Clinical trials in luminal Crohn's disease: A historical perspective

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Abstract

It goes back to 1932 when Dr. Burrill Bernard Crohn and co-workers published their landmark paper, describing regional ileitis as a disease entity. However, clinical trial research has been developing rather slowly in luminal Crohn's disease. It took until the early seventies before the first randomized clinical trial was set up by the National Co-operative Crohn's Disease Study (NCCDS) group. Although the efforts of this group triggered a first wave of clinical trials in Crohn's disease, the lack of guidelines for conducting a clinical trial in this research area resulted in a variety of study designs and much criticism. Besides having a rather small sample size and a short follow-up time, they were often characterized by vague and subjective assessment of disease activity and treatment response.

Following the advent of a new and very potent drug class in the late nineties, the anti-TNF agents, investigators started to re-think their study protocols and the first guidelines were set up by the regulatory authorities. Over the last 15 years, clinical trials in luminal Crohn's disease have been evolving significantly. Inclusion criteria have been shifting from clinical scores such as Crohn's Disease Activity Index (CDAI) to more objective disease activity parameters such as biomarkers (C-reactive protein...
faecal calprotectin) and endoscopic lesions. Primary endpoints have been developing from clinical response to corticosteroid-free remission and more ambitious end-points such as mucosal healing.

In this paper, we will give a historical overview on clinical trials in luminal Crohn’s disease, before and within the biologic era, and provide insight into how they have shaped our current understanding of trial designs in Crohn’s disease.

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1. Introduction

A clinical trial is currently defined by the World Health Organisation as any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.1 The main purpose of a clinical trial is to provide the strongest possible evidence to decide whether a new medication or treatment is safe and effective for a given disease.1

The very first recorded clinical trial was conducted by the prophet Daniel more than 2000 years ago and is described in the Old Testament.2 He set up a 10-day prospective trial, in which one group of young Hebrew men, trained to enter the royal service, received a non-standard diet with only vegetables to eat and water to drink (the "experimental group") and the "control group" received the conventional food of the royal court, consisting mainly of meat and wine. After ten days, the experimental group looked healthier and stronger to the king of Babylon and hence the new diet was continued.2 Although Daniel’s research set-up in theory fulfils the definition of a clinical trial, the methodology he used to prove his hypothesis would not be entirely acceptable today.

Although Dr. Burri Bernard Crohn described regional ileitis as a clinical entity in his landmark paper in 1932, it took until the late fifties before the first clinical trials in Crohn’s disease (CD) were conducted.3 Controlled trials published in the sixties lacked any protocol or statistical plan. The first international platform that developed and discussed clinical trial design and analysis, the "Society for Clinical Trials", was set up in 1978.4 A few years later, the U.S. Food and Drug Administration (FDA) started to focus on improvement of the analysis of data from clinical trials and founded a new division: the Center for Drug Evaluation and Research (CDER).4 Europe followed in 1995, with the establishment of the European Agency for the Evaluation of Medicinal Products, known today as the European Medicines Agency (EMA).5

The design of a clinical trial for luminal CD is challenging in several ways. CD covers a very heterogeneous population with different disease phenotypes resulting from a variety of abnormal genome — environmental interactions, that might even have diverse predominant pathophysiological pathways. In addition, clinical symptoms in CD are not very specific and hence do not always correlate with objective signs of disease activity.6 Before the advent of infliximab, the first biologic agent to be approved in CD, recommendations for conducting a clinical trial were not available, resulting in study designs and endpoints, which were confusing and difficult to interpret.

The first placebo-controlled anti-TNF trial, published in the New England Journal of Medicine in 1997 by Targan et al., opened a completely new era of clinical trial research in CD.7 The investigators started to re-think how to optimize their study protocols, to select patient populations and to homogenize endpoints and outcome measures. This was reflected by the concomitant publication of recommendations for conducting a clinical trial in CD by the EMA.8,9

Here, we provide a historical perspective on clinical trials in luminal CD, by separating two well-distinguished time frames: before and within the biologic era. In light of this historical background, we present some challenges and directions for conducting future trials in luminal CD.

2. Pitfalls of clinical trials before the biologic era

In the first half of the 20th century, the treatment of CD was limited to supportive cares and surgical interventions for
disease complications. The discovery of adrenocorticotropic hormone (cortisol) by Hench et al. in 1949 prompted some early investigators to test its potential in CD. In the very first uncontrolled clinical trial, published by Jones and Lennard-Jones in 1966, 22 of 30 CD patients initially responded to a treatment with corticosteroids or corticotrophin, but only 7 of 30 remained in “fair health” by corticosteroid maintenance therapy.12 Soon thereafter, the above results were confirmed in other uncontrolled clinical trials.13,14 Later, several pilot studies in the early seventies suggested the potential of azathioprine and sulfasalazine for the treatment of CD.15–17 Although we should be grateful to those pioneer clinical researchers because they revolutionized the treatment of CD, some major concerns with regard to these early clinical trials were put forward. They not only had small sample size, but they also were uncontrolled and characterized by a very heterogeneous and often vague assessment of disease activity and treatment response. To overcome this problem, the first randomized, placebo-controlled and large-scale multi-centre National Co-operative Crohn’s Disease Study (NCCDS) was set up in the US in 1971 to investigate the efficacy and safety of prednisolone, sulfasalazine and azathioprine in CD.18 In view of this study, the same study group developed the Crohn’s disease activity index (CDAI). The CDAI aimed to make clinical assessment reproducible and quantifiable and allowed true statistical analysis.19

The NCCDS was carried out in two parts: in the first part, patients with clinically active disease (CDAI > 150) were treated for 4 months with the assigned drug or placebo. In the second part, patients with quiescent disease (CDAI < 150) were given a smaller dose of the assigned treatment for 12–14 months to investigate the ability of the study drugs to maintain remission.18 The results of the NCCDS were published in 1979.20 In brief, sulfasalazine and prednisolone did better than placebo and the effect of azathioprine did not reach statistical significance.20 Although everyone agreed that the NCCDS was a major advance in clinical trial research on CD, the study was objected of some criticism.21 Notably, the authors used a CDAI of 150 as the cut-off between active and quiescent disease, but did not predefine a “significant drop in CDAI” to judge clinical response to the assigned treatment.20,21 Furthermore, the length of follow-up of CD patients was not considered sufficient to formally exclude a clinical effect of the study drugs, in particular for azathioprine.21 The most convincing evidence for the efficacy of azathioprine in maintaining remission in CD was a withdrawal trial published in the Lancet in 1978 by O’Donoghue et al.22 Fifty-one CD patients in “good health” whilst taking azathioprine for at least six months were allocated either to a group that continued azathioprine or to a group in which azathioprine was replaced by placebo.22 At one year, forty-one percent of the placebo group relapsed compared with 5% of the group that had continued azathioprine.22 Interestingly, relapse was defined as a significant deterioration in clinical state requiring a change in treatment, as judged by two blinded doctors.22 Almost at the same time, a two-year, double-blind crossover trial was published, that demonstrated the efficacy of 6-mercaptopurine, a metabolite of azathioprine, as a maintenance therapy in CD.23

In the early eighties, several clinical and combined clinical-biochemical scores were developed to quantify disease activity in CD, aiming to simplify assessment and make the CDAI more objective. Except for the Harvey Bradshaw index, developed in 1980,24 none of them (e.g. the Oxford Index, the Modified-Organisation Mondiale de Gastroenterologie (OMGE) index, the St. Mark’s Index and the Van Hees index) really survived.25

The European Cooperative Crohn’s Disease Study (ECCDS) published in 198426 was methodologically very similar to its US forerunner and confirmed the efficacy of sulfasalazine and methylprednisolone in active CD, but also investigated for the first time two different treatment strategies: monotherapy with either sulfasalazine or methylprednisolone versus a combination of these drugs. The study turned out that combined treatment with sulfasalazine and methylprednisolone was the most effective regimen.26

In 1984, the “Groupe d’Etude Therapeutique des Affections Inflammatoires du Tube Digestif” (GETAID) was founded to conduct high-quality and industry-independent clinical research in IBD. This group was the first to develop an endoscopic scoring system for CD, the Crohn’s Disease Endoscopic Activity Index (CDEIS)27 and shortly thereafter published its first practical application in a controlled trial in active CD patients that were started on corticosteroids.28 This study provided some important information that would have influenced the design and interpretation of all subsequent controlled trials. First, the limitations of the CDAI as a CD activity marker were confirmed by its lack of correlation with the CDEIS. Furthermore, the GETAID study showed that only 13% of the patients in clinical remission (CDAI < 150) on corticosteroid therapy were also in true endoscopic remission (defined as the “absence of any lesion” or the “presence of only healed lesions”).28 Moreover, in a follow-up study, they showed that the clinical effect of corticosteroids was only temporary.29 This information, coupled with the numerous associated side effects of corticosteroids certainly reduced the original enthusiasm for their use in CD.

It took until the early nineties before the newer mesalazine (5-ASA) preparations substituted the more toxic sulfasalazine, following a positive major multicenter trial by the Pentasa Crohn’s Disease Compassionate Use Study Group on 467 CD patients in 1993.30 This study used a change in the CDAI from baseline as the primary outcome criterion. However, subsequent double-blind randomized trials, although often similarly designed, did not consistently confirm these findings and the overall evidence currently suggests that 5-ASA has low or no efficacy in luminal CD, as underscored by the ACG guidelines.31,32

In 1994, Rutgeerts et al. published the results of a randomized double-blind 10-week trial comparing the efficacy of a controlled ileal release preparation of budesonide with systemic prednisolone in 176 CD patients with active ileal or ileocecal disease in the New England Journal of Medicine (NEJM).33 In the study, both clinical (CDAI and Harvey Bradshaw index) and biological parameters (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and orosomucoid) were used to measure outcomes. Whilst the study should have been powered as a non-inferiority trial, the authors powered it as a superiority trial. In addition, the negative result (non-superiority of controlled release budesonide) was wrongly interpreted as a proof of equivalence between the two drugs.33 Nevertheless, other
studies confirmed the effectiveness and the favourable safety profile of budesonide as compared to systemic corticosteroids. As a result, the European Crohn's and Colitis Organisation (ECCO) states that oral budesonide should be the preferred treatment in mild Crohn's ileitis.34

A major randomized, double-blind, placebo-controlled trial using methotrexate (MTX) in 141 CD patients was published in 1995.35 Being fully aware of the side-effects associated with long-term corticosteroid treatment, the study designers for the first time introduced corticosteroid-free remission as the primary outcome measure. Five years later, a methotrexate maintenance trial was published by the North American Crohn's Study Group.36 In this study, the primary outcome measure was the occurrence of a relapse of CD, defined by an increase in CDAI of 100 points from baseline, or the initiation of corticosteroids and/or an antimetabolite.36 Both studies were positive and methotrexate gained its place in the therapeutic arsenal for luminal CD.

Starting from 1995, the first proof-of-concept studies on the use of TNF antagonists for CD were published (Fig. 1).37

3. Challenges in clinical trials in the biologic era

The first clinical trial of an anti-TNF alpha for luminal CD was published in the NEJM in 1997,7 less than a year after the publication of the FDA guidelines for the conduction of clinical studies,8 and opened a completely new era of controlled trial (CT) research in IBD. Only two years later, the EMA published their “first points to consider on clinical investigation of medicinal products in the management of Crohn’s disease”, which came into operation in June 2001.9 This was a preliminary guidance document as it covered a field where experience was still limited. However it was the first time that consensus definitions for active disease (CDAI > 220), response (drop in CDAI from baseline of >70 points) and remission (CDAI < 150) were provided and that the preferred design for an induction and maintenance trial was outlined. These guidelines evolved as knowledge and experience was increasing amongst the investigators.

Table 1 gives an overview of the main clinical trials in luminal CD in the biologic era, and their main characteristics.

3.1. Moving towards objective signs of inflammation as inclusion criteria

Most trials in CD until now used clinically active disease as the inclusion criterion. This is in line with the current “EMA guideline on the development of new medicinal products for the treatment of Crohn’s disease” (2008) that states that “CD patients included in the trials should have active disease as determined by a CDAI score of at least 220”.54

However, it has become clear that these validated clinical scoring indices for CD, such as the CDAI, are mainly based on subjective clinical symptoms and are not reliably correlated with objective signs of inflammation (e.g. the presence of endoscopic lesions).6,28,55

In 2005, two major trials investigating the effect of certolizumab pegol and natalizumab (ENACT-1) as an induction treatment for CD failed to reach their primary endpoint (clinical response at week 12 and at week 10, respectively).39,40 Sub-analysis showed that this was mainly caused by the inclusion of patients without an elevated CRP. Indeed, in both studies these patients, although all having a CDAI above 220, had a numerically greater response to placebo than for the active drug, whereas patients with an elevated CRP had significantly greater response and remission rates with the active drug.

The results of these trials demonstrated that objective criteria for active inflammation are needed to demonstrate superiority of a therapeutic intervention over placebo achieve a response to biologicals.56 In this background, in a second induction study with natalizumab for CD, the ENCORE-trial, only patients with an elevated CRP were included. This study reached its primary endpoint (sustained response from week 8 through week 12).45

The SONIC trial, published in 2010, which compared infliximab monotherapy versus azathioprine monotherapy versus combination therapy with these two drugs for CD, finally confirmed that objective signs of inflammation (elevation of CRP levels and/or the presence of mucosal lesions) are mandatory for the efficacy of anti-TNF therapy.49 As a result, all recent and ongoing trials include objective signs of inflammation (elevated CRP level, elevated faecal calprotectin level, presence of mucosal lesions) in their inclusion criteria. As an example, the recently published GEMINI-2 study that investigated vedolizumab (an a4b7
integran antibody that blocks leukocyte trafficking to the gut) as an induction and maintenance therapy for CD, only included patients with a CDAI above 220 and at least one objective sign of inflammation (a serum C-reactive protein level higher than 2.87 mg per litre, 3 or more large ulcers or 10 or more aphthous ulcers on colonoscopy, or faecal calprotectin concentrations >250 μg per gramme of stool plus evidence of ulcers on small bowel imaging modalities). 53

It is anticipated that future revisions of the EMA and FDA guidelines will follow this trend towards a more objective definition of active CD. However, some caution should be taken when CRP alone is used as an inclusion criterion, as it is well known that around 32% of CD patients have a normal CRP level even in the presence of endoscopic severe lesions. 57 In addition, the correlation between CRP level and active disease is poor. 58

3.2. Is a placebo arm still ethical?

Giving the dramatic success of anti-TNF therapy in luminal CD, it gradually became unethical to continue to give placebo to patients suffering with active disease. In this view, the current guidelines of the EMA state that the study drug should be compared with and be "at least as effective and safe as the standard of care, which currently in the majority of cases includes corticosteroids". 54 However, it is well-known that the efficacy of corticosteroids is of short duration, and that they are associated in the long term with significant, unacceptable side-effects. 59 This EMA guideline has therefore rarely been put into practice. Instead, most major clinical trial designs dealt with the ethical concerns on the use of placebo by including open label administration of the active drug during induction phase of a maintenance trial, 43,44,50 and/or by allowing the possibility for open-label administration in case of non-response or relapse during the course of the trial. 7,38,43,44,50 This behaviour follows the EMA guideline stating that "Escape procedures for non-responders should be included in the protocol". 54 Most studies allow the concomitant use of steroids during the induction phase and/or the continuation of immunomodulators (thiopurine, methotrexate) during the maintenance phase, which can be considered as a way to avoid "true placebo" arms.

The SONIC trial was the first trial comparing an anti-TNF versus an active arm (azathioprine) without including a placebo arm, but this was a treatment strategy trial and hence, not designed to demonstrate the efficacy of a new drug. 49 So far, all clinical trials leading to drug approval in IBD were industry-driven placebo-controlled superiority trials, designed to comply with prerequisites of the Pharmaceutical Agencies. Today, such a "classical approach" not only raises ethical concerns, but is also far away from our daily clinical practice. Based on EMA and FDA recommendations, an active arm may be mandatory in upcoming trials. 54,60 In this regard, superiority trials will become less feasible, giving the huge number of study subjects needed to demonstrate that the new drug is superior to an already very potent comparator. Therefore, future investigators will likely switch their study design to

comparative effectiveness trials with a non-inferiority approach aiming to show that the new drug is not less effective as the current standard (which in most cases will be an anti-TNF agent). However, if the therapeutic armamentarium for CD expands significantly in the future, it is unlikely that any new drug will still gain access to the market unless it shows superiority to other standard treatments.

3.3. Dealing with placebo effect: is mucosal healing the clue?

One of the most worrying pitfalls of trial design is a high placebo effect. In 2004, Su et al. performed a systematic review and meta-analysis of placebo-controlled randomized clinical trials (RCTs) evaluating therapies for active CD. 61 The pooled estimates of the placebo rates of remission and response were 18% (95% confidence interval, 14%–24%; range, 0%–50%) and 19% (95% confidence interval, 13%–28%; range, 0%–46%), respectively, both with significant heterogeneity amongst studies. 61

Overall, placebo rates varied between 6.8% 53 and 49% 40 in the main RCTs (see Table 1).

In the meantime, it has become clear that the biggest fall of placebo responses is seen when the study duration is increased and when robust objective endpoints are chosen. 61 Whilst the EMA states that the "ideal measurement of the activity of CD does not exist, and that the CDAI is the best that is currently available", this statement has clearly been surpassed by now. 54

Following the report from the GETAID highlighting the disconnect between clinical and endoscopic disease activity, 28 an endoscopic sub-study from the ACCENT 1 trial of infliximab as maintenance therapy for CD demonstrated that 18% of patients with moderate to severe CD, as measured by the CDAI, had no endoscopic evidence of active CD, underscoring the disconnect between clinical symptoms and mucosal lesions. 55 On the other hand, a recent post-hoc analysis of the SONIC trial showed that about half of patients in clinical remission (CDAI < 150) still had evidence of endoscopically active disease. 6

Over time, a clear evolution of primary endpoints has been seen in clinical trials in luminal CD (Fig. 2). Whilst the very first trial used clinical response, subsequent trials started to use clinical remission and corticosteroid-free remission as primary endpoints. Only over the past years, mucosal healing has emerged as a major therapeutic goal in clinical trials in IBD. 62 The EXTEND trial was the first to use mucosal healing as a primary endpoint. 50 The definition of mucosal healing to be used in clinical trials is still debated for CD. 63 Obviously, the total disappearance of lesions is the simplest to use in clinical practice, but this definition does not take into account those patients with severe lesions that responded very well to their treatment, but still have a low level of residual endoscopic activity, e.g. some small ulcers. Currently, it is not known if these patients have a worse outcome compared with patients with a completely normalised mucosa. Nevertheless, a recently published consensus report defined mucosal healing as "the restoration of normal mucosal appearance by endoscopy of a previously inflamed region and the complete absence of ulceration and
<table>
<thead>
<tr>
<th>Trial name</th>
<th>Year of publication</th>
<th>Number of study sites</th>
<th>Number of patients</th>
<th>Main outcome parameter</th>
<th>Concomitant drug exposure</th>
<th>Previous anti-TNF exposure allowed?</th>
<th>Placebo-controlled?</th>
<th>Open-label?</th>
<th>Concomitant drug exposure</th>
<th>Study duration</th>
<th>Primary endpoint(s)</th>
<th>Placebo response (for primary endpoint)</th>
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<td>Targan et al.</td>
<td>1997</td>
<td>18</td>
<td>108</td>
<td>CDAI</td>
<td>5-ASA Corticosteroids AZA/6-MP</td>
<td>No</td>
<td>Yes</td>
<td>For non-responders at 4 weeks</td>
<td>12 weeks</td>
<td>Clinical response at 4 weeks</td>
<td>17%</td>
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<td>ACCENT-1</td>
<td>2002</td>
<td>55</td>
<td>573</td>
<td>CDAI</td>
<td>5-ASA Corticosteroids AZA/6-MP Methotrexate</td>
<td>No</td>
<td>Yes</td>
<td>Until week 2 and after week 14 for patients with loss of response.</td>
<td>54 weeks</td>
<td>1) Week 2 responders in clinical remission at week 30 2) Time to loss of response Clinical remission at week 6</td>
<td>1) 21% 2) 27%</td>
<td></td>
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<tr>
<td>Ghosh S et al.</td>
<td>2003</td>
<td>35</td>
<td>248</td>
<td>CDAI</td>
<td>5-ASA Corticosteroids AZA/6-MP</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>12 weeks Clinical remission at week 30</td>
<td>49%</td>
<td></td>
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<td>ENACT-1</td>
<td>2005</td>
<td>142</td>
<td>905</td>
<td>CDAI</td>
<td>Corticosteroids 5-ASA AZA/6-MP Methotrexate Antibiotics</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>12 weeks Clinical response at week 10</td>
<td>4%</td>
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<td>2005</td>
<td>142</td>
<td>339</td>
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<td>Corticosteroids 5-ASA AZA/6-MP Methotrexate Antibiotics</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>56 weeks Maintenance of response through week 36</td>
<td>28%</td>
<td></td>
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<td>Schreiber et al.</td>
<td>2005</td>
<td>58</td>
<td>292</td>
<td>CDAI</td>
<td>Corticosteroids 5-ASA AZA/6-MP Methotrexate Antibiotics</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>12 weeks Clinical response at week 12</td>
<td>35.6%</td>
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<td>2006</td>
<td>55</td>
<td>299</td>
<td>CDAI</td>
<td>5-ASA Corticosteroids AZA/6-MP Methotrexate</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>4 weeks Clinical remission at week 4</td>
<td>12%</td>
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<td>Year</td>
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<td>AZA/6-MP</td>
<td>Methotrexate</td>
<td>Antibiotics</td>
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<td>Primary Endpoint</td>
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<td>Duration</td>
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<td>53</td>
<td>276</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>56 weeks</td>
<td>Until week 4 and after week 4 if not in remission</td>
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<td>CHARMM</td>
<td>2007</td>
<td>92</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>56 weeks</td>
<td>Until week 4 and after week 12 in case of flare or sustained nonresponse</td>
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<td>ENCORE</td>
<td>2007</td>
<td>114</td>
<td>509</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>12 weeks</td>
<td>Clinical response at week 8 sustained through week 12</td>
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<td>2008</td>
<td>171</td>
<td>662</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>26 weeks</td>
<td>1) Clinical response at week 6 2) Clinical response at both weeks 6 and 26</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td>Maintenance of clinical response through week 26</td>
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<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>52 weeks</td>
<td>No analysis possible</td>
<td>Steroid-free clinical remission and no intestinal resection at 1) week 26 and 2) week 52</td>
<td>1345 Clinical trials in luminal Crohn’s disease</td>
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<td>SONIC^b^</td>
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<td>508</td>
<td>CDAI</td>
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<td>No</td>
<td>Yes</td>
<td>No</td>
<td>50 weeks</td>
<td>Steroid-free clinical remission at week 26</td>
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<td>EXTEND^50^</td>
<td>2012</td>
<td>19</td>
<td>135</td>
<td>Endoscopy</td>
<td>Corticosteroids 5-ASA</td>
<td>Yes</td>
<td>Yes</td>
<td>Until week 4 and after week 8 in case of flare or sustained nonresponse</td>
<td>52 weeks</td>
<td>Mucosal healing at week 12</td>
<td>13%</td>
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<td>CERTIFI^51^</td>
<td>2012</td>
<td>153</td>
<td>526</td>
<td>CDAI</td>
<td>Corticosteroids 5-ASA</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>36 weeks</td>
<td>Clinical response at 6 weeks</td>
<td>23.5%</td>
<td></td>
</tr>
<tr>
<td>MUSIC^52^</td>
<td>2013</td>
<td>14</td>
<td>89</td>
<td>Endoscopy</td>
<td>Corticosteroids 5-ASA</td>
<td>Yes (but no primary nonresponse)</td>
<td>No</td>
<td>Yes (full)</td>
<td>54 weeks</td>
<td>Mean change from baseline to week 10 in the CDEIS score</td>
<td>No analysis possible</td>
<td></td>
</tr>
<tr>
<td>GEMINI-2^53^</td>
<td>2013</td>
<td>285</td>
<td>1115</td>
<td>CDAI</td>
<td>Corticosteroids 5-ASA</td>
<td>Yes</td>
<td>Yes</td>
<td>Until week 6 (cohort 2) and after week 6 in case of lack of clinical response to vedolizumab induction therapy (cohort 1 and 2)</td>
<td>52 weeks</td>
<td>1) clinical remission at week 6 2) CDAI-100 response at week 6 3) clinical remission at week 52</td>
<td>1) 6.8% 2) 25.7% 3) 21.6%</td>
<td></td>
</tr>
</tbody>
</table>
macroscopic and histological signs of inflammation”. No clinical trial has used this extremely rigorous definition yet.

### 4. Perspectives

During the past 10–15 years, inclusion criteria for active disease, outcome measures and endpoints in CTs for luminal CD have clearly been shifting from subjective clinical scores towards objective parameters of active inflammation (endoscopy, CRP, faecal calprotectin etc.). Consistently, mucosal healing is the preferred primary endpoint in ongoing trials. In the last few years, the term “deep remission” has been introduced, to reflect a state of remission with a very low (or even zero) risk of disease progression. Although everyone agrees that deep remission combines clinical remission with objective parameters of inactive disease (biological and/or endoscopic remission), there is no consensus on its exact definition.\(^6\)\(^-\)\(^6\)\(^7\) The trend towards highly objective parameters of inflammation such as mucosal healing and deep remission to define treatment success may be the end of the placebo effect in luminal CD.\(^6\)\(^8\) In a post-hoc analysis of the EXTEND trials, the placebo-effect could be brought to zero by using deep remission at 1 year as the outcome criterium. In this analysis, the authors defined deep remission as the complete absence of mucosal ulceration and a CDAI less than 150.\(^6\)\(^9\)

In addition to disease outcomes, patient-reported outcomes (PROs), which measure the patients’ perspective, have the potential to become an important aspect of assessing CD. In this regard, the PRO-consortium (founded in cooperation with the FDA) is developing, evaluating, and qualifying PRO instruments for use in clinical trials.\(^7\)\(^0\)

The question remains whether we should use a symptom-based or a tailored treatment strategy to reach the aforementioned endpoints.\(^7\)\(^1\) The recently completed TAXIT trial, that included CD patients in clinical remission under infliximab maintenance therapy and with optimized infliximab trough levels, failed to demonstrate a clear benefit of a trough level-based approach versus a classical (i.e. symptom-based) approach in terms of clinical and biological remission rates at one year.\(^7\)\(^2\) However, the trough level-based approach led to a more efficient use of the drug, with more patients having optimal trough levels and less patients having antibody formation.\(^7\)\(^2\) In a recently published trial that compared an individualised (i.e. trough-level and antibody-based) approach with a routine dose escalation for patients with secondary loss of response to infliximab, it was found that the individualised approach was more cost-effective.\(^7\)\(^3\) The results of the TAILORIX trial, which investigates the impact of trough level-guided treatment on the rate of mucosal healing, are eagerly awaited.\(^7\)\(^4\)

Another important question is whether the achievement of robust endpoints effectively prevents long-term structural

### Table 2

| Expected characteristics of CTs in luminal CD as compared to the previous ones. |
|---|---|
| **Previous trials** | **Future trials** |
| **Definition of disease activity** | Subjective parameters (clinical indices) |
| **Study population** | Treatment naïve patients |
| **Study arms** | Study drug versus placebo |
| **Outcome measures** | Clinical symptoms |
| **Study duration** | Short-term |
| **Primary endpoint** | Clinical response/remission |
| **Placebo-effect** | High |
| | Objective parameters (endoscopy, serum inflammatory markers, faecal markers) |
| | Treatment naïve patients + treatment refractory patients |
| | Study drug versus active comparator |
| | Healing of inflammatory lesions assessed by imaging (endoscopy / cross-sectional) |
| | Long-term |
| | Mucosal healing |
| | Absence of bowel damage |
| | Absence of disability |
| | Low |
damage, surgical resection and the resulting loss of intestinal function. All available CTs evaluated the efficacy of drugs to induce and maintain clinical response/remission and/or mucosal healing. In order to investigate the potential for disease modification of anti-TNF agents, large prospective trials are needed. A first real disease-modification trial, REACT-2 (Randomized Evaluation of an Algorithm for Crohn’s Disease), is currently investigating whether an accelerated step-up treatment aiming to achieve and maintain deep remission leads to less CD-related complications compared with the classical step-care approach. Drugs able to prevent disease progression would then become truly reclassified as disease-modifying anti-inflammatory bowel disease drugs (DMDs). Scores to measure bowel damage and disability, respectively the Lémann score and the disability index, have recently been developed and validated, and will help to categorize and follow progression of damage and disability in these CD modification trials. Clearly such trials will have to be large and of long duration (beyond one year) as intestinal damage is a long-term complication of CD. As such, concerns have been raised on their practical feasibility. Cluster designs, in which study sites instead of individuals are randomized to compare treatment strategies, may help in this context by reducing the required sample size.

Another point to consider is that, in an era of economical crisis in which health care costs are rising, these CD modification trials will have to include cost-benefit analyses to convince health care authorities about overall benefits of early introduction of expensive drugs in the treatment of CD to change disease course and probably patients’ lives.

Clinical trials with new biologicals or compounds will have to be conducted in the post anti-TNF era. This means that, whereas previous anti-TNF exposure used to be an exclusion criterion in many previous trials, this will now rather become an inclusion criterion in some studies and in many a criterium for stratification of the study population. Hence, the results of clinical trials with new biologicals in the post-TNF era, like the GEMINI-2 trial and the CERTIFI trials, should be interpreted differently than in the past, as they will include a new class of patients with more severe, refractory CD that have already suffered from a complicated disease course (often with surgical interventions) (Table 2).

Another recent novelty that is changing the landscape of therapy in many fields in medicine is the introduction of biosimilar biologics. In terms of trial design these new drug type has brought to the field equivalence trials, because demonstration of the efficacy of the parent drug has previously followed the classical phases of drug development, and the biosimilar drug has to show the same biological and therapeutical effect. The EMA has recently issued its final guideline on biosimilar monoclonal antibodies, in which it is recognized that biosimilars cannot be identical to the primary compound, but must be similar to the original EU-approved molecules in terms of quality, safety, and efficacy. Assessment by EMA of applications for biosimilars is conducted in accordance with the guidelines of the Committee for Human Medicinal Products (CHMP), which highlight the studies necessary for demonstrating similarity of the proposed biosimilar to the reference product. These studies include pharmacokinetic and pharmacodynamic studies, both in vitro and animal models, as well as equivalence studies conducted in patients.

Competing interests

PH: Consulting fees from Abbvie and Vifor. Lecture fees from Abbvie.
FB: Consulting and lecture fees from ABBvie and MSD.
AH Consulting fees from MSD, Abbott, Ferring, Tillotts, Shire, Therakos, Pharmacos, and BMS.
JP: Consulting and lecture fees from ABBvie and MSD.
AA: Consulting fees from Abbvie, Hospira, Lilly, MSD. Lecture fees from Abbvie, Chiesi, Ferring, MSD, Nycomed, and Otsuka.

Acknowledgements

No funding was obtained for this manuscript.
PH drafted the manuscript. FB, AH, AA and JP reviewed the manuscript for its intellectual content. LPB coordinated the writing process and reviewed the manuscript for its intellectual content.

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