these studies show very encouraging results for vedolizumab in both UC and CD. This drug might offer a completely different therapeutic option to patients who are refractory to anti-TNF therapy.

Etrolizumab (humanized IgG1 monoclonal antibody to the β7 subunit of α4β7 and αEβ7 integrins) (Roche, Basel, Switzerland)

Etrolizumab is a monoclonal antibody to α4β7 and αEβ7 integrins. Its specific actions on α4β7 inhibit this glycoprotein's binding with its primary ligand MAdCAM-1. This phenomenon has a negative effect on gut-specific lymphocyte migration. αEβ7 integrin is expressed exclusively on mucosal intraepithelial T lymphocytes. αEβ7 binds selectively to E-cadherin on epithelial cells and has been proposed to play a role in the retention of T lymphocytes in the mucosa. Inhibiting αEβ7 integrins with etrolizumab antagonizes the retention of lymphocytes in the mucosa. A recent phase 1 showed suitable drug pharmacokinetics and reassuring safety data.[61] The clinical improvement witnessed prompted a further phase 2 study.

In a parallel, randomized, double-blind, placebo-controlled phase 2 study, 124 patients with refractory moderate-to-severe UC were recruited.[62] The primary efficacy endpoint was clinical remission at Week 10 (defined as a total Mayo score of ≤2 with no individual subscore >1) and a secondary endpoint of endoscopic remission at Week 10.

Patients were randomized in a 1:1:1 fashion to placebo or 100 mg sc of etrolizumab or 420 mg loading dose between Week 0 and Week 2 and 300 mg monthly. Stable medication was allowed to Week 10 and patient assessment with Mayo scoring was carried out at Weeks 0, 6 and 10.

At Week 10, etrolizumab at a dose of 100 mg sc showed the best clinical remission rates (20.5%) and endoscopic remission (10.3%) when compared with the other etrolizumab-exposed group and placebo. Patients who were anti-TNF naïve showed even more significant results in this group. Etrolizumab demonstrated full occupancy of integrin receptors in both colonic tissue and peripheral blood lymphocytes. The incidence of adverse events was comparable between the three groups. These encouraging results in this phase 2 study warrant further investigation in larger phase 3 studies.

Trichuris Suis (Coronado Biosciences, Burlington, MA, USA)

The prevalence of helminthic colonization is opposite to that of IBD. It is less common in areas of the world where IBD is prevalent: the Western world, thus bringing forward the hygiene hypothesis. Heminths down-regulate the host immune response to unrelated antigens. This property is beneficial to patients with IBD.[63] To this effect *Trichuris suis* seemed to be beneficial for IBD.[64] After successful initiary studies assessing safety and efficacy,[64] open-label clinical studies showed very promising results with 79.3% of patients experiencing a response and 72.4% achieving remission after ingesting individual aliquots of 2500 *Trichuris suis* ova (TSO) suspended in a solution every 3 weeks for 24 weeks.[65]

In a randomized, double-blind, placebo-controlled trial (TRUST-I), 250 patients with moderate-to-severe CD were randomized to receive 7500 ova ($n = 125$) or

placebo ($n = 125$) every 2 weeks for 12 weeks. The primary endpoint for the study was induction of response at 12 weeks, with induction of remission being a key secondary endpoint. It has been recently communicated by the pharmaceutical company that this trial failed its primary and secondary endpoint. Further data are awaited on the results of a phase 2, double-blind, randomized, placebo-controlled, multicentre study in Europe (TRUST-II), where the efficacy and safety of three different dosages of TSO are being evaluated in active CD.[66]

Similar positive findings have been described in UC. In a randomized, double-blind, placebo-controlled clinical trial to determine the safety and efficacy of TSO in 54 patients with active UC, subjects were treated with 2500 TSO every 2 weeks for 12 weeks. After the first 12 weeks, placebo-treated patients were switched to TSO for another 12-week period and TSO patients were treated with placebo. The primary measure of efficacy was a decrease in the UC disease activity index (UCDAI) >4. Clinical remission (UCDAI < 2) was a secondary endpoint. When the two study periods were combined, TSO was associated with significantly higher response rates in both the intention-to-treat and per-protocol cohorts.[67]

PF-04236921 (anti-IL-6) (Pfizer, New York city, USA)

IL-6 is a pleiotropic cytokine that contributes to Th17 differentiation. Moreover, increased level of IL-6 and soluble IL-6R have been associated with an increased IBD disease severity[68] and IL-6 gene polymorphism has been associated with early-onset CD.[69] Tocilizumab is a monoclonal antibody against IL-6R. In this phase 1 trial only 20% of patients went into remission.[70] Other biological therapies presently targeting IL-6 include C326, (currently undergoing a phase I trial in CD); and PF-04236921, currently recruiting patients with CD unresponsive to anti-TNF in a phase I/II trial.[71]

LT-02 (retarded-release phosphatidylcholine) (Dr Falk pharma GmbH, Heidelberg, Germany)

One of the proposed hypothesis for the aetiology of UC is a breakdown in the mucosal barrier leading to recurrent attacks on the mucosa by commensal colonic bacteria.[72,73] Phospholipids are one of the components of the mucus lining the colonic mucosa, consisting of up to 90% phosphatidylcholine (PC) and lysophosphatidylcholine (LPC).[74] It has been shown in rat perfusion models that PC is mostly produced in the jejunum and ileum and not in the colon. It has thus been postulated that the colonic PC moves down through intestinal motility from the small bowel.[75] Mucous aliquots from UC subjects show greatly reduced PC and LPC content when compared with normal controls and CD patients.[76] The hypothesis that a local increase in PC might decrease the inflammatory activity in UC was thus investigated.

In a phase IIA, double-blind, randomized, placebo-controlled study in 60 patients with chronic active, non-steroid dependent, UC, with a clinical activity index (CAI) of >4; retarded release PC-rich phospholipids and placebo were administered at a dose of 6 g daily over 3 months.[77] The primary endpoint was a change in CAI towards clinical remission (CAI < 3) or CAI improvement by >50%. Secondary endpoints included >50% changes in endoscopic activity index, histology and quality of life scores. Induction of clinical remission was attained in 53% of the PC-treated group as opposed to 10% of controls. A 70% improvement in the CAI score was recorded in the treated group compared with no change observed in the placebo group. This drug reached all of its secondary endpoints. In a small study, PC supplementation was found to be beneficial in steroid-refractory UC as well.[78] A later larger phase II ($n = 156$)[79] multicentre trial and a smaller dose-ranging study[80] showed that a dose of 3.2 g of PC was the most effective, with subjects in this arm of the trial doubling their remission rate (31.4%) when compared with placebo-exposed subjects. A European and US-based phase III study is planned to start in last quarter of 2013.[81]

Conclusion

Novel concepts in IBD are emerging across the field. Symptomatic remission should not be the sole goal for the IBD-practicing physician anymore. Our best efforts should be directed at achieving mucosal remission while minimizing intestinal damage which might have long-term sequelae on quality of life. Moreover, minimizing intestinal inflammation

decreases the risk of colorectal cancer. Early therapy is of paramount importance, with an accelerated step-up approach or step-down approach with combination therapy in high-risk patients. Individualized therapy will be the cornerstone of IBD management.

The window of opportunity to effectively treat patients with CD is narrow with disease progression causing complicated disease which may be refractory to treatment. Timely and effective escalation of therapy is important in UC as well. Protracted and untimely medical management in acute moderate-to-severe disease might lead to complications and adverse outcomes.

Newer drugs are available on the horizon with specific pathway-blocking agents becoming more routinely available. Patients who are refractory to anti-metabolite or anti-TNF therapies will hopefully be treated with other agents targeted to other molecules in the inflammatory process such as IL-12/23 pathway and the integrin glycoproteins which are pivotal in gut lymphocyte trafficking.

Better strategies and newer biological agents will give further options to gastroenterologist to more effectively treat their IBD patients and further improve their outcomes and quality of life.

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