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Clinical Benefit of Long-Term Adalimumab Treatment in Patients With Crohn's Disease Following Loss of Response or Intolerance to Infliximab: 96-Week Efficacy Data From GAIN/ADHERE Trials

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Abstract

Background and Aims: In the 4-week GAIN clinical trial, adalimumab was efficacious in inducing remission in patients with moderate-to-severe Crohn's disease [CD] who had prior loss of response/intolerance to infliximab. The efficacy and safety of adalimumab in these patients are reported here for up to 96 weeks or for 3 years, respectively, in the ADHERE open-label extension study.

Methods: Patients who completed GAIN could enrol in ADHERE and receive open-label adalimumab 40 mg every other week. Efficacy variables included clinical response (Crohn's Disease Activity Index [CDAI] decrease from baseline ≥70/≥100 points [CR-70/CR-100]) and remission [CDAI<150], steroid discontinuation and fistula remission [absence of drainage]. Data were reported using hybrid non-responder imputation [hNRI], last observation carried forward and as-observed analysis. Subgroup analyses were performed by randomized group in GAIN and by Week 4 efficacy in GAIN. Safety was also assessed.

Results: A total of 310 patients from GAIN enrolled in ADHERE. CR-70, CR-100 and remission rates at Week 96 were 39.0%, 35.5%, and 26.5% [hNRI], respectively. Of the patients with CR-70 response or remission at Week 4 of GAIN, 45.5% and 44.4% [hNRI], respectively, maintained the effect at Week 96. Steroid discontinuation and steroid-free remission rates increased from Week 12 to 96 in patients using corticosteroids at GAIN baseline.

Abbreviations. ADHERE, *A*dditional Long-Term Dosing with *H*UMIRA to *E*valuate Sustained *R*emission and *E*fficacy in CD; AE, adverse event; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CDAI, Crohn's Disease Activity Index; CHARM, Crohn's Trial of the Fully *H*uman Antibody *A*dalimumab for Remission *M*aintenance; CR-100, ≥100-point reduction in CDAI from GAIN baseline; CR-70, ≥70-point reduction in CDAI from GAIN baseline; CTCAE, Common Terminology Criteria for Adverse Events; EOW, every other week; EW, every week; GAIN, Gauging Adalimumab Efficacy in *I*nfliximab *N*onresponders; hNRI, hybrid non-responder imputation; LOCF, last observation carried forward; TEAE, treatment-emergent adverse event; TNF, tumour necrosis factor.

Conclusions: Long-term adalimumab maintenance therapy led to sustained clinical remission and response, and steroid discontinuation in a considerable proportion of patients with CD previously treated with infliximab. No new safety signals were observed in this patient population.

Key Words: Adalimumab; Crohn's disease; GAIN/ADHERE

1. Introduction

Crohn's disease [CD] is a chronic relapsing-remitting inflammatory condition affecting the gastrointestinal tract. The characteristic symptoms of CD—diarrhoea, abdominal pain, weight loss and fatigue—have a significant impact on patients' well-being and quality of life.[1] Current treatment approaches aim to induce and maintain clinical and endoscopic remission, and to improve the patient's quality of life. Minimizing corticosteroid exposure and the need for hospitalization and surgery related to complications, such as fistulae and stenosis, are important additional treatment goals.[2,3]

Several anti-tumour necrosis factor [TNF] biologic drugs are approved for use in CD and are recommended in clinical practice guidelines and other publications for the induction and maintenance of remission in patients with moderate-to-severe CD refractory to conventional therapy.[2–4] However, approximately one-third of patients receiving anti-TNF agents do not respond to treatment [primary failure], and a significant proportion [greater than one-third] experience a loss of response [secondary failure] or intolerance to treatment.[5,6] Specifically, patients who have been treated with the chimeric monoclonal antibody infliximab can develop human anti-chimeric antibodies, which have been associated with reduced duration of response and/or acute or delayed infusion-related reactions.[7] There is limited evidence from randomized controlled trials on the long-term use of a second anti-TNF therapy in patients with secondary failure or intolerance to prior anti-TNF treatment in CD.[5]

Adalimumab [HUMIRA®] is a fully human, monoclonal immunoglobulin G1 anti-TNF, which has demonstrated efficacy in the induction and maintenance of remission and mucosal healing in patients with moderate-to-severe CD who were naïve to or had failed on prior anti-TNF therapy.[8–15] The 4-week GAIN [***G***auging ***A***dalimumab Efficacy in ***I***nfliximab ***N***onresponders] trial [NCT00105300] investigated adalimumab 160/80 mg induction therapy in adult patients with CD who had symptoms despite infliximab therapy [secondary failure] or who could not tolerate infliximab due to adverse events [AEs].[11] GAIN demonstrated that adalimumab treatment induced clinical remission, defined as Crohn's Disease Activity Index [CDAI] < 150, in a significantly higher proportion of patients than placebo at Week 4 [21% vs 7%, respectively; $p < 0.001$].[11] Patients who completed the 4-week GAIN study were eligible to participate in a long-term open-label extension study, ADHERE [***A***dditional Long-Term ***D***osing with ***H***UMIRA to ***E***valuate Sustained ***R***emission and ***E***fficacy in CD], which investigated adalimumab maintenance therapy.

Here, we report long-term efficacy and safety data for patients with CD who completed the 4-week GAIN trial and enrolled in ADHERE.

2. Materials and Methods

2.1. Study design

GAIN was a 4-week, multicentre [52 centres in the USA, Canada, Belgium and France], randomized, double-blind, placebo-controlled Phase 3 trial [ClinicalTrials.gov Identifier: NCT00105300] to assess the efficacy and safety of adalimumab in the induction of clinical remission in patients with CD previously treated with infliximab.[11] The protocol was approved by the institutional review board at each study site, and all patients were required to provide written informed consent. The study methodology and entry criteria have been described in detail previously.[11] Eligible patients were aged 18–75 years with a diagnosis of CD for ≥4 months [confirmed by radiologic or endoscopic evaluation] and with moderate-to-severe disease activity at baseline, defined as a CDAI of 220–450. Patients had to be intolerant to infliximab or must have previously responded to infliximab and then lost response. Patients were randomized to receive placebo or induction doses of adalimumab [AbbVie Inc., North Chicago, IL, USA] of 160 mg and 80 mg at Weeks 0 and 2, respectively. Patients were followed to Week 4.

ADHERE was an open-label, Phase 3 extension study [ClinicalTrials.gov Identifier: NCT00195715] to investigate the long-term maintenance of response and the safety and tolerability of repeated administration of adalimumab. ADHERE included patients from both GAIN[11] and CHARM [***C***rohn's Trial of the Fully ***H***uman Antibody ***A***dalimumab for ***R***emission ***M***aintenance].[9,12] The ADHERE study protocol was reviewed and approved by an independent ethics committee or institutional review board at each study site, and all patients provided written informed consent. The study methodology and entry criteria for ADHERE have been described in detail previously.[14] Patients were recruited into GAIN from November 23, 2004, and the last subject last visit in GAIN was on January 23, 2006. Patients who did not complete GAIN were excluded from ADHERE, as were patients with abnormal laboratory or other test results, or any other reason that the investigator considered would make them unsuitable to participate.

All patients entering ADHERE received open-label adalimumab 40 mg every other week [EOW] up to a maximum duration of 240 weeks. Patients could escalate to adalimumab 40 mg every week [EW] dosing for disease flare [defined as a recurrence of active disease, with an increase in CDAI of ≥70 points compared with their CDAI at Week 4 of GAIN and a CDAI of ≥220] or for consistent non-response [defined as not achieving clinical response [CR]-70, i.e. a decrease in CDAI of ≥70 points from baseline of GAIN. During the study, patients were to continue their prior CD therapies and concomitant medications. Dose adjustment [increase or decrease] of concurrent CD medications was permitted after ≥3 months' exposure to open-label adalimumab. Steroid tapering was allowed from Week 8 of ADHERE if the patient had achieved CR-70. There was no forced or protocol-directed steroid taper. Dose reduction of concomitant medications was permitted for Grade ≥3 CD-related AEs [Common Terminology Criteria for Adverse Events [CTCAE]]. Patients were to be withdrawn from the study early if the investigator considered their response to be unsatisfactory, if they had clinically significant abnormal laboratory results or if they were diagnosed with malignancy or dysplasia of the gastrointestinal tract. ADHERE terminated at each study site when country and local [if applicable] regulatory and reimbursement approval of adalimumab had been achieved, and the long-term safety registry [PYRAMID;

ClinicalTrials.gov Identifier: NCT00524537] had opened for enrolment. As a result, ADHERE was closed at all participating sites as of December 2008.

2.2. Clinical assessments and outcome measurements

Efficacy was evaluated in all patients who transitioned from GAIN and who received at least one dose of adalimumab in ADHERE using CDAI collected at ADHERE baseline, Weeks 2, 4, 8 and 12, and 12-weekly thereafter until the study termination visit. Efficacy data are reported at Weeks 8, 12, 24, 48, 72, and 96 of ADHERE for all end points, except for steroid-related end points, which are reported from Week 12 given tapering was only allowed from Week 8 onwards.

The efficacy end points were: CR-70; CR-100, defined as a ≥100-point reduction in CDAI from GAIN baseline; and clinical remission, defined as a CDAI of <150. Steroid-free clinical remission, defined as a CDAI of <150 and discontinuation of steroids, was assessed in patients receiving corticosteroids at GAIN baseline. Steroid discontinuation was also assessed in the same patient population. Fistula remission, defined as absence of draining fistulae, assessed using gentle compression during physical examination, was reported for patients who presented with draining fistulae [perianal or abdominal] at GAIN baseline. Subgroup analyses were performed in patients who achieved CR-70 or clinical remission at Week 4 of GAIN, by randomized treatment [adalimumab or placebo] in GAIN, and by reason for infliximab failure [loss of response or intolerance].

To allow assessment of the time to symptomatic response during GAIN, a *post hoc* analysis of three patient-reported diary components [PROs] of the CDAI [abdominal pain, frequency of liquid/very soft stools and general well-being] was performed. Daily subscores of abdominal pain severity [0 = none, 1 = mild, 2 = moderate, 3 = severe], frequency of liquid/very soft stools [measured by the number of liquid or very soft stools per day], and general well-being [0 = generally well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible] were summed and reported for the randomized treatment groups [adalimumab or placebo] at Days 1–7. Lower scores indicated improvement.

Treatment-emergent AEs [TEAEs] were reported for any patient who transitioned from GAIN and received at least one dose of adalimumab in ADHERE. Treatment-emergent AEs were defined as any AE with onset on or after the first dose of adalimumab [in either GAIN or ADHERE] and up to 70 days after the last dose of adalimumab in ADHERE. Adverse events were classified by the Medical Dictionary for Regulatory Activities [version 11.1] preferred terms and graded according to CTCAE [version 3.0].

2.3. Statistical analyses

Continuous variables were described by mean ± standard deviation [SD]. Categorical efficacy end points were analysed by hybrid non-responder imputation [hNRI], last observation carried forward [LOCF] and as-observed methods. Hybrid non-responder imputation was defined by use of the non-responder imputation rule, whereby patients with missing data were imputed as non-responders, except when patients discontinued from the study owing to study site closure due to approval of adalimumab in the respective country, in which case they were analysed using LOCF from that point onwards. Patients who escalated from EOW to EW dosing were not imputed as non-responders and were considered according to their observed responses. In the LOCF analysis, patients were not included if they had a missing ADHERE baseline value.

3. Results

3.1. Patients

Details of the patient disposition in the GAIN study have been described previously.[11] Of the 325 patients included in GAIN, 310 completed treatment with either adalimumab [*n* = 154] or placebo [*n* = 156] and enrolled in ADHERE. Table 1 gives the baseline demographics and disease characteristics of the patients. Approximately two-fifths [38.4%] of patients were using steroids, and almost a third [31.6%] were receiving immunomodulators [Table 1]. The flow of patients through ADHERE is summarized in Figure 1. At Week 96 [almost 2 years from the start of GAIN], approximately half of the patients [*n* = 151] remained in the study [Figure 2]. As of the final study termination date [December 2008], 121 patients remained in the study. Adverse events were the most frequent reason for discontinuation [Figure 1]. During ADHERE, 164 patients [52.9%] escalated from 40 mg adalimumab EOW to 40 mg EW [of these, 89 were randomized to adalimumab and 75 to placebo in GAIN]. Relevant to efficacy analyses by LOCF, 5/310 patients had a missing ADHERE baseline value.

3.2. Efficacy

3.2.1. Clinical response: CR-70 and CR-100

Using the more conservative hNRI analysis, response rates [CR-70 and CR-100] peaked at Week 12 and thereafter displayed a downward numerical trend through Week 96, with CR-70 decreasing from 64.8% [201/310] to 39.0% [121/310; Figure 2A] and CR-100 from 55.2% [171/310] to 35.5% [110/310; Figure 2B]. Response rates as measured by LOCF and as-observed analysis were fairly

Table 1. Baseline demographics and disease characteristics [ADHERE intent-to-treat population[a]].

Variable	Open-label adalimumab 40 mg [*n* = 310]
Female, *n* [%]	202 [65.2]
Age [years], mean [SD]	38.3 [11.9]
Weight [kg], mean [SD]	71.8 [19.1]
Nicotine use, *n* [%]	104 [33.5]
Disease duration [years], median [range]	10.2 [0.6–46.7]
Disease location[b]	
Ileum	224 [72.3]
Colon	209 [67.4]
Other	86 [27.7]
Rectum	72 [23.2]
Presence of fistula	43 [13.9]
Concomitant medication, *n* [%][c]	
Corticosteroid[d]	119 [38.4]
Immunomodulator[e]	98 [31.6]
Aminosalicylates[f]	151 [48.7]

SD, standard deviation.

[a]Age, weight and concomitant medication data are from baseline of the preceding 4-week study [GAIN]; all other data are from ADHERE baseline.

[b]Disease may be indicated in more than one location.

[c]Medication use determined at baseline visit of GAIN.

[d]Budesonide, betamethasone, dexamethasone, deflazacort, cortisone, clo-prednol, corticosteroids, fluocortolone, glucocorticoids, glucocorticosteroids, hydrocortisone, methylprednisolone, prednisolone, prednisone, parametha-sone, or prednylidene.

[e]Azathioprine, ciclosporin, mercaptopurine, or methotrexate.

[f]Aminosalicylic acid, balsalazide, mesalazine, sulfasalazine, or olsalazine.

stable over time from Week 8 to 96 in ADHERE [Figure 2A and B]; at Week 96 of ADHERE, 61.0% [186/305, LOCF] of patients achieved CR-70 response [Figure 2A] and 52.8% [161/305, LOCF] of patients achieved CR-100 response [Figure 2B].

3.2.2. Clinical remission: CDAI < 150

Approximately one-third of patients who entered ADHERE from GAIN were in clinical remission at Week 12 of ADHERE (32.3% [100/310], hNRI), and the rates remained quite stable up to Week 96 (26.5% [82/310], hNRI) [Figure 2C]. Remission rates were broadly similar between hNRI and LOCF analysis methods, but were numerically higher for as-observed outcomes, with 53.6% of patients [81/151] achieving remission at Week 96 of ADHERE.

3.3.3. Maintenance of response and remission

Maintenance of CR-70 and remission, in patients meeting these criteria at Week 4 of GAIN, were achieved in 78.4% [105/134, hNRI] and 68.9% [31/45, hNRI] of patients, respectively, at Week 12 of ADHERE [Figure 3A and B]. Similar to the trend observed in hNRI response and remission rates [Figure 2], a downward numerical trend was observed in maintenance of response and remission [hNRI] through ADHERE, particularly from Week 24. At Week 96, 45.5% [61/134, hNRI] and 44.4% [20/45, hNRI] of patients maintained CR-70 and remission, respectively [Figure 3A and B]. Using LOCF and as-observed analyses, CR-70 and remission were generally maintained from Week 8 to 96 in ADHERE [Figure 3A and B], although as-observed remission rates peaked at 90.5% [19/21] at Week 96 [Figure 3B]. In LOCF analysis, 73.7% [98/133] and 77.3% [34/44] of patients maintained CR-70 and remission, respectively, at Week 96 of ADHERE [Figure 3A and B].

3.2.4. Steroid-free remission and discontinuation of steroids

The proportion of patients receiving corticosteroids at GAIN baseline who achieved steroid-free clinical remission increased from 22.3% [25/112, as observed] at Week 12 to 50.0% [27/54, as observed] at Week 96 [Figure 4A]. Similar increased steroid-free clinical remission rates were observed with time in the subgroups of patients with CR-70 or remission at GAIN Week 4, although numerically higher steroid-free remission rates were observed in these subgroups [and particularly in the remission subgroup] relative to the overall population [Figure 4A]. The proportion of patients receiving corticosteroids at GAIN baseline who discontinued steroids also increased over time, from 33.9% [38/112, as observed] at Week 12 to 72.2% [39/54, as observed] at Week 96 [Figure 4B]. A pattern of numerically higher steroid sparing in the subsets of patients achieving response or remission at Week 4 of GAIN was observed [Figure 4B].

3.2.5. Fistula remission

The rate of fistula remission among patients who presented with draining fistulae at GAIN baseline was 50.0% [21/42] at Week 8 of ADHERE and increased to 70.0% [21/30] at Week 48, and it remained at ~60% until Week 96 [Figure 5, as observed].

3.2.6. Subgroup analyses of efficacy by randomized group in GAIN

Long-term clinical efficacy with adalimumab in ADHERE was also assessed by randomized treatment arm [to adalimumab or placebo] in GAIN, using hNRI. Patients randomized to adalimumab in GAIN, and therefore receiving an induction regimen, achieved numerically higher CR-70, CR-100, and remission rates at Week 8 of ADHERE than those receiving placebo [Figure 6A–C]; these numerical differences, albeit small, were maintained for all three end points at all time

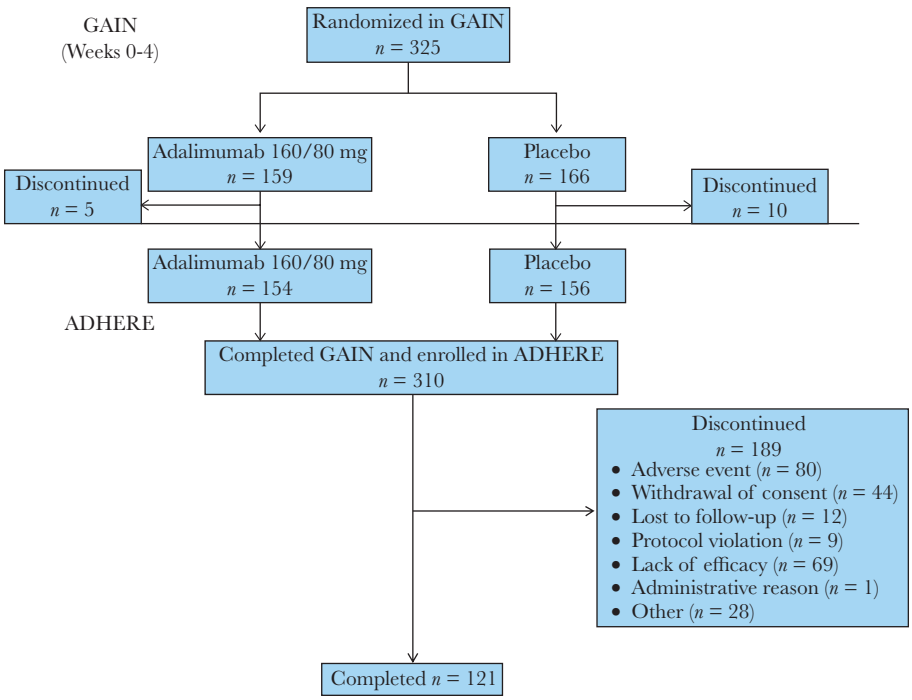

Figure 1. Patient disposition. During ADHERE, 164 patients increased dosage from 40 mg adalimumab EOW to 40 mg EW [of whom 89 were randomized to adalimumab and 75 to placebo in GAIN].[11] EOW, every other week; EW, every week.

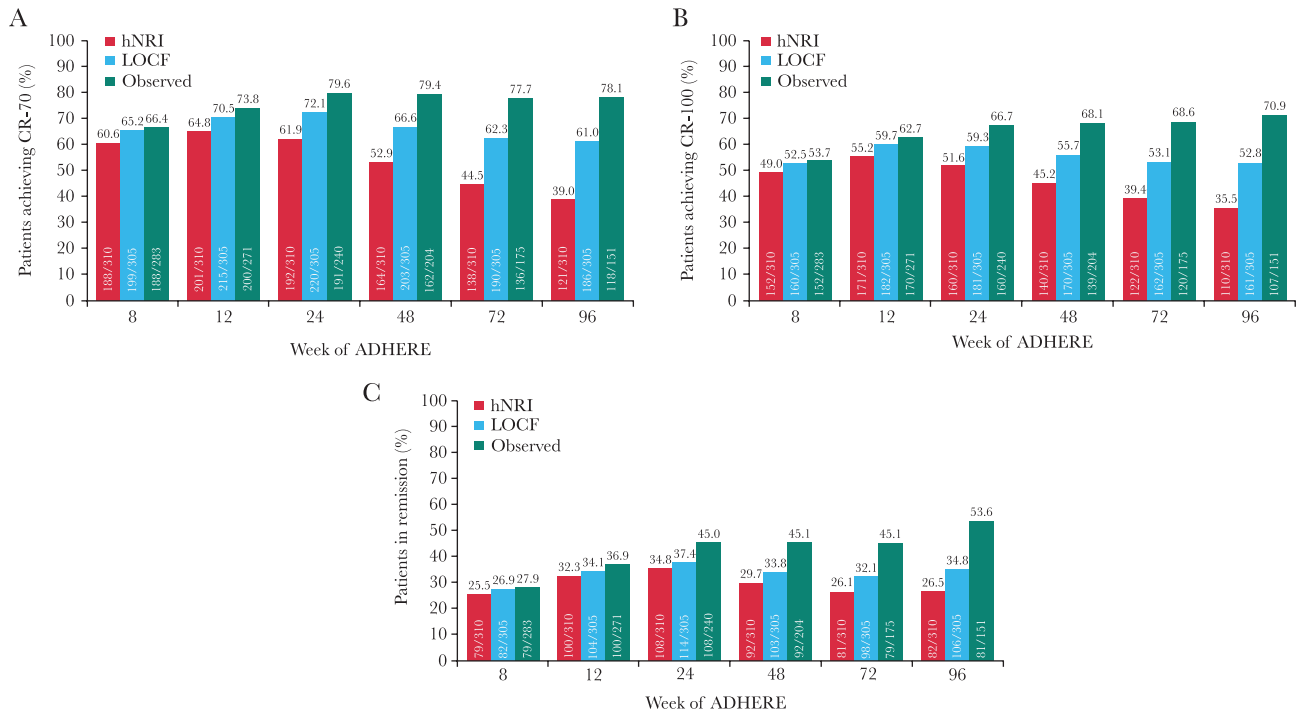

Figure 2. Clinical response [A] CR-70 and [B] CR-100, and [C] remission [CDAI < 150] by ADHERE study visit. hNRI, LOCF, and as-observed analysis of all patients who entered ADHERE from GAIN, intent-to-treat population [*n* = 310]. CDAI, Crohn's Disease Activity Index; CR-70, decrease in CDAI of ≥70 points from baseline of GAIN; CR-100, decrease in CDAI of ≥100 points from baseline of GAIN; hNRI, hybrid non-responder imputation; LOCF, last observation carried forward.

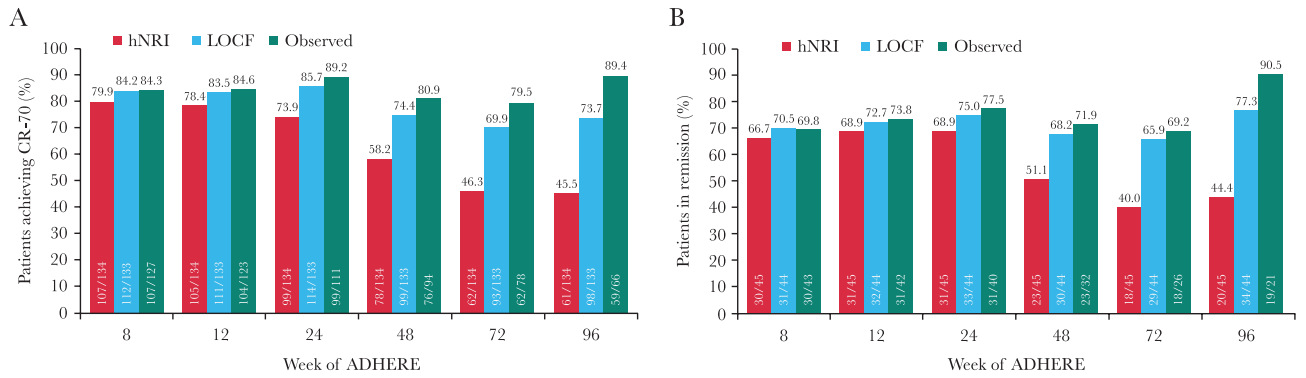

Figure 3. Maintenance of [A] clinical response [CR-70] and [B] remission [CDAI < 150] by ADHERE study visit. [A] Patients with CR-70 response at Week 4 of GAIN [*n* = 134]; [B] patients with remission at Week 4 of GAIN [*n* = 45]. hNRI, LOCF, and as-observed analysis. CDAI, Crohn's Disease Activity Index; CR-70, decrease in CDAI of ≥70 points from baseline of GAIN; hNRI, hybrid non-responder imputation; LOCF, last observation carried forward.

points through ADHERE, with a single exception of CR-70 at Week 72 [Figure 6A–C]. Rates of steroid-free remission were numerically higher up to Week 96 in ADHERE in patients randomized to adalimumab in GAIN relative to patients randomized to placebo in GAIN [Figure 6D, as observed]. A similar pattern was observed for discontinuation of steroids in ADHERE up to Week 96 [Figure 6E, as observed].

3.2.7. Subgroup analysis of efficacy by loss of response or intolerance to infliximab

When long-term efficacy was analysed by reason for infliximab failure [loss of response or intolerance], a numerically higher proportion of patients with loss of response to infliximab achieved CR-70 and CR-100 response [Supplementary Figures 1A and B, hNRI]. No clear trends in long-term clinical remission rates were observed in the infliximab failure subgroups. From Weeks 8 to 24, patients with intolerance to infliximab achieved numerically higher remission rates, whereas patients with loss of response to infliximab reported numerically higher rates from Weeks 48–96 [Supplementary Figure 1C, hNRI].

3.2.8. Improvement in CDAI PRO subscores in GAIN

Given the severity of CD activity in the patients entering GAIN and that they had already failed on previous treatments including infliximab, the rapidity of response to treatment is an important consideration. Over Days 1–7 in GAIN, the daily sum of three PRO subscores of the CDAI decreased faster in patients randomized to adalimumab versus placebo, with a significant difference by Day 4, which was maintained on Days 5–7 [Supplementary Figure 2].

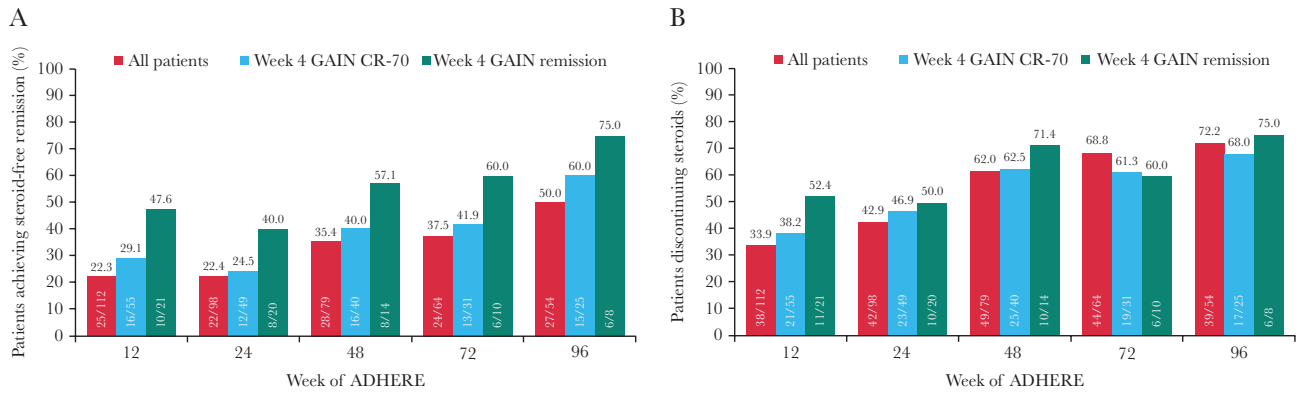

Figure 4. [A] Steroid-free clinical remission [CDAI < 150] and [B] discontinuation of steroids by ADHERE study visit, in patients receiving corticosteroids at baseline of GAIN. All patients [*n* = 119]; patients with CR-70 at Week 4 of GAIN [*n* = 57]; patients with remission at Week 4 of GAIN [*n* = 21], as-observed analysis. CDAI, Crohn's Disease Activity Index; CR-70, decrease in CDAI of ≥70 points from baseline of GAIN.

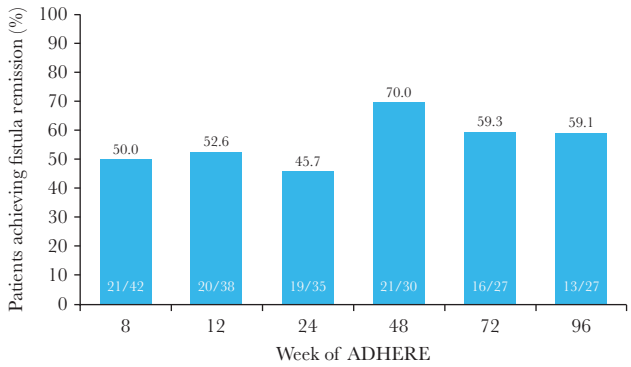

Figure 5. Fistula remission [absence of draining fistulae]. Patients who presented with draining fistulae at baseline in GAIN, as-observed analysis, intent-to-treat population.

3.3. Safety

A total of 310 patients received at least one dose of adalimumab in GAIN or ADHERE, comprising 494.9 patient-years of exposure. The mean [±SD] duration of exposure was 583.1 [±372.3] days.

Treatment-emergent AEs were experienced by 301/310 [97.1%] of patients [Table 2]. The most frequently occurring AEs were CD [representing worsening disease; 51.6% of patients], abdominal pain [23.5%], arthralgia [22.3%], nasopharyngitis [20.6%], upper respiratory tract infection [20.0%], and nausea [20.0%]. A total of 115/310 patients [37.1%] reported 212 serious AEs [42.8 events/100 patient-years], the most common of which were worsening of CD [16.1% of patients] and abdominal pain [8.4% of patients]. A total of 33 events of serious infection [6.7 events/100 patient-years] were reported by 27 patients [8.7%]. Opportunistic infections were reported in 13 patients [4.2%], the majority of which were non-systemic candidiasis. In addition, one patient had acute pulmonary histoplasmosis and one patient had coccidioidomycosis; both events resolved with treatment. Nine patients [2.9%] reported 12 events of malignancy [2.4 events/100 patient-years]. These included five patients with non-melanoma skin cancer [three patients with basal cell carcinoma, two patients with squamous cell carcinoma], and three of these patients were previously exposed to or taking thiopurine medication at GAIN baseline. In addition, one patient each had an anal cancer, lymphoma, thyroid cancer and recurrent vaginal cancer. One patient developed severe demyelinating disease that was considered to be possibly related to treatment; the event subsequently resolved. Allergic reactions were reported by six patients [1.9%], including four patients with urticaria and two patients with hypersensitivity; there were no cases of anaphylaxis. There were no cases of tuberculosis or deaths among patients who enrolled from GAIN. No clinically meaningful changes from baseline in vital signs or clinical laboratory parameters were reported, with the exception of transient elevation of liver function parameters.

4. Discussion

Long-term maintenance of clinical remission and response was demonstrated in ADHERE in patients with CD who had previously failed on infliximab therapy, and then received adalimumab or placebo induction therapy in GAIN followed by adalimumab maintenance therapy up to 96 weeks. Clinically meaningful rates of steroid discontinuation, steroid-free clinical remission, and fistula healing were also achieved and maintained with long-term adalimumab treatment. Compared with the overall population, patients with response or remission at Week 4 of GAIN achieved consistently higher numerical rates of steroid-free remission through to Week 96 in ADHERE. No new safety signals were reported with prolonged use of adalimumab in this anti-TNF experienced patient population.

The contribution of adalimumab induction therapy to efficacy outcomes was also investigated. Original randomization to adalimumab in GAIN was associated with higher remission and response rates at entry to ADHERE compared with patients who received placebo in GAIN. However, differences were generally small and converged beyond Week 48 for the CR-70 and CR-100 end points. The benefit of induction therapy with adalimumab appeared to be more pronounced on steroid use.

Our results are consistent with the 4-year follow-up data reported for patients who enrolled in ADHERE from the CHARM study.[14] CHARM included both patients who were naïve to anti-TNF therapy and those who had previously received infliximab.[9] Higher rates of remission versus placebo were demonstrated for both these subgroups, with a slightly higher proportion of anti-TNF-naïve patients achieving remission than those with prior exposure.[9]

GAIN was, to our knowledge, the first randomized, placebo-controlled trial to investigate use of a second anti-TNF antibody specifically after secondary failure or intolerance to infliximab.[11] GAIN demonstrated that use of adalimumab as a second anti-TNF is a potential option for induction therapy in these patients.[11] Our *post hoc* analysis of patient-reported CDAI components from 7-day

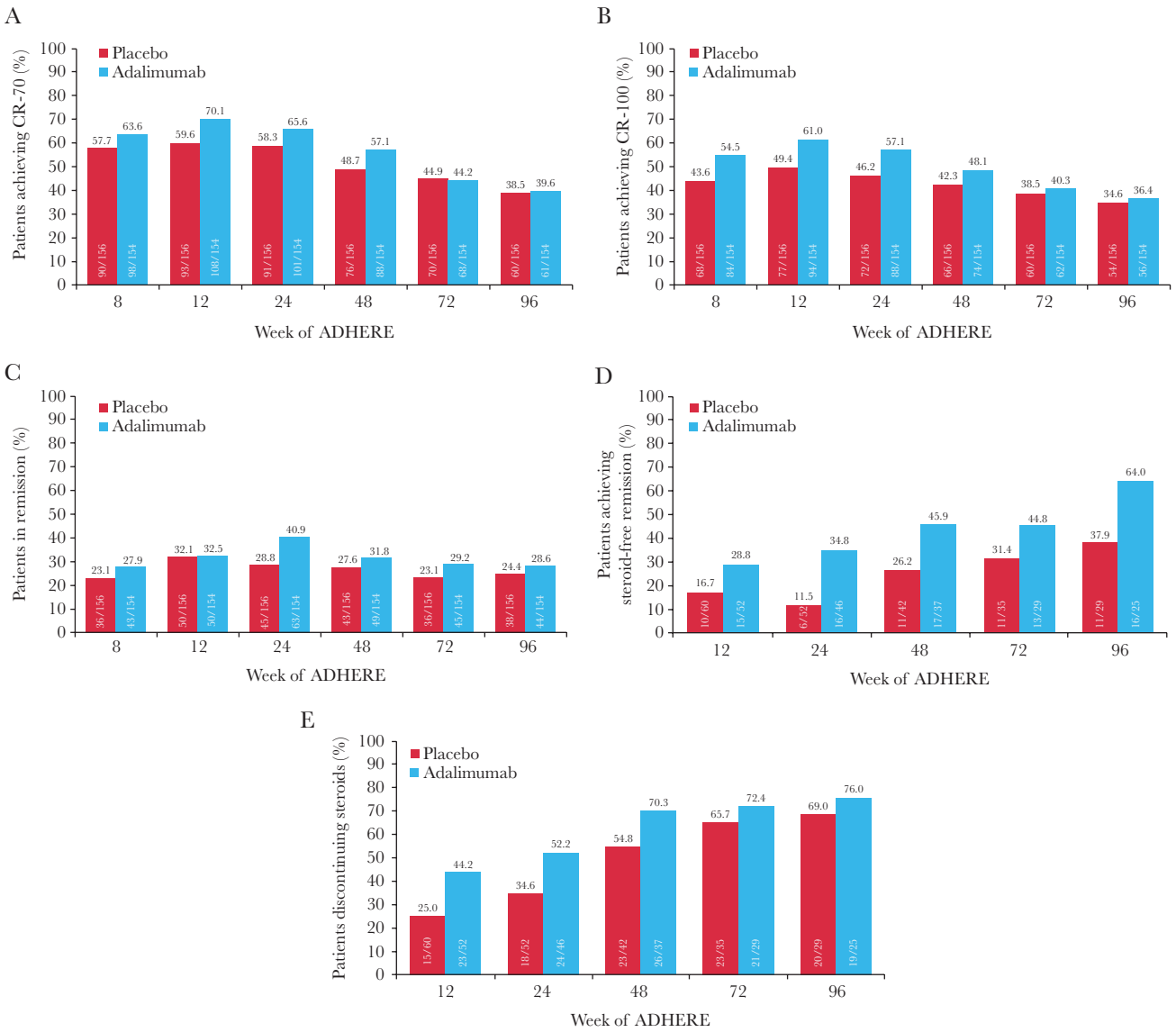

Figure 6. Clinical efficacy in ADHERE, by randomization to placebo or adalimumab in GAIN. Clinical response [A] CR-70 and [B] CR-100, and [C] remission [CDAI < 150] by ADHERE study visit, hNRI analysis [placebo: *n* = 156, adalimumab: *n* = 154]. [D] Steroid-free remission and [E] discontinuation of steroids, by ADHERE study visit, as-observed analysis [placebo: *n* = 65, adalimumab: *n* = 54]. CDAI, Crohn's Disease Activity Index; CR-70, decrease in CDAI of ≥70 points from baseline of GAIN; CR-100, decrease in CDAI of ≥100 points from baseline of GAIN; hNRI, hybrid non-responder imputation.

diaries in GAIN demonstrated adalimumab provides early-onset patient benefits within the first week of treatment. These data indicating early benefit are in agreement with the total CDAI measurements in GAIN, where the adalimumab group showed statistically significantly lower mean CDAI than patients in the placebo group after 1 week of treatment.[11]

The main findings of this analysis of data from ADHERE confirm that long-term use of adalimumab maintains remission and response and is well tolerated in patients with prior loss of response or intolerance to infliximab. Several systematic reviews and small open-label studies have also investigated switching to adalimumab therapy after infliximab failure or intolerance.[16–22] Collectively, the available evidence supports use of adalimumab as a viable treatment option for the substantial population of patients who are no longer able to continue infliximab therapy due to loss of response or allergic reactions.[11,16–22]

Clinical studies have also demonstrated the efficacy of the anti-TNF certolizumab pegol after infliximab failure.[23,24] Furthermore, it has been reported from a meta-analysis that response rates for a second anti-TNF are higher among those patients who develop intolerance to infliximab than in those with primary or secondary failure of response,[5] an observation that is consistent with reports in rheumatology.[25] In addition, subgroup analysis of the CHARM data suggests that greater efficacy with adalimumab EW dosing over EOW dosing may be achieved in subgroups of patients with prior loss of response to infliximab and elevated C-reactive protein levels.[26]

The 2016 European Crohn's and Colitis Organisation guidelines include evidence-based consensus on medical management of CD following confirmed loss of response to an anti-TNF agent.[3] It is indicated that this should first be managed by dose optimization, with dose increase or interval shortening considered as equivalent strategies. If dose optimization is ineffective, switching to a different

Table 2. Overview of treatment-emergent AEs[a] [safety population].

AE	Adalimumab [*n* = 310] [494.9 PY]	
	n [%]	Events [per 100 PY]
Any AE	301 [97.1]	3721 [751.9]
Serious AE	115 [37.1]	212 [42.8]
Deaths	0	0
AE leading to discontinuation	80 [25.8]	110 [22.2]
AEs of special interest		
Infection	228 [73.5]	697 [140.8]
Serious infection	27 [8.7]	33 [6.7]
Malignancy	9 [2.9]	12 [2.4]
Injection-site reaction	53 [17.1]	98 [19.8]
Opportunistic infection [excluding tuberculosis]	13 [4.2]	19 [3.8]
Tuberculosis	0	0
Congestive heart failure-related	0	0
Demyelinating disease	1 [0.3]	1 [0.2]
Hepatic-related AEs	19 [6.1]	27 [5.5]
Allergic reaction	6 [1.9]	6 [1.2]
Lupus-like syndrome	1 [0.3]	1 [0.2]
Hematologic-related AEs	6 [1.9]	7 [1.4]

AE, adverse event; PY, patient-years.

[a]A treatment-emergent AE was defined as any AE with onset on or after the first dose of adalimumab in GAIN or ADHERE, up to 70 days after the last dose of adalimumab.

anti-TNF agent is recommended. In addition, where available, it is stated that measurement of serum anti-TNF trough levels and anti-drug antibodies could be used to guide the optimization strategy. Indeed, switching to a second anti-TNF after infliximab failure or intolerance is an approach already adopted in clinical practice in CD.[5] Further studies and analyses are needed to investigate these observations so that strategies for use of a second anti-TNF, or switching to another class of therapeutic, can be optimized.

The AE profile of long-term adalimumab treatment reported here is consistent with the safety profile of adalimumab established in ~12 years of exposure from across the global clinical development programme in CD, rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, and juvenile idiopathic arthritis,[27] and with real-world experience in patients with CD.[28] The overall rate of any AE [97.1%] was largely accounted for by worsening of CD. Adverse events of special interest that have been associated with anti-TNFs were reported at low frequencies. In particular, serious infections, which are the most frequently reported serious AEs of interest in the global CD trials,[29] were reported at a frequency of <10%. No cases of tuberculosis and no deaths were reported during the study.

Limitations of ADHERE include the lack of a comparator arm. In addition, the patients recruited were required to have either prior loss of response or intolerance to infliximab, and the criteria used to define a loss of response were broad and were applied retrospectively. Also, patients were lost from the study due to termination because country and local [if applicable] regulatory and reimbursement approval of adalimumab had been achieved, and the long-term safety registry [PYRAMID; NCT00524537] had opened for enrolment. In addition, patients entering ADHERE had differing exposure histories to adalimumab due to randomization in GAIN, where patients randomized to adalimumab had received an induction regimen comprising 4 weeks of adalimumab exposure before enrolment in ADHERE, but patients randomized to placebo in GAIN received no induction regimen. As patients in ADHERE knew they were receiving adalimumab given the open-label design, differences between subgroups [adalimumab versus placebo in GAIN] should be interpreted with caution. Finally, steroid tapering was not forced or directed by the study protocol.

In conclusion, adalimumab can induce and maintain long-term clinical remission and response, reported here through to 96 weeks, in patients with CD with prior loss of response or intolerance to infliximab. No new safety signals were observed with adalimumab long-term maintenance therapy in patients previously treated with infliximab.

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Conflict of Interest

RP has received consultant and/or lecture fees from AbbVie, Amgen, AstraZeneca, Axcan Pharma [now Aptalis], Biogen Idec, Bristol-Myers Squibb, Centocor, ChemoCentryx, Eisai Medical Research Inc, Elan Pharmaceuticals, Ferring, Genentech, GlaxoSmithKline, Janssen, Merck Sharp & Dohme Corp, Millennium Pharmaceuticals Inc [now Takeda], Ocera Therapeutics Inc, Otsuka America Pharmaceutical, Pfizer, Shire Pharmaceuticals, Prometheus Laboratories, Schering-Plough Corporation, Synta Pharmaceuticals Corp, Teva, UCB Pharma and Warner Chilcott.

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Author Contributions

RP, WJS, GD'H, DCW, SB, JFM, JP, and AMR were involved in the concept and design of the study. RP, WJS, GD'H, DCW, SB, J-fM, JP, and AMR analysed and interpreted the study data. RP was the principal investigator for this study. All authors critically reviewed the content of this manuscript and approved the version for final submission.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

References

1. Becker HM, Grigat D, Ghosh S, *et al.* Living with inflammatory bowel disease: a Crohn's and Colitis Canada survey. *Can J Gastroenterol Hepatol* 2015;**29**:77–84.
2. Terdiman JP, Gruss CB, Heidelbaugh JJ, Sultan S, Falck-Ytter YT; AGA Institute Clinical Practice and Quality Management Committee. American Gastroenterological Association Institute guideline on the use of thiopurines, methotrexate, and anti-TNF-α biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. *Gastroenterology* 2013;**145**:1459–63.
3. Gomollón F, Dignass A, Annese V, *et al.*; ECCO. 3rd European evidence-based Consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management. *J Crohns Colitis* 2017;**11**:3–25.
4. Dignass A, Van Assche G, Lindsay JO, *et al.*; European Crohn's and Colitis Organisation (ECCO). The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: current management. *J Crohns Colitis* 2010;**4**:28–62.
5. Gisbert JP, Marín AC, McNicholl AG, Chaparro M. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. *Aliment Pharmacol Ther* 2015;**41**:613–23.
6. Gordon JP, McEwan PC, Maguire A, Sugrue DM, Puelles J. Characterizing unmet medical need and the potential role of new biologic treatment options in patients with ulcerative colitis and Crohn's disease: a systematic review and clinician surveys. *Eur J Gastroenterol Hepatol* 2015;**27**:804–12.
7. Baert F, Noman M, Vermeire S, *et al.* Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003;**348**:601–8.
8. Hanauer SB, Sandborn WJ, Rutgeerts P, *et al.* Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006;**130**:323–33; quiz 591.
9. 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.
10. Sandborn WJ, Hanauer SB, Rutgeerts P, *et al.* Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut* 2007;**56**:1232–9.
11. Sandborn WJ, Rutgeerts P, Enns R, *et al.* Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med* 2007;**146**:829–38.
12. Panaccione R, Colombel JF, Sandborn WJ, *et al.* Adalimumab sustains clinical remission and overall clinical benefit after 2 years of therapy for Crohn's disease. *Aliment Pharmacol Ther* 2010;**31**:1296–309.
13. Rutgeerts P, Van Assche G, Sandborn WJ, *et al.*; EXTEND Investigators. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology* 2012;**142**:1102–11.e2.
14. Panaccione R, Colombel JF, Sandborn WJ, *et al.* Adalimumab maintains remission of Crohn's disease after up to 4 years of treatment: data from CHARM and ADHERE. *Aliment Pharmacol Ther* 2013;**38**:1236–47.
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.e5.
16. Sandborn WJ, Hanauer S, Loftus EV Jr, *et al.* An open-label study of the human anti-TNF monoclonal antibody adalimumab in subjects with prior loss of response or intolerance to infliximab for Crohn's disease. *Am J Gastroenterol* 2004;**99**:1984–9.
17. Youdim A, Vasiliauskas EA, Targan SR, *et al.* A pilot study of adalimumab in infliximab-allergic patients. *Inflamm Bowel Dis* 2004;**10**:333–8.
18. Hinojosa J, Gomollón F, García S, *et al.*; Spanish Scientific Group on Crohn's Disease and Ulcerative Colitis. Efficacy and safety of short-term adalimumab treatment in patients with active Crohn's disease who lost response or showed intolerance to infliximab: a prospective, open-label, multicentre trial. *Aliment Pharmacol Ther* 2007;**25**:409–18.
19. Ma C, Panaccione R, Heitman SJ, Devlin SM, Ghosh S, Kaplan GG. Systematic review: the short-term and long-term efficacy of adalimumab following discontinuation of infliximab. *Aliment Pharmacol Ther* 2009;**30**:977–86.
20. Oussalah A, Babouri A, Chevaux JB, *et al.* Adalimumab for Crohn's disease with intolerance or lost response to infliximab: a 3-year single-centre experience. *Aliment Pharmacol Ther* 2009;**29**:416–23.
21. Panaccione R, Loftus EV Jr, Binion D, *et al.* Efficacy and safety of adalimumab in Canadian patients with moderate to severe Crohn's disease: results of the Adalimumab in Canadian SubjeCts with ModErate to Severe Crohn's DiseaSe [ACCESS] trial. *Can J Gastroenterol* 2011;**25**:419–25.
22. Da W, Zhu J, Wang L, Lu Y. Adalimumab for Crohn's disease after infliximab treatment failure: a systematic review. *Eur J Gastroenterol Hepatol* 2013;**25**:885–91.
23. Hanauer SB, Panes J, Colombel JF, Bloomfield R, Schreiber S, Sandborn WJ. Clinical trial: impact of prior infliximab therapy on the clinical response to certolizumab pegol maintenance therapy for Crohn's disease. *Aliment Pharmacol Ther* 2010;**32**:384–93.
24. Sandborn WJ, Abreu MT, D'Haens G, *et al.* Certolizumab pegol in patients with moderate to severe Crohn's disease and secondary failure to infliximab. *Clin Gastroenterol Hepatol* 2010;**8**:688–95.e2.
25. Scrivo R, Conti F, Spinelli FR, *et al.* Switching between TNFalpha antagonists in rheumatoid arthritis: personal experience and review of the literature. *Reumatismo* 2009;**61**:107–17.
26. Sandborn WJ, Colombel JF, D'Haens G, *et al.* Association of baseline C-reactive protein and prior anti-tumor necrosis factor therapy with need for weekly dosing during maintenance therapy with adalimumab in patients with moderate to severe Crohn's disease. *Curr Med Res Opin* 2013;**29**:483–93.
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. Singh S, Heien HC, Sangaralingham LR, *et al.* Comparative effectiveness and safety of anti-tumor necrosis factor agents in biologic-naïve patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2016;**14**:1120–9.e6.
29. Colombel JF, Sandborn WJ, Panaccione R, *et al.* Adalimumab safety in global clinical trials of patients with Crohn's disease. *Inflamm Bowel Dis* 2009;**15**:1308–19.