Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial

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Summary

Background Biomarkers of intestinal inflammation, such as faecal calprotectin and C-reactive protein, have been recommended for monitoring patients with Crohn's disease, but whether their use in treatment decisions improves outcomes is unknown. We aimed to compare endoscopic and clinical outcomes in patients with moderate to severe Crohn's disease who were managed with a tight control algorithm, using clinical symptoms and biomarkers, versus patients managed with a clinical management algorithm.

Methods CALM was an open-label, randomised, controlled phase 3 study, done in 22 countries at 74 hospitals and outpatient centres, which evaluated adult patients (aged 18–75 years) with active endoscopic Crohn's disease (Crohn's Disease Endoscopic Index of Severity [CDEIS] >6; sum of CDEIS subscores of >6 in one or more segments with ulcers), a Crohn's Disease Activity Index (CDAI) of 150–450 depending on dose of prednisone at baseline, and no previous use of immunomodulators or biologics. Patients were randomly assigned at a 1:1 ratio to tight control or clinical management groups, stratified by smoking status (yes or no), weight (<70 kg or ≥70 kg), and disease duration (≤2 years or >2 years) after 8 weeks of prednisone induction therapy, or earlier if they had active disease. In both groups, treatment was escalated in a stepwise manner, from no treatment, to adalimumab induction followed by adalimumab every other week, adalimumab every week, and lastly to both weekly adalimumab and daily azathioprine. This escalation was based on meeting treatment failure criteria, which differed between groups (tight control group before and after random assignment: faecal calprotectin ≥250 µg/g, C-reactive protein ≥5mg/L, CDAI ≥150, or prednisone use in the previous week; clinical management group before random assignment: CDAI decrease of <70 points compared with baseline or CDAI >200; clinical management group after random assignment: CDAI decrease of <100 points compared with baseline or CDAI ≥200, or prednisone use in the previous week). De-escalation was possible for patients receiving weekly adalimumab and azathioprine or weekly adalimumab alone if failure criteria were not met. The primary endpoint was mucosal healing (CDEIS <4) with absence of deep ulcers 48 weeks after randomisation. Primary and safety analyses were done in the intention-to-treat population. This trial has been completed, and is registered with ClinicalTrials.gov, number NCT01235689.

Findings Between Feb 11, 2011, and Nov 3, 2016, 244 patients (mean disease duration: clinical management group, 0·9 years [SD 1·7]; tight control group, 1·0 year [2·3]) were randomly assigned to monitoring groups (n=122 per group). 29 (24%) patients in the clinical management group and 32 (26%) patients in the tight control group discontinued the study, mostly because of adverse events. A significantly higher proportion of patients in the tight control group achieved the primary endpoint at week 48 (56 [46%] of 122 patients) than in the clinical management group (37 [30%] of 122 patients), with a Cochran–Mantel–Haenszel test-adjusted risk difference of 16·1% (95% CI 3·9–28·3; p=0·010). 105 (86%) of 122 patients in the tight control group and 100 (82%) of 122 patients in the clinical management group reported treatment-emergent adverse events; no treatment-related deaths occurred. The most common adverse events were nausea (21 [17%] of 122 patients), nasopharyngitis (18 [15%]), and headache (18 [15%]) in the tight control group, and worsening Crohn's disease (35 [29%] of 122 patients), arthralgia (19 [16%]), and nasopharyngitis (18 [15%]) in the clinical management group.

Interpretation CALM is the first study to show that timely escalation with an anti-tumour necrosis factor therapy on the basis of clinical symptoms combined with biomarkers in patients with early Crohn's disease results in better clinical and endoscopic outcomes than symptom-driven decisions alone. Future studies should assess the effects of such a strategy on long-term outcomes such as bowel damage, surgeries, hospital admissions, and disability.

Funding AbbVie.

Introduction

Crohn's disease is a chronic, progressive, and disabling condition that causes inflammation of any segment in the gastrointestinal tract and, eventually, development of strictures, fistulas, or abscesses that require surgery in about half of patients within 10 years of diagnosis.[1–3] Conventional management of Crohn's disease with corticosteroids, immunomodulators, and tumour necrosis

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Research in context

Evidence before this study

We searched PubMed for articles published up to Aug 11, 2017, in any language, with the search terms "Crohn's disease", "early combined immunosuppression", "azathioprine combination", and "therapeutic goals". We identified three publications of randomised controlled trials using biologics and azathioprine in the treatment of Crohn's disease (Top-Down, SONIC, and REACT) and one publication of recommendations from an expert panel that determined treat-to-target goals in Crohn's disease (STRIDE). The Top-Down and REACT trials have shown that combined immunosuppression was effective in inducing clinical remission, decreasing corticosteroid use, and decreasing the risk of major adverse outcomes (defined as occurrence of surgery, hospital admission, or a serious disease-related complication in patients with Crohn's disease). The SONIC trial has shown that combination treatment of anti-tumour necrosis factor inhibitor and azathioprine was more effective in achieving clinical remission than azathioprine monotherapy or anti-tumour necrosis factor inhibitor monotherapy. Recommendations by an expert panel (STRIDE) defined the therapeutic goal in Crohn's disease as clinical and endoscopic remission, but did not have a practical algorithm to achieve this goal. The panel recommended use of faecal calprotectin and C-reactive protein, biomarkers of inflammation, to monitor patients to reach the goal of remission; however, there is insufficient evidence to recommend treatment optimisation on the basis of biomarkers alone. Indeed, few studies have shown the usefulness of faecal calprotectin and C-reactive protein in monitoring patients with Crohn's disease.

Added value of this study

CALM is a phase 3, multicentre, randomised, open-label, active-controlled efficacy and safety study in patients with moderate to severe Crohn's disease who were naive to immunomodulators and biologics. To our knowledge, this is the first study to show that a tight control algorithm of disease activity with stringent criteria including C-reactive protein, faecal calprotectin, Crohn's Disease Activity Index, and prednisone use increased the proportion of patients with Crohn's disease who reached the mucosal healing target (Crohn's Disease Endoscopic Index of Severity score <4) and an absence of deep ulcers at 48 weeks after randomisation compared with clinical management using Crohn's Disease Activity Index and prednisone use only. Tight control of disease activity based on biomarkers also improved other endoscopic and clinical outcomes, including steroid-free remission. The safety profile was similar between treatment groups and consistent with the known safety profile of adalimumab in Crohn's disease.

Implications of all the available evidence

This study reinforces the evidence supporting the efficacy of early biologic therapy and the use of objective markers of inflammation in making therapeutic decisions in Crohn's disease. No new safety signals were identified with treatment escalation; the safety profile of study treatments was similar to the known safety of adalimumab monotherapy and combination therapy and adalimumab dosing schedules in Crohn's disease.

factor (TNF) inhibitors and other biologics (following this sequence of treatment) might not adequately control the underlying inflammation and could delay the initiation of the most effective treatment.[4] This approach might also put patients at risk of infections, morbidity, and mortality because of the prolonged use of corticosteroids.[5,6] Additionally, the presence and severity of symptoms are not necessarily indicative of endoscopic status in patients with Crohn's disease and might not be reliable criteria to guide adjustment of treatment to control persistent mucosal inflammation.

Treatment goals in Crohn's disease now aim at more than just controlling symptoms.[7] In 2015, the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) programme, initiated by the International Organisation for the Study of Inflammatory Bowel Diseases (IOBD) defined a treat-to-target approach for Crohn's disease, with the aim of achieving both clinical and endoscopic remission.[8] The expert consensus from the IOBD also concluded that biomarkers of inflammation, such as faecal calprotectin (FC) or C-reactive protein (CRP), might be useful to detect residual intestinal inflammation and might facilitate patient monitoring. However, the panel advised that persistent elevations in these biomarkers should not be used alone to adjust therapy, because of scant evidence available at the time.

The CALM study was designed to investigate the effectiveness and safety of two treatment algorithms in achieving mucosal healing in patients with Crohn's disease by escalating treatment on the basis of prespecified treatment failure criteria: clinical symptoms and biomarkers of inflammation in the tight control algorithm, or clinical symptoms alone in the clinical management algorithm.

Methods

Study design

CALM was a multicentre, randomised, open-label, active-controlled, two-group, phase 3, efficacy and safety trial, which was done in 22 countries at 74 hospitals and outpatient centres, to assess two treatment algorithms, tight control and clinical management, in patients with moderate to severe Crohn's disease. The study protocol was approved by the relevant ethics committees or institutional review boards and was executed in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable local regulations.

Protocol deviations (eg, violations of inclusion or exclusion criteria or incorrect treatment or dose) were

monitored at study entry and throughout the study. All protocol deviations were assessed in real time for their effect on data integrity and patient safety to determine whether the patient should continue in the study.

Participants

Adult patients were enrolled in the study, age 18–75 years, with Crohn's disease at baseline and a diagnosis of ileal, colonic (including rectal), or ileocolonic Crohn's disease (as confirmed by endoscopy not >6 years before baseline). Key inclusion criteria were: (1) moderate to severe Crohn's disease at baseline, defined as Crohn's Disease Activity Index (CDAI)[9] scores of 220–450 for patients not receiving prednisone at baseline, 200–450 for patients receiving 20 mg prednisone (or less) for 7 days or more before baseline, and >150–450 for patients receiving more than 20 mg prednisone for 7 days or more before baseline; (2) active endoscopic disease, defined as a total Crohn's Disease Endoscopic Index of Severity (CDEIS) of more than 6 and a sum of CDEIS subscores of more than 6 in one or more segments with ulcers; and (3) CRP of 5 mg/L or more, FC of 250 µg/g or more, or both. Key exclusion criteria were previous or current use of biologics or immunomodulators, more than two previous courses of corticosteroids, or current use of corticosteroids for more than 3 months before screening. Patients with any fibrotic stricture (passable or non-passable and regardless of symptoms), draining perianal fistulas, or non-perianal fistulas were excluded (see appendix p 2 for a complete list of inclusion and exclusion criteria). Patients gave written informed consent.

Randomisation and masking

9 weeks after baseline, patients were randomly assigned to the tight control or clinical management group in a 1:1 ratio, stratified by smoking status (yes or no), weight (<70 kg or ≥70 kg), and disease duration (≤2 years or >2 years). To facilitate recruitment, an amendment on Sept 29, 2011, allowed patients with active disease (CDAI >220) to be randomly assigned early (between baseline and originally scheduled randomisation) if one of the following conditions were met: (1) the patient was receiving corticosteroid therapy for 4 weeks of duration, including 2 weeks of at least 40 mg prednisone or an equivalent dosage per day (or ≥9 mg budesonide per day); (2) intolerance or a medical contraindication to steroid therapy; or (3) the investigator assessed that it was in the best interest of the patient. Investigators enrolled the patients. The patient number and group of each stratum were assigned by a central randomisation schedule generated by AbbVie (Chicago, IL, USA) using WebRando software for randomisation and ClinPhone, an interactive voice and web response system for patient allocation. The subject randomisation schedule was generated by a designated person in the AbbVie statistics department, who was not involved in the rest of the study. The investigators and patients were masked to patient allocation and post-screening FC and CRP results, but treatments were open label.

Procedures

All eligible patients received a prednisone burst of up to 40 mg/day starting at baseline (9 weeks before randomisation). Prednisone was tapered with a schedule that was set by each investigator at his or her discretion. 1 week before randomisation, patients' blood and stool samples, CDAI, and prednisone use were assessed during a site visit (figure 1). At randomisation, open-label treatment options were determined on the basis of whether failure criteria listed in figure 1 had been met. Patients who were randomly assigned to groups early and patients who met any of the failure criteria 1 week before group allocation received 160 mg adalimumab at week 0 and 80 mg adalimumab at week 2, followed by 40 mg every other week. Patients who did not meet the treatment failure criteria at randomisation did not receive adalimumab. All patients could continue prednisone treatment at the discretion of the investigator (on the basis of the rapidity and tolerance of the taper).

During the post-randomisation treatment period, open-label treatment in both groups was escalated in a stepwise manner at 12, 24, and 36 weeks if patients met any of the post-randomisation treatment failure criteria, including laboratory assessments of serum concentrations of CRP and stool concentrations of FC at 11, 23, and 35 weeks (figure 1). The CDAI threshold for the clinical management group was different from that of the tight control group because it was meant to mirror treatment in clinical practice at the time the study was designed, whereas the more stringent criteria in the tight control group were meant to guide treatment escalation decisions using clinical remission, normalised biomarkers, and discontinuation of corticosteroids. Patients who did not meet the treatment failure criteria stayed on their previously assigned treatment option. At 24 and 36 weeks after randomisation, patients receiving 40 mg adalimumab every week were de-escalated to receive 40 mg adalimumab every other week and patients receiving 40 mg adalimumab every week and 2·5 mg/kg per day azathioprine were de-escalated to 40 mg adalimumab every other week and 2·5 mg/kg per day azathioprine. Patients who did not complete a prednisone taper could continue to receive prednisone throughout the post-randomisation treatment period, but could not re-initiate once tapered off. Only patients with a CDAI of 300 or more who were initiating treatment with 40 mg adalimumab every week and 2·5 mg/kg per day azathioprine could restart prednisone. Final assessment of patients occurred at 48 weeks after randomisation. CDAI was measured every 12 weeks and at unscheduled visits.

Patients who needed treatment escalation before the next site visit and who had a CDAI of more than 300 for two consecutive visits, as measured 7 days apart (where

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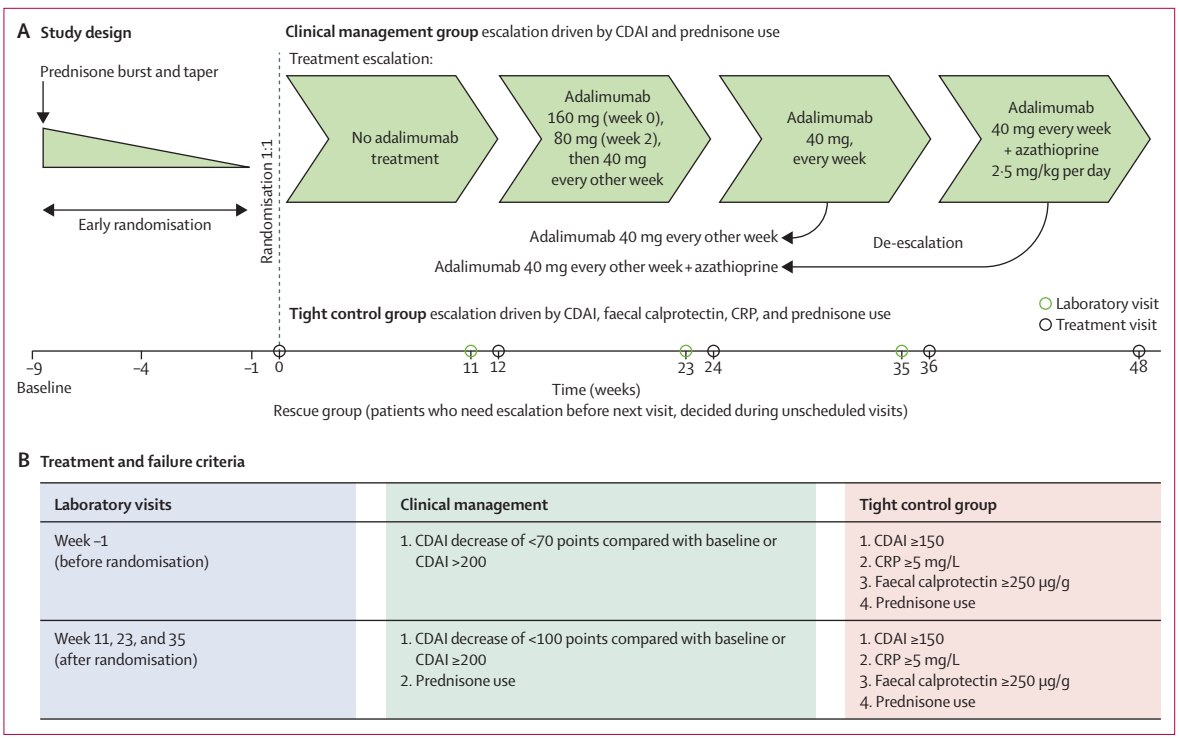

B Treatment and failure criteria

Laboratory visits	Clinical management	Tight control group
Week −1 (before randomisation)	1. CDAI decrease of <70 points compared with baseline or CDAI >200	1. CDAI ≥150 2. CRP ≥5 mg/L 3. Faecal calprotectin ≥250 µg/g 4. Prednisone use
Week 11, 23, and 35 (after randomisation)	1. CDAI decrease of <100 points compared with baseline or CDAI ≥200 2. Prednisone use	1. CDAI ≥150 2. CRP ≥5 mg/L 3. Faecal calprotectin ≥250 µg/g 4. Prednisone use

Figure 1: **CALM study design**
CDAI=Crohn's disease activity index. CRP=C-reactive protein.

the first CDAI measurement of >300 was at or after 4 weeks from initiation of the current therapeutic option), or patients for whom the investigator decided that it was in their best interests, were moved to a rescue group and followed the tight control management algorithm. Rescue therapy was not allowed if patients were within 6 weeks of the final study visit.

Ileocolonoscopies to assess CDEIS were done at study sites during screening and at 48 weeks after randomisation or early termination. Endoscopists were trained to assess endoscopies in a standardised manner.

A central laboratory (Genova Diagnostics, Ashville, NC, USA) measured FC using an established assay and CRP using a particle-enhanced immunoturbidimetric assay and a turbidimetric/immunoturbidimetric assay. FC concentration has been shown to have a sensitivity of 87% and specificity of 67% for endoscopically active Crohn's disease, whereas CRP concentration has shown a sensitivity of 49% and specificity of 92% for inflammatory bowel disease.[10]

Outcomes

The primary endpoint of the study was the proportion of patients with mucosal healing, defined as a CDEIS of less than 4 and no deep ulcers 48 weeks after randomisation. Because the study had several secondary endpoints (unranked), we report only those most relevant to the primary endpoint in this report. These include the following assessments 48 weeks after randomisation: (1) deep remission (CDAI <150, CDEIS <4 and no deep ulcers, absence of draining fistula, discontinuation of corticosteroids for ≥8 weeks); (2) biological remission (FC <250 µg/g, CRP <5 mg/L, and CDEIS <4); (3) CDEIS of less than 4; (4) overall CDEIS of less than 4 plus CDEIS of less than 4 in every segment; (5) complete endoscopic remission (CDEIS=0); and (6) endoscopic response (CDEIS decrease of >5 points). Steroid-free remission (CDAI <150 and discontinuation of steroid use for ≥8 weeks), clinical remission (CDAI <150), mean change from baseline in CDAI, and mean change from baseline in CRP were assessed over time. Additional secondary endpoints are listed in the appendix and will be reported in subsequent articles.

Adverse events were monitored in all patients who were randomly assigned, from the time of administration up to 70 days after discontinuation of study drugs, except in patients who continued to receive adalimumab after the end of the study. New adverse events in these patients were reported through the post-marketing reporting mechanism. Serious adverse events were collected from the time at which patients signed the informed consent. Tuberculosis was tested for with a purified protein derivative skin test or an interferon-γ release assay and confirmed using chest x-ray during screening for all patients, and then annually for patients who completed the study. Adverse events were tabulated by system organ class and preferred term using the MedDRA dictionary, version 19.0.

Statistical analysis

Sample size was calculated using nQuery Advisor 6·0. To achieve 90% power, assuming mucosal healing and no deep ulceration rates of 44·0%[11] in the tight control group and 23·5% in the clinical management group[12] until the end of the 48 week post-randomisation treatment period, 120 participants per group were needed using Fisher's exact test (two-sided) at a 0·05 α level. Patients who were in screening or who had been enrolled into the prednisone burst and taper portion of the study when the minimum sample size was met were able to enrol in the study.

Efficacy endpoints and safety were analysed in the modified intention-to-treat population, defined as enrolled and randomly assigned patients. Missing values after randomisation for primary and secondary endpoints and for remission over time were imputed using non-responder imputation; data for patients who discontinued the study or who moved to the rescue group were also subject to non-responder imputation. Changes from baseline in CDAI and CRP concentration were imputed using the last observation carried forward method.

Primary endpoint and categorical secondary endpoints were compared in the tight control and clinical management groups using the Cochran–Mantel–Haenszel (CMH) test, stratified by smoking status (yes or no) and weight (<70 kg or ≥70 kg) at screening. The CMH-based two-sided 95% CIs for the difference in proportions between groups were calculated. The secondary endpoints for the difference in change from baseline between groups were analysed using an ANCOVA model including factors of treatment, screening smoking status (yes or no), weight (<70 kg or ≥70 kg), and baseline scores as covariates. Although disease duration (≤2 years or >2 years) was a randomisation stratum, it was not used in CMH or ANCOVA analyses to avoid zero cell issue because most patients had a disease duration of 2 years or less. The secondary endpoints were tested at a nominal significance level of 0·05 with no adjustment of multiplicity. Safety analyses were summarised by study group and presented as number and proportion of patients and rate (number of events per 100 patient-years). All analyses were performed with SAS software version 9.4 (SAS Institute Inc, Cary, NC USA). This trial is registered with ClinicalTrials.gov, number NCT01235689.

Role of the funding source

AbbVie funded the study, contributed to the study design, participated in the collection, analysis, and interpretation of the data, and in preparation and approval of this report. All authors had access to all study data, reviewed and approved the final report, and take full responsibility for the accuracy of the data and statistical analysis. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

Results

Between Feb 11, 2011 and Nov 3, 2016, 460 patients were screened, 205 were excluded, 11 were enrolled but not randomly assigned, and 244 were randomly allocated to the tight control (n=122) or clinical management (n=122) groups (figure 2). The most common reason for screening failure was not meeting inclusion criteria or meeting exclusion criteria. Among patients who failed screening, 65 (32%) did not meet increased FC or CRP criteria. Three (2%) of 122 patients in the tight control group and 24 (20%) of 122 patients in the clinical management group moved to rescue therapy. 86 (35%) of 244 patients had notable protocol deviations, including violations of inclusion or exclusion criteria, receiving the incorrect treatment or dose, or receiving excluded concomitant treatment. No patients met withdrawal criteria, which included abnormal lab results or adverse events; the investigator believing that it was in the best interests of the patient to withdraw; the patient requesting withdrawal; violating the inclusion or exclusion criteria; use of prohibited medications; pregnancy; development of dysplasia, malignancy, lupus-like syndrome, multiple sclerosis, or demyelinating disease; or non-compliance by the patient to study procedures, without being withdrawn.

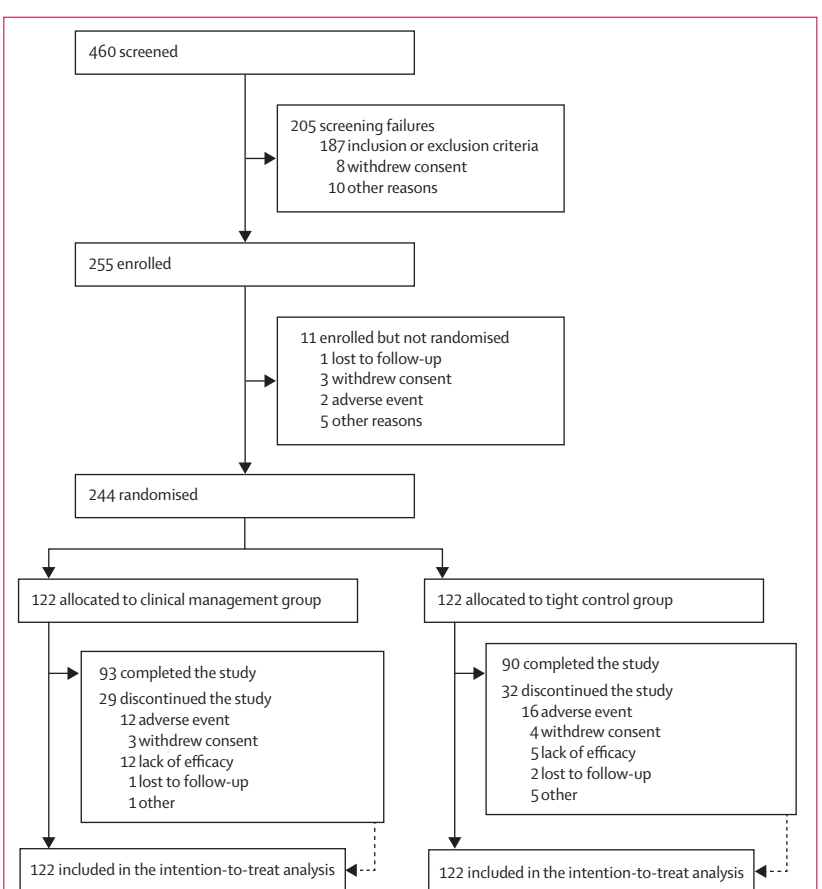

Figure 2: **Trial profile**

	Clinical management (n=122)	Tight control (n=122)
Sex		
Female	69 (57%)	72 (59%)
Male	53 (43%)	50 (41%)
Race		
White	113 (93%)	113 (93%)
Other	9 (7%)	9 (7%)
Mean age (SD; years)	31·1 (11·4)	32·1 (12·0)
Mean weight (SD; kg)	66·3 (12·3)	66·3 (13·7)
Disease duration (years)		
Mean (SD)	0·9 (1·7)	1·0 (2·3)
Median (min–max)	0·2 (0·0–12·7)	0·2 (0·0–13·2)
Mean CDAI (SD)	267·7 (58·4)	273·3 (59·5)
Mean CDEIS (SD)	14·3 (6·9)	13·4 (6·0)
Disease location*		
Ileum	14 (12%)	21 (17%)
Colon	37 (30%)	34 (28%)
Ileum–colon	65 (53%)	64 (53%)
Other	6 (5%)	3 (2%)
Surgeries	8 (7%)	12 (10%)
Stool faecal calprotectin		
<250 µg/g	17 (14%)	24 (20%)
≥250 µg/g	105 (86%)	96 (80%)
Serum C-reactive protein		
<5 mg/L	19 (16%)	27 (22%)
≥5 mg/L	103 (84%)	95 (78%)
Mean concentration (SD; mg/L)	27·0 (30·6)	26·4 (32·3)
Median concentration (mg/L; min–max)	16·1 (0·4–172·6)	13·6 (0·2–157·1)
Smoker	33 (27%)	31 (25%)

Data are n (%) unless otherwise stated. CDAI=Crohn's Disease Activity Index. CDEIS=Crohn's Disease Endoscopic Index of Severity. *Ileal disease location is proximal to ileocaecal valve to the jejunum, and colon disease location is distal to the ileocaecal valve to the anal verge.

Table 1: **Patients' baseline characteristics**

The appendix details the types of deviations and numbers of affected patients per group. None of the deviations was considered to have affected the study outcome or interpretation of the study results. 93 (76%) of 122 patients in the clinical management group and 90 (74%) of 122 patients in the tight control group completed the study. Primary reasons for discontinuation in both groups were similar.

Patient characteristics in both groups were similar at baseline (table 1). Mean disease duration was similar in both groups. 98 (80%) patients in the tight control group and 97 (80%) patients in the clinical management group were exposed to prednisone at or after screening. Mean exposure of prednisone during the entire study, excluding the use before randomisation, was 1369·9 (1137·7) mg per patient in the tight control group and 1505·7 (1029·8) mg per patient in the clinical management group. 69 (57%) patients in the tight control group and 63 (52%) patients in the clinical management group were randomly assigned early. The appendix shows the timing of randomisation.

The study's primary endpoint of mucosal healing (CDEIS <4) and no deep ulcers at 48 weeks after randomisation was met in 56 (46%) patients in the tight control group compared with 37 (30%) patients in the clinical management group, with a CMH-adjusted risk difference of 16·1% (95% CI 3·9 to 28·3; p=0·010; figure 3A). A higher proportion of patients in the tight control group achieved the following key secondary endpoints 48 weeks after randomisation than in the clinical management group: deep remission, with a CMH-adjusted risk difference of 14·5% (2·9 to 26·0; p=0·014); biological remission, with a CMH-adjusted risk difference of 14·5% (4·1 to 25·0; p=0·006); and an overall CDEIS of less than 4, with a CMH-adjusted risk difference of 16·1% (3·9 to 28·3; p=0·010; figure 3B). No significant differences were observed between the groups regarding the proportion of patients with an overall CDEIS of less than 4 plus a CDEIS of less than 4 in every segment (CMH-adjusted risk difference of 5·9% [95% CI −5·2 to 17·0]; p=0·299), complete endoscopic remission (1·7% [−7·9 to 11·3]; p=0·728), or endoscopic response (11·5% [−0·8 to 23·9]; p=0·067; figure 3B). A significantly higher proportion of patients achieved steroid-free remission in the tight control group than the clinical management group (figure 3C) and clinical remission (CDAI <150; appendix) at 11, 23, 35, and 48 weeks after randomisation. A significantly greater mean change from baseline in CDAI was observed in the tight control group than in the clinical management group at 11, 35, and 48 weeks (appendix). The mean change from baseline in CRP concentration was not significantly different between tight control and clinical management (appendix).

The number of patients receiving each treatment option at randomisation and 12, 24, and 36 weeks after randomisation who completed the study and did not move to the rescue group (n=88 in the tight control group and n=78 in the clinical management group) is shown in figure 4. At randomisation, more patients in the tight control group received adalimumab every other week than in the clinical management group. Over time, more patients in the tight control group advanced in the treatment algorithm earlier than in the clinical management group. For example, more patients in the tight control group escalated to adalimumab every week at 12 weeks and to adalimumab every week plus azathioprine at 24 weeks than in the clinical management group. Additionally, more patients de-escalated from the weekly dosing to every other week at 24 weeks and from adalimumab every week plus azathioprine to adalimumab every other week plus azathioprine at 36 weeks in the tight control group than in the clinical management group (figure 4). Overall, more treatment adjustments

occurred in the tight control group than in the clinical management group.

In the tight control group, 50 patients met treatment failure criteria at 11 weeks, 39 patients at 23 weeks, and 20 patients at 35 weeks after randomisation (appendix). Post-hoc exploratory analyses showed that the decision to escalate included increased FC concentration for 31 (62%) of 50 patients (at 11 weeks after randomisation) and 22 (56%) of 39 patients (at 23 weeks after randomisation) and increased CRP concentration for 23 (46%) of 50 patients (11 weeks post-randomisation) and 18 (46%) of 39 patients (23 weeks post-randomisation). At week 35, FC and CRP concentrations contributed equally to the decision to escalate in nine (45%) of 20 patients. Fewer patients were escalated on the basis of CDAI and use of prednisone at weeks 11, 23, and 35. In the clinical management group, 24 patients met failure criteria at 11 weeks, nine patients at 23 weeks, and seven patients at 35 weeks (appendix). Prednisone use was the main driver of the decision to escalate at 11 and 23 weeks. At 35 weeks, in all patients in the clinical management group who were escalated, this decision was made on the basis of increased CDAI.

Overall, 105 (86%) of 122 patients in the tight control group and 100 (82%) of 122 patients in the clinical management group reported treatment-emergent adverse events (table 2). The rate of adverse events in both groups was similar, and a similar proportion of patients reported treatment-emergent serious adverse events. The rate of serious adverse events was lower in the tight control group than in the clinical management group. The proportion of patients reporting serious infections in the tight control group (six [5%] of 122) and in the clinical management group (12 [10%] of 122) were not substantially different. Among patients with serious infection, two (2%) in the tight control group and seven (6%) in the clinical management group reported abdominal or anal abscesses. Prevalence and rate of other adverse events from patients in the tight control and clinical management groups were similar. No new safety signals were found in either group.

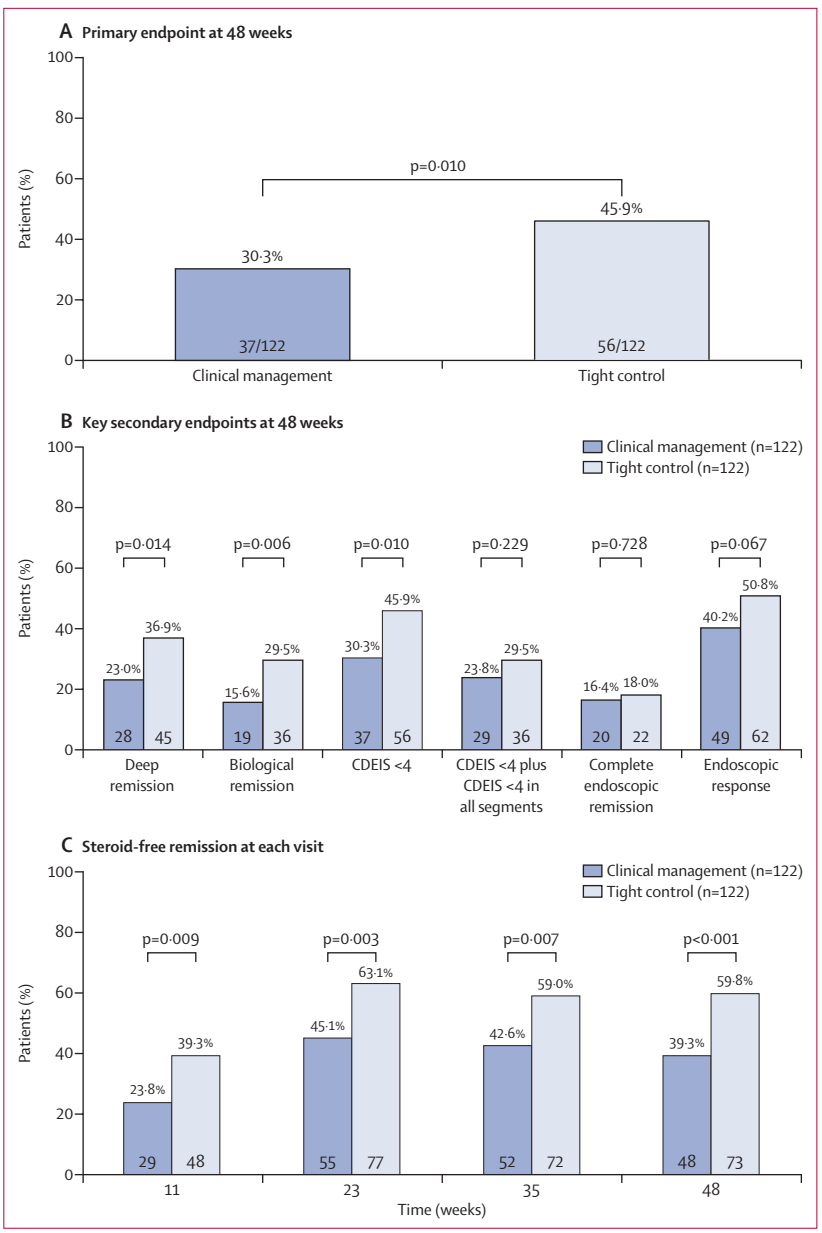

Figure 3: **Proportion of patients achieving study endpoints at 48 weeks after randomisation**
(A) Proportion of patients with mucosal healing (CDEIS <4) and no deep ulcers at 48 weeks after randomisation (also expressed within the bars as number of patients/total patients in each group). (B) Secondary endoscopic endpoints at 48 weeks after randomisation (also expressed within the bars as number of patients). (C) Steroid-free remission (Crohn's Disease Activity Index <150 and no corticosteroids for ≥8 weeks) during the post-randomisation period (also expressed within the bar as number of patients). CDEIS=Crohn's Disease Endoscopic Index of Severity.

Discussion

The CALM study shows that a treatment algorithm based on concentrations of FC and CRP to monitor inflammatory activity and clinical symptoms (tight control) led to superior outcomes compared with the algorithm based on clinical management alone in patients with early Crohn's disease. The tight control algorithm led to rapid optimisation of therapy and, therefore, to a higher proportion of patients achieving mucosal healing (CDEIS <4) and no deep ulcers on endoscopy, deep remission (CDAI <150 and CDEIS <4 and no deep ulcers, no draining fistula, and no prednisone use for 8 weeks or more), biological remission (FC <250 μg/g, CRP <5 mg/L, and CDEIS <4), and steroid-free remission (CDAI <150 with no prednisone for 8 weeks).

Early use of anti-TNF therapy has been advocated because it gives a greater chance of achieving clinical remission, mucosal healing, and preserving bowel integrity than late use.[13] In a subgroup analysis of patients with moderately to severely active Crohn's disease who were given adalimumab, patients with disease duration of less than 2 years were more likely to achieve remission than patients with longer disease duration during 3 years

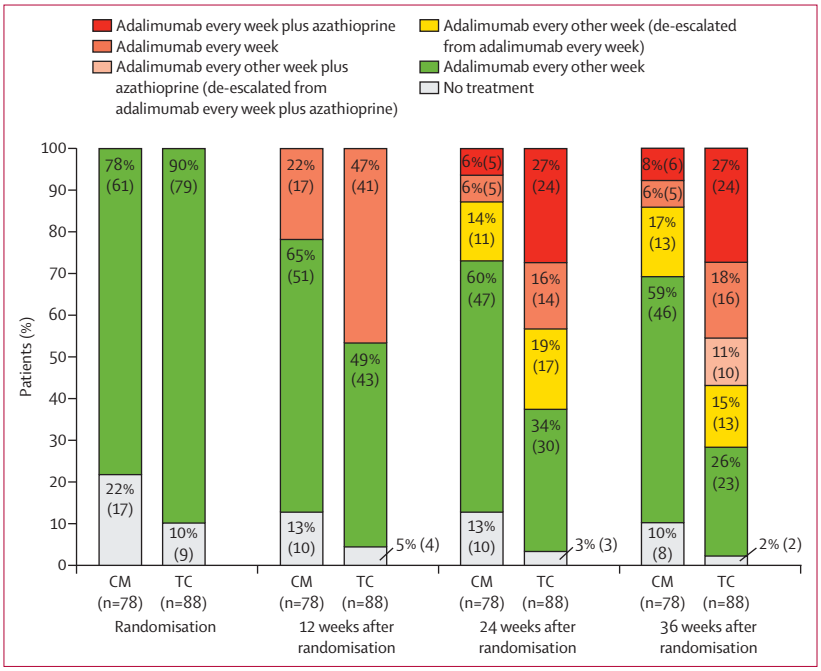

Figure 4: **Proportion of patients receiving each treatment option at and after randomisation**
Data are expressed as % (n). Data are from patients who completed the study and did not move to the rescue group. CM=clinical management group. TC=tight control group.

	Clinical management (n=122)		Tight control (n=122)	
	Patients (%)	Events (events/100 patient-years)*	Patients (%)	Events (events/100 person-years)†
Adverse events	100 (82%)	634 (694·4)	105 (86%)	636 (643·1)
Serious adverse events	25 (21%)	45 (49·3)	22 (18%)	32 (32·4)
Adverse events leading to adalimumab discontinuation	16 (13%)	25 (27·4)	17 (14%)	18 (18·2)
Infection	57 (47%)	110 (120·5)	61 (50%)	116 (117·3)
Serious infection	12 (10%)	15 (16·4)	6 (5%)	7 (7·1)
Opportunistic infection excluding oral candidiasis and tuberculosis	0	0	0	0
Active tuberculosis	0	0	1 (1%)‡	1 (1·0)
Latent tuberculosis	2 (2%)	2 (2·2)	1 (1%)	1 (1·0)
Malignancy	0	0	1 (1%)	1 (1·0)
Deaths	0	0	0	0

*91·3 person-years of data were obtained in the clinical management group. †98·9 person-years of data were obtained in the tight control group. ‡Pulmonary tuberculosis.

Table 2: **Treatment-emergent adverse events**

of continued treatment.[14] Higher proportions of patients in combined clinical and endoscopic remission (so-called deep remission) were observed among patients with less than 2 years of Crohn's disease in another study than in patients with more than 2 years of Crohn's disease.[15] Our study results reinforce previous findings that patients with recent onset of disease (mean disease duration 0·9–1·0 years) benefit from early biological treatment: higher overall proportions of patients had mucosal healing and steroid-free remission in the clinically managed group than observed in previous studies of adalimumab used in a traditional step-up manner in patients with a longer average disease duration.[12,16] Even in these patients with recent onset, in whom good endoscopic and clinical outcomes are anticipated, the tight control approach led to even greater clinical benefits than clinical management without an increased risk.

Delaying administration of effective therapy for Crohn's disease can put patients at an increased risk of developing complications. A concept of early immunosuppression addressing this concern by administering biologics combined with immunomodulators after corticosteroid induction has shown superior outcomes compared with a conventional step-up therapy in both referral centres and community-based practices.[4,11,17] In our study, we used a novel approach to optimise adalimumab dosing before adding azathioprine, on the basis of individual response, to minimise exposure to azathioprine and improve outcomes.

The REACT study[4] showed a decrease in the risk of major adverse outcomes, including surgeries and hospital admissions, after treatment with early combined immunosuppression based on a rapid step-up algorithm of adalimumab combined with an antimetabolite as a first-line treatment in patients with established Crohn's disease after failure of corticosteroids, when compared with conventional management. We need to determine whether early individualised optimisation of therapy based on biomarkers and symptoms, such as in the CALM study, will also lead to fewer irreversible disease-related structural complications than with therapy individualisation based on symptoms alone.

The STRIDE consensus recommended a treat-to-target goal in Crohn's disease to be endoscopic remission (resolution of ulceration, as observed by ileocolonoscopy) and clinical remission (resolution of abdominal pain and diarrhoea or altered bowel habits).[8] Endoscopic remission and deep remission, defined as the absence of mucosal ulceration and CDAI of less than 150, have shown to be consistently associated with better long-term outcomes.[15] However, the ability to undertake repeated endoscopic assessment and the patient acceptance of this procedure are probably prohibitive. Studies have shown that inflammatory biomarkers, such as CRP and FC, might be useful adjuncts to identify patients at risk for negative outcomes. In a study[18] of 43 patients with Crohn's disease, increased concentrations of FC predicted relapse of disease activity. A systematic analysis[19] of six studies of inflammatory bowel disease, including Crohn's disease, has shown that increased concentrations of FC on at least two consecutive measurements were associated with a higher risk of relapse within 2–3 months in asymptomatic patients, and that normal FC values were associated with a lower risk of relapse. In another study[20] of 87 patients with Crohn's disease, FC concentrations of greater than

250 µg/g were associated with the presence of large ulcers and FC concentrations of 250 µg/g or less predicted endoscopic remission. An increase in CRP concentration is associated with clinical disease activity, endoscopic inflammation, and severely active histological inflammation in patients with Crohn's disease.[21] However, the usefulness of CRP, a non-specific marker of intestinal inflammation, in monitoring patients with Crohn's disease remains unclear. Although CRP has been shown to be a predictive factor of Crohn's disease relapse in patients with increased CRP concentrations at diagnosis,[22] some patients with low CRP concentrations still have active disease[23] and an increased CRP concentration is not always due to active disease.[24] Our study showed that patients in the tight control group had better outcomes due to a quicker treatment escalation when guided by increased concentrations of FC or CRP, or both, and by clinical symptoms, than those whose treatment decisions were based on clinical symptoms alone. These findings emphasise the role biomarkers can serve in identifying underlying inflammation in Crohn's disease and the need for monitoring patients with objective criteria.

Despite more intensive immunosuppression as a result of faster treatment escalation to weekly adalimumab (with or without azathioprine) in the tight control group than in the clinical management group, the proportions of patients who had an adverse event at 48 weeks of treatment were similar in both groups, as were the rate of adverse events. The proportions of patients with (and the rate of) serious adverse events and serious infections were lower in the tight control group than in the clinical management group. Adalimumab every week has previously been shown to be well tolerated and has a safety profile similar to the every other week dosing at 56 weeks.[16] Similar proportions of adverse events have been observed in patients given adalimumab monotherapy or combination therapy in short-term studies,[25] but combined use was associated with a greater risk of malignancy in an analysis that included longer follow-up.[26] The lower exposure-adjusted rate of serious adverse events in the tight control group than in the clinical management group could be related to superior control of Crohn's disease activity. This suggestion is supported by a lower number of patients with serious infections because of abscesses in the tight control group than in the clinical management group. A 2016 analysis[6] of patients with Crohn's disease who were given adalimumab found that higher disease activity was associated with significantly increased risks of both serious and opportunistic infections. The frequency and rate of adverse events and serious adverse events in the CALM study were consistent with the adalimumab safety profile from global clinical trials in patients with Crohn's disease and across approved indications;[27,28] no new safety signals were identified.

Our study has several limitations. First, endoscopies were assessed by site readers, which could have created an inclusion bias and scoring heterogeneity. However, interobserver agreement in measuring CDEIS has been shown to be good.[29,30] Additionally, agreement between CDEIS determined by trained site and central readers has been shown to be excellent, suggesting that site readings by trained endoscopists could be used in clinical trials.[31] In our study, investigators were instructed to assess all endoscopies in a standardised way, and the same endoscopist was to assess all endoscopies from an individual patient. Another limitation of CALM was its open-label design, which could have biased clinical and endoscopic assessments, and short duration of follow-up (48 weeks), which did not allow assessment of whether the superior efficacy findings with tight control would lead to better long-term outcomes or whether the safety profile would change with longer use. The CALM entry criteria specified a maximum disease duration of 6 years and no exposure to anti-TNF agents and immunomodulators to identify patients with a lower likelihood of accumulated bowel damage who would be more responsive to the study treatments. Whether the findings of CALM could be expected in a population of patients with longer disease duration or more treatment experience is unknown. Lastly, the prednisone taper schedule and continuation of prednisone treatment was at the investigator's discretion. Because the duration of taper could affect the treatment option at randomisation differentially between treatment groups (because the use of prednisone only defined treatment failure at randomisation in the tight control group), earlier introduction of adalimumab could have affected the outcomes observed 48 weeks after randomisation.

The CALM study has shown for the first time, to our knowledge, that tight control of inflammation in patients with Crohn's disease, with objective markers of disease activity and clinical symptoms to drive treatment decisions, achieved better endoscopic and clinical outcomes than conventional care based on symptoms alone. Early treatment escalation to adalimumab was well tolerated and proactive biomarker monitoring reduced the use of corticosteroids.

Contributors

J-FC, RP, PB, ML, FB, TV, AD, GN, AA, XH, ST, SD, WR, WJS, PR, DH, SS, and GD'H participated in the conception and study design, conduct of the study, including selection, treatment, and follow-up of patients, data interpretation, and preparation and review of the manuscript. EN, BH, QZ, and PM participated in data interpretation and manuscript preparation and review. JP, KW, AMR, and RBT participated in the conception and study design, data interpretation, and preparation and review of the manuscript. All authors provided a final review and approved the manuscript.

Declaration of interests

J-FC reports personal fees from AbbVie, Amgen, Boehringer Ingelheim, Celgene Corporation, Celltrion, Eli Lilly, Enterome, Ferring Pharmaceuticals, Genentech, Janssen, MedImmune, Merck & Co, Pfizer, Protagonist Therapeutics, PPM Services, Second Genome, Seres Therapeutics, Shire, Takeda, Theradiag, Intestinal Biotech Development, and Genfit outside the submitted work; and grants from AbbVie, Janssen, and Takeda outside the submitted work. RP reports grants and personal fees from AbbVie outside the submitted work. PB reports personal fees

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References

1 Peyrin-Biroulet L, Loftus EV Jr, Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol* 2010; **105:** 289–97.

2 Thia KT, Sandborn WJ, Harmsen WS, Zinsmeister AR, Loftus EV Jr. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. *Gastroenterology* 2010; **139:** 1147–55.

3 Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. *Lancet* 2017; **389:** 1741–55.

4 Khanna R, Bressler B, Levesque BG, et al. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. *Lancet* 2015; **386:** 1825–34.

5 Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol* 2006; **4:** 621–30.

6 Osterman MT, Sandborn WJ, Colombel JF, et al. Crohn's disease activity and concomitant immunosuppressants affect the risk of serious and opportunistic infections in patients treated with adalimumab. *Am J Gastroenterol* 2016; **111:** 1806–15.

7 Colombel JF, Mahadevan U. Inflammatory bowel disease 2017: innovations and changing paradigms. *Gastroenterology* 2017; **152:** 309–12.

8 Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol* 2015; **110:** 1324–38.

9 Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology* 1976; **70:** 439–44.

10 Mosli MH, Zou G, Garg SK, et al. C-reactive protein, fecal calprotectin, and stool lactoferrin for detection of endoscopic activity in symptomatic inflammatory bowel disease patients: a systematic review and meta-analysis. *Am J Gastroenterol* 2015; **110:** 802–20.

11 Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; **362:** 1383–95.

12 Rutgeerts P, Van Assche G, Sandborn WJ, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology* 2012; **142:** 1102–11 e2.

13 Feagan BG, Lémann M, Befrits R, et al. Recommendations for the treatment of Crohn's disease with tumor necrosis factor antagonists: an expert consensus report. *Inflamm Bowel Dis* 2012; **18:** 152–60.

14 Schreiber S, Reinisch W, Colombel JF, et al. Subgroup analysis of the placebo-controlled CHARM trial: increased remission rates through 3 years for adalimumab-treated patients with early Crohn's disease. *J Crohns Colitis* 2013; **7:** 213–21.

15 Colombel JF, Rutgeerts PJ, Sandborn WJ, et al. Adalimumab induces deep remission in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2014; **12:** 414–22.

16 Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; **132:** 52–65.

17 D'Haens G, Baert F, van Assche G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008; **371:** 660–67.

18 Tibble JA, Sigthorsson G, Bridger S, Fagerhol MK, Bjarnason I. Surrogate markers of intestinal inflammation are predictive of relapse in patients with inflammatory bowel disease. *Gastroenterology* 2000; **119:** 15–22.

19 Heida A, Park KT, van Rheenen PF. Clinical utility of fecal calprotectin monitoring in asymptomatic patients with inflammatory bowel disease: a systematic review and practical guide. *Inflamm Bowel Dis* 2017; **23:** 894–902.

20 D'Haens G, Ferrante M, Vermeire S, et al. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. *Inflamm Bowel Dis* 2012; **18:** 2218–24.

21 Solem CA, Loftus EV Jr, Tremaine WJ, Harmsen WS, Zinsmeister AR, Sandborn WJ. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. *Inflamm Bowel Dis* 2005; **11:** 707–12.

22 Liverani E, Scaioli E, Digby RJ, Bellanova M, Belluzzi A. How to predict clinical relapse in inflammatory bowel disease patients. *World J Gastroenterol* 2016; **22:** 1017–33.

23 Florin TH, Paterson EW, Fowler EV, Radford-Smith GL. Clinically active Crohn's disease in the presence of a low C-reactive protein. *Scand J Gastroenterol* 2006; **41:** 306–11.

24 Jones J, Loftus EV Jr, Panaccione R, et al. Relationships between disease activity and serum and fecal biomarkers in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2008; **6:** 1218–24.

25 Colombel JF, Jharap B, Sandborn WJ, et al. Effects of concomitant immunomodulators on the pharmacokinetics, efficacy and safety of adalimumab in patients with Crohn's disease or ulcerative colitis who had failed conventional therapy. *Aliment Pharmacol Ther* 2017; **45:** 50–62.

26 Osterman MT, Sandborn WJ, Colombel JF, et al. Increased risk of malignancy with adalimumab combination therapy, compared with monotherapy, for Crohn's disease. *Gastroenterology* 2014; **146:** 941–49.

27 Burmester GR, Panaccione R, Gordon KB, McIlraith MJ, Lacerda AP. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. *Ann Rheum Dis* 2013; **72:** 517–24.

28 Colombel JF, Sandborn WJ, Rutgeerts P, et al. Comparison of two adalimumab treatment schedule strategies for moderate-to-severe Crohn's disease: results from the CHARM trial. *Am J Gastroenterol* 2009; **104:** 1170–79.

29 Khanna R, Zou GY, D'Haens G, et al. Reliability among central readers in the evaluation of endoscopic findings from patients with Crohn's disease. *Gut* 2016; **65:** 1119–25.

30 Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). *Gut* 1989; **30:** 983–89.

31 Cote-Daigneault J, Peerani F, Katsanos K, et al. Agreement between Crohn's disease endoscopy severity scores derived from live local, delayed local video-recorded and central readings. *Gastroenterology* 2017; **152** (suppl 1)**:** S209–10.