Evolving concepts in Phase I and II Drug Development for Crohn's Disease

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Abbreviations: AP, Abdominal Pain; ADA, Anti-Drug Antibodies; CD, Crohn's Disease; CDAI; Crohn's Disease Activity Index; CDEIS, Crohn's Disease Endoscopic Index of Severity; EI, Endoscopic Indices; FDAI, Fistula Draining Assessment Index; MRE, Magnetic Resonance Enterography; MaRIA, Magnetic Resonance Index of Activity; PRO, Patient Reported Outcome; PD, Pharmacodynamic; PK, Pharmacokinetic; PoC, Proof of Concept; PDAI; Perianal Disease Activity Index; SES-CD, Simplified Endoscopic Index of Severity; SF, Stool Frequency; TNF, Tumor Necrosis Factor; UC, Ulcerative Colitis; VAI, Van Assche Index.

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Abstract

The highest attrition rates during drug development programs occur at the proof of concept stage. Given the large number of molecules under development for Crohn's disease, a need exists to improve the efficiency of early drug development by fast-tracking promising agents and terminating ineffective ones. Multiple opportunities are available to achieve these goals, including the use of more responsive outcome measures, and the incorporation of sophisticated pharmacokinetic modeling and/or highly specific pharmacodynamic markers into exposure–based dosing regimens and novel trial designs. In this article we review these strategies and propose an integrated paradigm of early drug development in Crohn's disease.

Rationale

The past decade has seen remarkable progress in medical therapy for Crohn's disease (CD) that has been driven by advances in both clinical and basic science. New discoveries regarding molecular pathogenesis, candidate pathway identification by genetic association studies and transcriptome analysis, and the ability to perform translational medicine studies in humans have been key drivers of this evolution. From a clinical perspective, emphasis on identifying valid and responsive outcome measures[1-3], re-examination of pharmacokinetic (PK)/pharmacodynamic (PD) relationships[4-6] and more rigorously designed and larger trials have been notable developments.

The success of tumor necrosis factor (TNF) antagonist therapy has resulted in significant pharmaceutical industry investment in inflammatory bowel disease (IBD); over 800 clinical trials targeting IBD are currently planned or underway[7] and a wealth of additional agents are in preclinical development. Whilst this situation has great potential for improved patient care, it also poses a likely challenge to future progress in drug development.[8] This abundance of therapeutic potential places an unprecedented strain on investigator and patient resources that may already be strained. Failure to solve this problem is likely to result in a high rate of program failure and withdrawal of capital from the field.

Thus, early phase drug development in CD must become more efficient. Although this paradigm and a potential approach to drug development in ulcerative colitis (UC) has been proposed[9, 10], we feel the need to address similar concerns for drug development in CD may be more imperative. Consider the conventional model of CD drug development

(Figure 1); a dose-escalation PK/safety study in healthy volunteers is typically followed by a phase 2a combined proof of concept (POC)/parallel and multiple group dose-finding induction trial that employs the use of a clinical outcome measure such as a change in the Crohn's Disease Activity Index (CDAI) score or CDAI–defined remission (typically CDAI<150) as the primary endpoint. Detection of statistically significant differences using CDAI-based outcomes requires randomization of approximately 50 patients per treatment group. This model is problematic because the current rate of recruitment for CD trials is an average of 0.1 to 0.2 patients per center per month and may require up to 125 centers to recruit a three-armed trial (N=150) within one year.[11] Additionally, high placebo rates compromise the ability to detect meaningful therapeutic effects, and may be evidenced in data recently reported for agents in clinical development.[12, 13] Efficient drug development in CD will likely require an integrated strategy that features use of objective outcome measures of inflammation (endoscopy, histopathology, cross-sectional imaging and biomarkers (Table 1), patient-based dosing centered on PK/PD evidence, and novel trial design (Figure 1). In this article we outline the challenges and opportunities inherent to the development of a more efficient paradigm for early drug development in CD.

Components of an integrated approach to CD drug development

Efficient outcome measures

Conventional outcome measures for CD trials are predominantly symptom-based and empirically derived. The most frequently used efficacy measure in CD clinical trials is the CDAI[14] which is a composite of patient reported outcomes (PROs; pain, stool frequency, general well-being), physical signs and a laboratory parameter (haematocrit). Although

use of the CDAI as a primary outcome measure has led to regulatory approval of effective treatments for CD, it has poor specificity to detect active inflammation[15]. Furthermore, whilst it was developed according to accepted methodology 40 years ago, it was not created according to rigorous criteria for development of an evaluative index, nor was it developed with any patient input.[16] Regulatory authorities now mandate the use of PROs in CD trials, but no validated CD PROs, as defined by the criteria set forth by the United States Food and Drug Administration (FDA) currently exist.[17] This circumstance is a challenge because an extensive and lengthy process, that is both resource intensive and costly, is required to develop these instruments.[16] Candidate PROs should be based on items generated from qualitative interviews with patients for whom inflammatory burden is well characterized. These items must be shown to be feasible and interpretable by patients and clinicians.[18] Item reduction, index generation and formal reliability and responsiveness testing follow sequentially. Initiatives currently underway to create valid PRO instruments will take years to complete.

An empirically derived interim PRO measure, “PRO2”, has been developed to meet regulatory requirements for a symptom-based (non-CDAI) outcome measure.[19] PRO2 is a two-item index comprised of the stool frequency (SF) and abdominal pain (AP) items from the CDAI. The total PRO2 score is the sum of the weighted daily SF and AP item scores. Item thresholds are an average daily AP score ≤1 point and average daily SF ≤1.5 point. Effect size estimates for treatments of known efficacy (rifaxamin and methotrexate) were similar using either PRO2 or CDAI defined criteria in the original derivation study, and PRO2 benchmarks corresponding to CDAI scores of 150, 220 and

450 were determined to be 8, 14, and 34, respectively.[19] Other studies, using data from trials of different agents, have shown that SF cutoffs ≥3 or alternative thresholds for a weighted 2-item PRO have improved sensitivities and/or specificities to detect clinical outcomes (typically CDAI-defined remission) (Table 2), suggesting that additional research is needed to define the optimal index.[20,1] Weighting of the PRO items creates a greater range of scores with potentially superior discrimination that will likely result in the index mapping more closely to the original CDAI. However, weighting of PRO2 may not be acceptable to regulatory authorities, since this is derived by physicians rather than patients. Although symptom-based assessments, such as the CDAI are statistically inefficient, PRO2 is likely to serve as an interim outcome measure of symptomatic response in RCTs until a formalized PRO instrument is developed and validated, a process which could take several years. Alternative, more objective measures of inflammation such as endoscopy, magnetic resonance enterography (MRE) and histopathology should be considered for future early drug development programs.

Endoscopy

As well as demonstrating a beneficial effect on PROs, regulatory authorities also require demonstration of a beneficial effect on an objective measure of inflammation, namely endoscopy, for approval of new drugs. A precedent exists for this model in other areas. In the registration trials of Cimzia™ (certolizumab pegol) for rheumatoid arthritis, for example, meaningful improvement of a PRO (the disability index of the health assessment questionnaire), and an objective inflammatory endpoint based on radiographic assessment (American College of Rheumatology response [20%] criterion

and a modified total Sharp/van der Heijde score) were required as criteria for treatment success.[21] A similar paradigm has started to emerge in CD clinical trials.

Use of endoscopy at both the enrolment stage and as an outcome measure has the greatest potential to improve trial efficiency in CD. At the enrolment stage, centrally read endoscopy has been shown to minimize site investigator bias and reduce placebo rates in ulcerative colitis trials by ensuring patients have sufficiently active disease and excluding those patients whose symptoms are not due to inflammation.[22-25] Although empiric data are currently lacking for CD, similar principles are likely to apply. Data from the certolizumab MUSIC study of endoscopic mucosal improvement in CD showed that site investigators consistently overestimated lesion severity compared to central endoscopy readers at all time points, particularly at enrolment.[26] In the SONIC trial, 18% of patients who met the CDAI-based criterion for enrolment (220-450 points) did not have either active disease at ileocolonoscopy or an elevated CRP concentration.[1] A *post-hoc* analysis excluding these patients increased the estimate of treatment effect for combination therapy with infliximab and azathioprine compared with azathioprine monotherapy. These data support the requirement for endoscopically-confirmed active disease as an inclusion criterion for induction trials. The theoretical advantages of blinded centrally–read endoscopy as a component of a trial outcome measure are a more precise characterization of treatment response inherent to consistent scoring by expert readers, and the availability of visual images for auditing by regulatory agencies.

Two endoscopic indices (EIs) are currently available and have been previously used in CD clinical trials: the Crohn's Disease Endoscopic Index of Severity (CDEIS)[27] and the Simplified Endoscopic Index of Severity (SES-CD)[28] (Supplementary Tables 1 and 2). The inherent complexities of the CDEIS, particularly estimation of surface area on a 10-cm scale and estimation of ulcer depth from a two dimensional image, led to development of the SES-CD. Multiple studies have identified poor correlation of the EIs with the CDAI[29] setting the stage for a debate regarding the relative value of measuring inflammation directly with endoscopy or indirectly, through the secondary consequences of inflammation (pain, stool frequency) that are relevant to patients.

Preliminary validation data for both EIs were obtained during their original development, although systematic evaluation of instrument operating properties has only recently taken place. One study, that employed rigorous methods, demonstrated "susbstantial" to "almost perfect" overall inter-rater agreement for both the CDEIS and SES-CD.[30,29] A consensus process subsequently generated scoring conventions for poor performing index items in an attempt to improve their reliability. Inter-rater reliability for scoring of the SES-CD improved following training on these conventions, but was not improved for scoring of the CDEIS.[31] Based upon these data we believe that the SES-CD is likely to be the EI of choice for CD clinical trials. Although studies to rigorously assess the relative responsiveness of these EIs are currently underway, multiple questions remain regarding the validity of EIs, including the optimal method to account for unobserved segments and whether removal of stenosis, which is unlikely to be a responsive descriptor, improves index performance.

The use of EIs in clinical trials has historically focused on the binary outcome of remission, although this dichotomization of data results in loss of information. Use of these instruments as continuous measures has the potential to increase statistical efficiency by using all available data. For example, a recent study that evaluated the responsiveness of the SES-CD and CDEIS suggested per group sample sizes of 15-27 to detect statistically significant treatment effects (*personal communication*). This increased efficiency is attractive for early proof of concept and dose finding studies. Nevertheless, accurate definition of the responsiveness and minimum clinically important difference for the EI are unmet needs that limit wide-spread application of this approach. Recently, empiric thresholds have been selected for eligibility (such as a total SES-CD score ≥6 for ileo-colonic disease or ≥4 for isolated ileal disease) and for outcome assessment (including an SES-CD decrease of 50% or an absolute SES-CD score ≤4 for ileo-colonic disease or ≤2 for isolated ileal disease). Studies have used the following SES-CD total score benchmarks to define disease activity derived by consensus opinion rather than by objective data: remission (0-2), mild inflammation (3-6), moderate inflammation (7-16), and severe inflammation (>16).[32] These parameters require confirmation through research using large endoscopic datasets derived from placebo-controlled trials of treatments of known efficacy.

The optimal time point for measuring endoscopic improvement and mucosal healing in CD trials is unknown. In an endoscopic sub-study of the infliximab ACCENT1 trial, colonoscopy was performed at weeks 0, 10, and 54.[33] Week 54 mucosal healing (defined

as absence of all ulcerations) rates were much higher than those at week 10 (50% vs 30%, respectively). Similar patterns of mucosal healing (absence of ulcers) were observed in the adalimumab EXTEND trial; greater treatment effects compared to placebo were observed at week 52 (24% vs. 0% for placebo, P<0.001) compared to week 12 (27% vs. 13% for placebo, P=0.06).[34] A recent phase 2a trial of eldelumab (anti-IP-10) showed similar relatively low rates of endoscopic improvement (50% reductions in SES-CD) at week 11 (timing of primary endpoint) among patients with a total SES-CD score >2 at baseline (29.6% and 26.1%, for the 10 mg/kg and 20 mg/kg doses respectively).[35] The SONIC trial included a secondary endpoint of mucosal healing at week 26, which was achieved by 49.3% of patients in the combination arm (azathioprine and infliximab), 30.1% in the infliximab arm and 16.5% in the azathioprine arm. Although these data suggest that the timing of an optimal endoscopic endpoint may be at least 12 weeks, emerging data may support even later time points, such as 16 or even up to 26 weeks from baseline. This timing, however, may depend on both the outcome definition (endoscopic improvement and/or mucosal healing) and mechanistic factors inherent to the drug. Interim assessment of symptoms at an earlier time point might be warranted to address the extended length of placebo treatment and to allow for patients to either discontinue study treatment or switch to open label treatment for non-response.

Although a clear imperative exists for the inclusion of both patient-focused and objective measures of disease activity in CD clinical trials, the numerous factors outlined above as well as whether these outcomes should be assessed individually or as composite

endpoints continue to be critical research challenges with significant potential to influence the efficiency of early drug development.

Magnetic Resonance Imaging

MRE has an established role in clinical practice for evaluation of patients with CD. MRE findings are highly predictive of inflammatory activity, can categorize severity, identify stricturing or penetrating complications, and arguably informs patient management to a greater extent than information obtained from endoscopy.[36, 37] MRE may also be an important outcome component of long term trials of interventions designed to improve the natural history of CD, characterized by progressive bowel damage in most patients. The Lemann index[38] was recently developed with the aim of measuring cumulative structural bowel damage over time. However, MRE has not been widely adopted as an outcome measure in clinical trials primarily because the operating properties of the existing MRE indices are incompletely understood.

Several MRE-based quantitative indices of activity have been developed, however only the Magnetic Resonance Index of Activity (MaRIA) and London indices were derived using endoscopy or surgical resection specimens as a gold standard comparator.[39, 40] The MaRIA is a composite score that takes into account bowel wall thickness, gadolinium enhancement, ulceration and oedema, and is highly correlated with endoscopy.[39] Initial validation studies using the MaRIA index have demonstrated reliability and responsiveness to change following treatment with effective therapies.[41,42] The London index is a composite score that takes into account the semi-quantitative measurement of

wall thickness and a qualitative assessment of mural signal intensity on T2-weighted sequences, which are used to calculate an acute inflammation score. This index was shown to be correlated with histopathological inflammation in terminal ileal biopsies.[40] A representative MRE image from a patient with CD is shown in Figure 2. The corresponding MaRIA and London scores are described in the accompanying legend.

Implementation of MRE in clinical trials has specific advantages for both eligibility assessment and as an outcome measure. MRE may be more efficient than ileocolonoscopy for patient selection, because all intestinal segments are visualized, whereas the ileum cannot be examined in up to 25% of patients with active ileitis.[43] In a study assessing the reliability of the MaRia score in 20 patients with CD, MRE was capable of detecting more proximal small bowel inflammation not detected by ileocolonoscopy, as well as penetrating intramural disease and abscesses that would typically be contraindications to trial inclusion.[44] MRE may thus be used to select a more homogeneous, and potentially more responsive patient population by excluding patients with significant stenosis or penetrating complications. The advantage of MRE to ensure visualization of all intestinal segments is also relevant when used for outcome assessment. In keeping with US FDA and European Medicine Agency (EMA) guidance regarding the use of imaging tests as outcomes, MRE images can be centrally read off-site by independent adjudicators, and central reading by specialist radiologists minimizes reader-related sources of variance. These properties underscore the great potential of MRE as an outcome measure in early CD trials, however several challenges remain before MRE can be routinely incorporated into CD trials, including: refinement of existing

indices, demonstration of responsiveness to change with a treatment of known efficacy, standardization of imaging protocols as well as practical and economic considerations.

Histopathology

Histopathology has considerable potential as an outcome measure in CD, but has some notable challenges in comparison to UC. First, unlike UC, CD has a patchy distribution within involved segments, is transmural in nature and may occur anywhere throughout the gastrointestinal system, including locations that are difficult to biopsy. Second, no evidence–based approach to tissue sampling currently exists. In clinical practice the usual approach is to avoid biopsying tissue from the centre of ulcers because this location contains necrotic tissue which is uninformative. Accordingly, clinicians usually sample the ulcer edge. However, histopathology is not used to assess disease activity in clinical practice and as a result data on the optimal number of biopsy samples and distance from the edge of the ulcer that provides the best information are unknown.[45] Whilst histological indices for CD do exist,[46] none of these scoring systems have been validated according to modern biometric standards,[47] in distinction to UC where two new histologic scoring systems, the Robarts Histopathology Index[48] and the Nancy index[49] have been developed using appropriate methodologies. Development of a valid CD histopatholgic index according to accepted methodology[50] is a lengthy process[51, 52] which raises the possibility of using either of the existing UC indices on an interim basis until a fully validated CD-specific instrument is available. Finally, whilst histopathologic remission is associated with better long term outcomes such as reduced rates of corticosteroid use and hospitalization and surgery in preliminary case series for UC[53], the value of histopathologic disease

activity as a prognostic factor in CD is unknown and large scale cohort studies are needed to address this question.

Development of a CD-specific histopathologic index or validation of either of the existing UC indices for CD would provide a continuous scoring system for evaluation of inflammatory activity that would complement an EI and increase sensitivity for detection of treatment effects in early phase studies.

Pharmacokinetics and Pharmacodynamics

Substantial inter- and intra-individual variability in PK has been identified for all biologic treatments for CD.[54-57] Multiple covariates influence drug PK including development of anti-drug antibodies (ADA), serum albumin concentration, use of concomitant immunosuppressives, body weight, gender, prior biologic therapy and the degree of systemic inflammation. Traditional population-based PK modeling, which uses baseline covariates to adjust parameter estimates, is valuable for refining dose-regimens, however physiologic conditions change dynamically following treatment. Accounting for the time-dependent nature of covariates has been shown to reduce between-patient variability for parameter estimates in a population PK model for certolizumab pegol, making the model more representative of patient-drug exposure with sustained treatment.[58] Measured or estimated systemic drug exposure in CD has been shown to correlate with response as measured by clinical and endoscopic outcomes or biomarkers.[59, 60] Recently, preemptive dose escalation based on infliximab trough concentrations in patients with suboptimal drug exposure has been shown to increase the proportion of CD patients in clinical

remission and concomitantly decrease serum C-reactive protein (CRP) concentrations, thereby prospectively confirming the causal relationship between drug exposure and response.[61] Dosing based on exposure is likely to be a valuable tool in early phase trials of biologics for reducing primary non-response and non-remission rates owing to suboptimal PK.[62] In this regard, we are aware of two drug development programmes that have elected to conduct concurrent conventional fixed dose and exposure based dosing strategies in ~~a~~ phase 2 trials.[63, 64] Whilst this approach may require a greater number of patients initially, it is likely to be more efficient should large differences in drug clearance exist at the population level.[65]

Although endoscopy is the current gold standard pharmacodynamic readout for correlation with PK, a meta-analysis on the diagnostic accuracy of serum CRP, fecal calprotectin and stool lactoferrin showed that all three biomarkers can be sensitive markers of endoscopically-defined disease activity in patients with CD.[66] Nevertheless, some limitations exist to this approach. First, biomarker expression is highly variable at the patient level. For example, a substantial proportion of patients with endoscopically active CD have a normal serum CRP. Second, the distribution of biomarker concentrations is highly skewed which requires either transformation of data or application of non-parametric testing procedures. Despite these limitations use of biomarkers of inflammation has shown potential to improve the efficiency of early phase trials. In a phase 2a study of MEDI2070, a monoclonal antibody that binds to the p19 subunit of IL-23, in patients with active CD, Sands and colleagues compared outcomes using a clinical effect (defined as clinical response [≥100 point drop from baseline CDAI]

OR clinical remission [CDAI <150]) alone with the composite endpoint of a clinical effect and a ≥50% reduction from baseline CRP or fecal calprotectin. At week 8, 49.2% of patients treated with MEDI2070 had a clinical effect compared to 26.7% of those treated with placebo (P = 0.010). Whereas a similar percentage (42.4%) of patients treated with MEDI2070 achieved the composite outcome compared to the clinical effect alone, only 10% of patients treated with placebo achieved the composite outcome (P<0.001 for the comparison with the MEDI2070 group).[67]

Immunohistochemistry and Target Engagement

Application of modern translational medicine techniques has great potential to increase the efficiency of early drug development. Direct measurement of target engagement in either peripheral blood, or more relevantly in intestinal tissue, can serve as the basis for a more comprehensive understanding of PK/PD relationships compared to indirect assessment of these relationships using only clinical outcomes. Whilst several examples exist of this paradigm in cancer drug development[68, 69] there are comparatively few in IBD. For example, to quantitate $\alpha_4\beta_7$ receptor occupancy by vedolizumab in serum, a flow cytometric interference assay was developed to measure MAdCAM-1 Fc binding to $\alpha_4\beta_7$ receptors.[70] In the phase 2 dose-ranging study of vedolizumab in active UC, near complete $\alpha_4\beta_7$ receptor saturation was achieved at all measurable serum concentrations.[71] Yet in later phase 3 trials an exposure-response relationship was apparent.[72] Biomarkers can also be used for patient stratification. In a phase 2 trial of a β7 integrin antagonist, Vermeire et al recently demonstrated greater clinical efficacy in patients with high colonic concentrations of the target adhesion molecule.[73, 74] This finding

has multiple implications for future drug development programmes and clinical practice, including the possibility of limiting treatment to patients with specific biomarker concentrations or potentially adjusting drug dosing as a function of target tissue concentration. Standardized methods for collection, processing, storage and analysis of tissue samples must be developed to realize the maximal benefits from this approach.

Special Populations - Fistulizing disease

Early drug development for particular subtypes of CD require special consideration. Perianal fistula, which occur in about one-third of patients, are associated with a disabling disease course.[75, 76] The only proven treatment for these patients is infliximab, which is effective in the short term in approximately two-thirds of patients. Despite a distinct unmet need, few trials of new agents have been initiated for this indication. Although the reasons for this are not obvious, one factor is the limitations of currently available methods to quantify fistula disease activity.

Several clinical activity indices have been developed to evaluate fistulizing CD, the most commonly used being the Fistula Drainage Assessment (FDAI) and the Perianal Disease Activity Index (PDAI).[77, 78] Nevertheless, these indices have not been validated and their operating properties are unknown. Several research initiatives to develop new instruments are underway. A new PRO for perianal fistulae has been designed by the St. Mark's group in the United Kingdom and is currently undergoing validation. MRI holds the greatest promise as a quantitative assessment of fistula disease activity, and MRE is currently considered the gold standard imaging technique to assess perianal fistulae in

clinical practice. The most frequently used MRI-index to measure fistula disease activity is the Van Assche Index (VAI). However, this empirically designed index has important limitations with respect to item responsiveness[79, 80] and could benefit from modification and further validation studies. The development of validated instruments to assess fistula activity and healing in CD is a clear unmet need.

Trial Design Considerations

Minimization of placebo response is essential to optimize assay sensitivity during drug development. Randomized controlled trials (RCTs) in CD have shown heterogeneous and sometimes large placebo rates which may have prevented identification of effective therapies. A meta-analysis of placebo rates in CD RCTs conducted 15 years ago concluded that increasing study visits and duration increased placebo rates, whereas trials enrolling patients with more active disease reduced them.[81] The results of a more contemporary meta-analysis (Supplementary Appendix) of induction trials of biological agents in CD found pooled placebo response and remission rates of 31% (95% CI, 28%-36%; n = 44) and 16% (95% CI 13-19%; n=45), respectively. The corresponding results for maintenance trials of biological agents were 28% (95% CI 22-36%) and 21% (95% CI 16-27%) respectively (Supplementary Table 3).

Apart from enabling sample size calculation for standard frequentist trial design, these contemporary pooled placebo meta-analysis results can be utilised to inform Bayesian trial designs. A fundamental difference in comparison to classical frequentist design is that Bayesian methods use all relevant and available patient-outcome data during the

conduct of trial, and also incorporate historical information. Results are reported as probabilities of treatment effects, can be analyzed at any stage during trial conduct, and can help inform decisions about drug development programs. To our knowledge, only one trial in IBD has been published using this methodology.[82] This approach allowed early termination of a drug development programme for an IL-17 monocloncal antibody after randomization of only 59 patients; fewer than would have been enrolled by frequentist design.

Phase II clinical trials in CD are typically designed on the basis of detecting a minimally important treatment difference in a primary clinical endpoint. The success of the study is thus dependent on the accuracy of these original assumptions. Adaptive trial designs can incorporate a greater degree of flexibility by enabling planned modifications based upon review of accumulating information during the conduct of a trial. This feature can address some of the uncertainties that are unavoidable in the original design assumptions.[83] In phase II trials, this approach has the potential to increase efficiency by eliminating ineffective treatment arms or altering the randomization ratio to increase the probability of assigning patients to effective treatment arms. To operationalize this concept practically, outcome data must be incorporated into a central database whilst patients are being accrued, which must also be linked to the software that determines treatment assignment.[84] This approach holds great potential in phase II IBD trials; the evolution of centralized reading of endoscopy raises the novel possibility of adapting randomization "real-time" based upon blinded review of endoscopy as a secondary endpoint, whilst retaining the primary clinical endpoint. With careful planning and acceptance of these

designs by regulators, adaptive designs hold promise as efficient methodologies in CD drug development.

Conclusions and future directions

Efficient drug development in CD requires re-evaluation of conventional paradigms. In our view the greatest opportunity lies in further refinement of endoscopic measures in combination with direct measurement of target engagement in tissue. Such an approach is becoming the standard for early phase trials in UC. Notwithstanding that CD is a more challenging environment, several notable success stories relevant to this paradigm have occurred that should encourage the research community to utilise novel ways to expedite the process of getting new drugs to market in the most efficient manner.

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Figure Legends

Figure 1. Current and evolving paradigms for early drug development in UC

Efficient drug development in CD will likely require evolution to an integrated strategy that employs the use of objective outcome measures of inflammation (endoscopy, histopathology, cross-sectional imaging and biomarkers), patient-based dosing centered on PK/PD evidence, and novel trial design.

Figure 2. A patient with Crohn's disease and activity in the terminal ileum

The MaRIA index grades disease activity using relative contrast enhancement (a-d), by measuring wall thickness (e) and identifying the presence of edema (f, arrow) and ulcerations (g, arrow). Both ulcerations and edema were present in this patient. The MaRIA score in the terminal ileum of this patient was 29.56 (severe inflammation).

For scoring of the London index, wall thickness (e) and mural T2 signal (f) are assessed to calculate an acute inflammation score (AIS). The extended version of the London index also includes a qualitative evaluation of enhancement (d) and perimural T2 signal intensity (f). In this patient, there is a moderate increase in mural T2 signal (f, arrow), moderate degree of Gd enhancement (d) and small fluid rim surrounding the terminal ileum (f, arrowhead). The AIS and extended AIS in the terminal ileum of this patient were 7.69 and 12.42 respectively.

Tables

Table 1. Overview of current and emerging measures of disease activity for use in Crohn's Disease clinical trials

	Current state	**Challenges and/or areas of future research**
Disease activity measure		

Endoscopy	• Favored by regulatory agencies as an objective measure of inflammation
	  • Central reading of endoscopy may
	  o reduce bias that arises due to investigator knowledge of patients' clinical status
	  o allows for a more precise characterization of treatment response due to consistency of scoring
		• Characterization of outcome index responsiveness and further index validation
		• Identification of outcome thresholds for clinical trial eligibility and endpoint definitions
		• Optimal time point for measuring endoscopic outcomes
		• Relative value when used alone or as component of a composite outcome unknown

	○ facilitate review/audit of visual images by regulatory agencies • The SES-CD and the CDEIS are the indices most commonly used in clinical trials	
Magnetic Resonance Imaging	• Established role in evaluation of patients with CD • Findings are highly predictive of inflammatory activity • Allows visualization of all intestinal segments • Readily identifies disease-related complications compared with endoscopy • Images may be centrally read	• Further characterization of operating characteristics of existing indices • Demonstration of index responsiveness • Imaging protocol standardization • Economic considerations

	• The MaRIA and London indices are the indices most commonly used in clinical trials	
Histology	• Not used to assess disease activity in clinical practice although histologic remission is associated with improved long-terms outcomes • Slide images may be centrally read	• Patchy and transmural nature of CD • Evidence-based methods for tissue sampling (biopsy number and location relative to ulcer edge) • Development of valid histopathologic index • Value of histopathologic disease activity as a prognostic factor
Biomarkers	• More direct measurement of target engagement and can better inform PK/PD relationships	• Few precedents in IBD/CD • Development of standardized methods for collection, storage and analysis of tissue samples

	• Can assist in patient stratification at trial enrolment or in dose adjustment during trial conduct	

Table 2. Sensitivity and specificity of a 2-item PRO to detect clinical remission*

	Sensitivity:Specificity		
	GEMINI II	**CERTIFI**	**SONIC**
	Vedolizumab (Week 6)	Ustekinumab (Week 8)	Infliximab (Week 26)
PRO Definition			
SF≤1.5 AP≤1	48%:96%	55%:97%	63%:87%
SF≤3 AP≤1	67%:88%	73%:94%	78%:80%
Weighted SF+AP≤50	57%:94%	68%:95%	79%:85%
Weighted SF+AP≤75	76%:80%	92%:85%	94%:64%

*Based on data presented at the FDA public workshop: *Gastroenterology Regulatory Endpoints & Advancement of Therapeutics* (http://www.great3.org)

Conflicts of Interest

Vipul Jairath has received scientific advisory board fees from AbbVie and Sandoz; and speaker's fees from Takeda and Janssen. Barrett G. Levesque has received consulting fees from Nestle Health Sciences, AbbVie, and Takeda Pharma. Niels C. Vande Casteele is a Postdoctoral Fellow of the Research Foundation - Flanders (FWO), Belgium (grant number 1260714N) and has received consultancy fees from MSD, Janssen Biologics BV, UCB, Pfizer, and Takeda; and lecture fees from AbbVie. Reena Khanna has received honoraria from AbbVie, Janssen, and Takeda Pharma. Mahmoud H. Mosli has received advisory board fees from Alhikma Pharmaceuticals and honoraria from AbbVie. Pieter Hindryckx has received consulting fees from Abbvie and Takeda; speaker's fees from Ferring, Falk Pharma, Vifor Pharma, Tillotts Pharma, Takeda and Abbvie. Simon Travis has received Grants/Research Support from AbbVie, Lilly, UCB, Vifor, and Norman Collison Foundation; Consulting Fees from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Chemocentryx, Cosmo, Ferring, Giuliani SpA, GlaxoSmithKline, Lilly, MSD, Neovacs, NovoNordisk, Norman Collison Foundation, Novartis, NPS Pharmaceuticals, Pfizer, Proximagen, Receptos, Shire, Sigmoid Pharma, Takeda, Topivert, UCB, VHsquared and Vifor; Speaker fees from AbbVie, Ferring, Takeda. Marjolejn Duijvenstein has nothing to disclose. Jordi Rimola has received Research Support from Genentech; Consulting Fees from Boehringer Ingelheim, Genentech, Robarts Clinical Trials, Bioclinica; Speaker fees from AbbVie,MSD Takeda. Julian Panes has received consulting fees from Abbvie, Boehringer Ingelheim, Galapagos, Genentech-Roche, GSK, Jansen, Pfizer, Second Genome, Takeda, and Tigenix; and speaker fees from Abbvie, Jansen, MSD, and Pfizer. Geert D'Haens has received consulting fees from AbbVie, ActoGeniX NV, Amgen, AM-Pharma BV, Boehringer-Ingelheim, ChemoCentryx, Centocor/Jansen Biologics, Cosmo Technologies, Elan/Biogen, EnGene Inc, Ferring Pharmaceuticals, Gilead Sciences, Given Imaging, GSK, Merck Research Laboratories, Merck Serono, Millenium Pharmaceuticals, Novo Nordisk, NPS Pharmaceuticals, PDL Biopharma, Pfizer, Receptos, Salix Pharmaceuticals, Schering Plough, Shire Pharmaceuticals, Sigmoid Pharma Ltd, Teva Pharmaceuticals, Tillotts Pharma AG, and UCB Pharma; research grants from AbbVie, GSK, Falk, Janssen, Merck, and Given Imaging; and lecture/speakers bureaux fees from AbbVie, Jansen, Merck, Takeda, UCB, and Shire. William J. Sandborn has received consulting fees from AbbVie, ActoGeniX NV, AGI Therapeutics Inc, Alba Therapeutics Corp, Albireo, Alfa Wasserman, Amgen, AM-Pharma BV, Anaphore, Astellas, Athersys Inc, Atlantic Healthcare Ltd, Aptalis, BioBalance Corp, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, Celek Pharmaceuticals, Cellerix SL, Cerimon Pharmaceuticals, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado Biosciences, Cytokine Pharmasciences, Eagle Pharmaceuticals, EnGene Inc, Eli Lilly, Enteromedics, Exagen Diagnostics Inc, Ferring Pharmaceuticals, Flexio Therapeutics Inc, Funxional Therapeutics Ltd, Genzyme Corp, Gilead Sciences, Given Imaging, GSK, Human Genome Sciences, Ironwood Pharmaceuticals, KaloBios Pharmaceuticals, Lexicon Pharmaceuticals, Lycera Corp, Meda Pharmaceuticals, Merck Research Laboratories, Merck Serono, Millenium Pharmaceuticals, Nisshin Kyorin Pharmaceuticals, Novo Nordisk, NPS Pharmaceuticals, Optimer Pharmaceuticals, Orexigen Therapeutics Inc, PDL Biopharma, Pfizer, Procter and Gamble, Prometheus Laboratories, ProtAb Ltd, Purgenesis Technologies Inc, Relypsa Inc, Roche, Salient Pharmaceuticals, Salix Pharmaceuticals, Santarus, Schering Plough, Shire Pharmaceuticals, Sigmoid Pharma Ltd, Sirtris Pharmaceuticals, SLA Pharma UK Ltd, Targacept, Teva Pharmaceuticals, Therakos, Tillotts Pharma AG, TxCell SA, UCB Pharma, Viamet Pharmaceuticals, Vascular Biogenics Ltd, Warner Chilcott UK Ltd and Wyeth; research grants from AbbVie, Bristol-Myers Squibb, Genentech, GSK,

Janssen, Milennium Pharmaceuticals, Novartis, Pfizer, Procter and Gamble, Shire Pharmaceuticals and UCB Pharma; payments for lectures/speakers bureaux from AbbVie, Bristol-Myers Squibb and Janssen; and holds stock/stock options in Enteromedics. Brian G. Feagan has received grant/research support from Millennium Pharmaceuticals, Merck, Tillotts Pharma AG, AbbVie, Novartis Pharmaceuticals, Centocor Inc., Elan/Biogen, UCB Pharma, Bristol-Myers Squibb, Genentech, ActoGenix, and Wyeth Pharmaceuticals Inc.; consulting fees from Millennium Pharmaceuticals, Merck, Centocor Inc., Elan/Biogen, Janssen-Ortho, Teva Pharmaceuticals, Bristol-Myers Squibb, Celgene, UCB Pharma, AbbVie, Astra Zeneca, Serono, Genentech, Tillotts Pharma AG, Unity Pharmaceuticals, Albireo Pharma, Given Imaging Inc., Salix Pharmaceuticals, Novonordisk, GSK, Actogenix, Prometheus Therapeutics and Diagnostics, Athersys, Axcan, Gilead, Pfizer, Shire, Wyeth, Zealand Pharma, Zyngenia, GiCare Pharma Inc., and Sigmoid Pharma; and speakers bureaux fees from UCB, AbbVie, and J&J/Janssen.

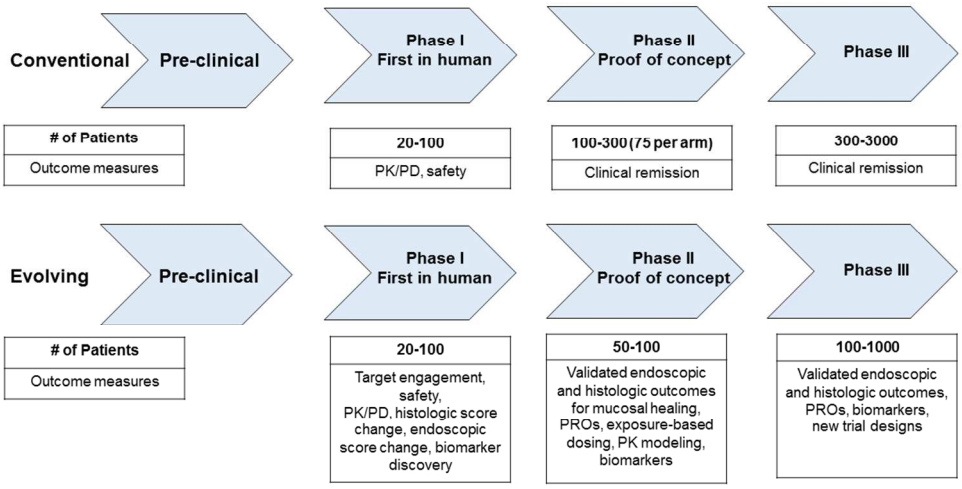

Figure 1. Current and evolving paradigms for early drug development in UC\r\nEfficient drug development in CD will likely require evolution to an integrated strategy that employs the use of objective outcome measures of inflammation (endoscopy, histopathology, cross-sectional imaging and biomarkers), patient-based dosing centered on PK/PD evidence, and novel trial design.
338x190mm (96 x 96 DPI)

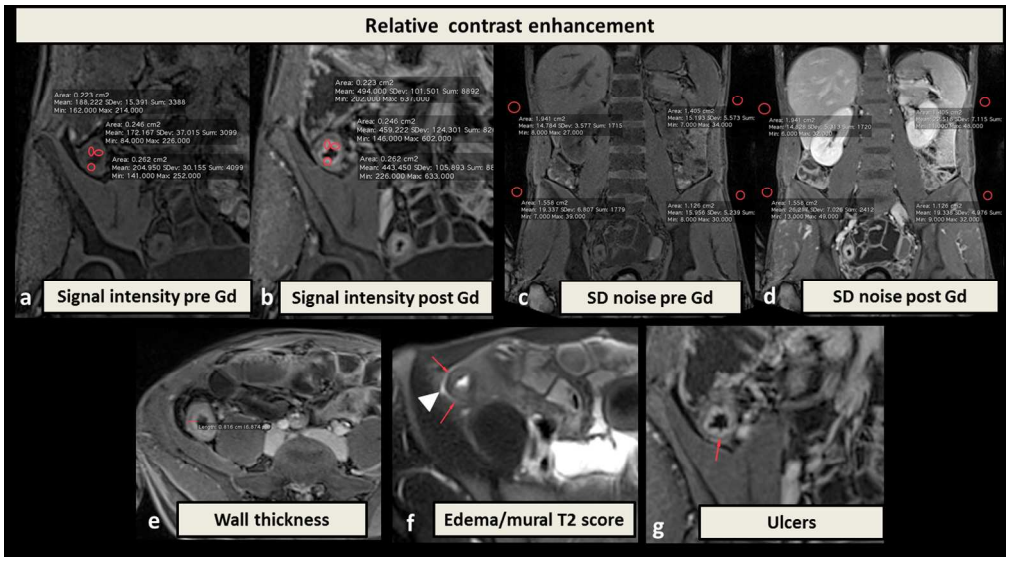

Figure 2. A patient with Crohn's disease and activity in the terminal ileum
The MaRIA index grades disease activity using relative contrast enhancement (a-d), by measuring wall thickness (e) and identifying the presence of edema (f, arrow) and ulcerations (g, arrow). Both ulcerations and edema were present in this patient. The MaRIA score in the terminal ileum of this patient was 29.56 (severe inflammation).
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256x141mm (150 x 150 DPI)

Supplementary Table 1. Crohn's Disease Index of Severity (CDEIS)

	Rectum	Sigmoid & Left Colon	Transverse Colon	Right Colon	Ileum	
Deep ulceration If present, score 12, If absent, score 0						**Total 1**
Superficial ulceration If present, score 6**,** If absent, score 0						**Total 2**
Surface involved by the disease measured in cm*						**Total 3**
Ulcerated surface measured in cm*						**Total 4**

Total 1 + Total 2 + Total 3 + Total 4 =	**A**
Number (n) of segments totally or partially explored (1-5) =	**n**
Total **A** divided by n =	**B**
Ulcerated Stenosis If present anywhere, score 3**,** If absent, score 0 =	**C**
Non-Ulcerated Stenosis If present anywhere, score 3**,** If absent, score 0 =	**D**
TOTAL B + C + D =	

Supplementary Table 2. Simple Endoscopic Score for Crohn's Disease (SES-CD).

Variable	0	1	2	3
Presence of ulcers	None	Aphthous ulcers 0.1 to 0.5 cm	Large ulcers 0.5 to 2 cm	Very large ulcers >2 cm
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

	Ileum	Right colon	Transverse colon	Left colon	Rectum	TOTAL
Presence of ulcers 0-3						
Ulcerated surface 0-3						
Affected surface 0-3						
Presence of narrowings 0-3						
					***SES-CD=**	

Supplementary Table 3. Meta-analysis of placebo response and remission rates for induction trials of biological therapies.

Author	Year	Drug	No Placebo Subjects	Remission		Response	
				No	%	No	%
Hanauer[1]	2006	Adalimumab	74	9		18	
Watanabe[2]	2012	Adalimumab	23	3		4	
Sandborn[3]	2007	Adalimumab	166	12		41	
Schreiber[4]	2005	Certolizumab	73	17		26	
Sandborn[5]	2007	Certolizumab	329	57		87	
Winter[6]	2004	Certolizumab	25	5		13	
Sandborn[7]	2011	Certolizumab	216	53		71	
D'Haens[8]	1999	Infliximab	8	-		-	
Sandborn[9]	2001	CDP571	58	2		15	
Sandborn[10]	2004	CDP571	132	27		36	
Stack[11]	1997	CDP571	10	0		0	
Takazoe[12]	2009	AMJ300	71	-		-	
Targan[13]	1997	cA2	25	1		4	
Ito[14]	2004	MRA (anti-IL6)	13	0		4	

Sandborn[15]	2005	natalizumab	181	55		88	
Ghosh[16]	2003	natalizumab	63	17		24	
Sandborn[17] *CD-IP arm	2012	abatacept	128	8		18	
Hommes[18]	2006	fontolizumab	43	5		14	
Reinisch[19]	2010	fontolizumab	40	7		15	
Reinisch[20]	2006	fontolizumab	10	4		6	
Hueber[21]	2012	secukinumab	20	-		-	
Sands[22]	2014	vedolizumab	207	25		47	
Feagan[23]	2009	vedolizumab	58	12		24	
Targan[24]	2007	natalizumab	250	40		81	
Gordon[25]	2001	Natalizumab	12	1		-	
Sandborn[26]	2013	vedolizumab	148	10		39	
Dotan[27]	2010	Semapimod	55	-		22	
Schreiber[28]	2006	BIRB 796	62	0		0	
Sandborn[29]	2001	Etanaracept	20	4		9	
Keshav[30]	2013	CCX282-B	144	37		71	
Sandborn[31]	2008	Ustekinumab	53	9		21	

Lemann[32]	2006	Infliximab	56	16		-	
Mansfield[33]	2007	Lenalidomide	28	7		11	
Rutgeerts[34]	2012	Adalimumab	65	18		42	
Sandborn[31]	2008	Ustekinumab	53	9		21	
Sandborn[35]	2012	Ustekinumab	132	14		31	
Van Deventer[36]	1997	Recombinant human IL-10	13	3		3	
Fedorak[37]	2000	Recombinant human IL-10	23	0		-	
Schreiber[38]	2000	Recombinant Human Interleukin 10	66	11		18	
Sands[39]	2002	rhIL-11	50	8		19	
Sands[40]	1999	rhIL-11	15	0		1	
Mannon[41]	2004	anti-IL12p40	16	1		4	
Sands[42]	2010	apilimod	73	10		21	
van der Woude[43]	2010	Anti CD3	7	-		0	
Rutgeerts[44]	2006	Onercept	38	9		14	

Appendix A: Description of the meta-analysis of placebo response and remission rates

This systematic review was conducted as part of a concurrent project on placebo rates in CD trials. We searched MEDLINE, EMBASE and CENTRAL to identify studies meeting the following eligibility: (1) A placebo–controlled induction and/or maintenance trial in adult patients (>18 years) with active CD using the CDAI or HBI as criteria for enrolment and/or assessment of response/remission; (2) duration of at least 2 weeks for induction, and 4 months for maintenance of remission trials. From these results we then selected out trials of biological therapies. The search overall yielded 7357 citations of which 2854 were duplicates and removed. Of the remaining 4503 records screened, 497 full text articles were selected and reviewed for eligibility of which there were 65 induction phase studies with 44 biological studies, and 42 maintenance phase studies with 16 biological trials. Search strategy and results of our contemporary pooled placebo rates of remission and response for CD trials. The meta-analysis for response and remission for induction and maintenance trials was conducted with random-effects.

Appendix B: Search strategy for meta-analysis of placebo response and remission rates

MEDLINE and EMBASE

1 random$.tw.

2 factorial$.tw.

3 (crossover$ or cross over$ or cross-over$).tw.

4 placebo$.tw.

5 single blind.mp.

6 double blind.mp.

7 triple blind.mp.

8 (singl$ adj blind$).tw.

9 (double$ adj blind$).tw.

10 (tripl$ adj blind$).tw.

11 assign$.tw.

12 allocat$.tw.

13 crossover procedure/

14 double blind procedure/

15 single blind procedure/

16 triple blind procedure/

17 randomized controlled trial/

18 or/1-17

19. exp Crohn disease/ or crohn*.mp.

20. 18 and 19

Cochrane Library (CENTRAL)

Crohn

SR-IBD

Crohn

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