Ustekinumab versus adalimumab for induction and maintenance therapy in biologic-naive patients with moderately to severely active Crohn's disease: a multicentre, randomised, double-blind, parallel-group, phase 3b trial

*Bruce E Sands, Peter M Irving, Timothy Hoops, James L Izanec, Long-Long Gao, Christopher Gasink, Andrew Greenspan, Matthieu Allez, Silvio Danese, Stephen B Hanauer, Vipul Jairath, Tanja Kuehbacher, James D Lewis, Edward V Loftus Jr, Emese Mihaly, Remo Panaccione, Ellen Scherl, Oksana B Shchukina, William J Sandborn, on behalf of the SEAVUE Study Group**

Lancet 2022; 399: 2200–11

See **Comment** page 2169

*Members are listed in the appendix (pp 3–12)

Dr Henry D Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA (Prof B E Sands MD); **Department of Gastroenterology, Guy's and St Thomas' NHS Foundation Trust, London, UK** (P M Irving MD); **School of Immunology and Microbial Sciences, King's College London, London, UK** (P M Irving); **Immunology Global Medical Affairs, Janssen Pharmaceutical Companies of Johnson & Johnson, Horsham, PA, USA** (T Hoops MD); **Janssen Scientific Affairs, Horsham, PA, USA** (J L Izanec MD, L-L Gao PhD, C Gasink MD, A Greenspan MD); **Gastroenterology Department, Hôpital Saint-Louis, Assistance Publique-Hôpitaux de Paris (AP-HP), INSERM U1160, Université de Paris, Paris, France** (Prof M Allez MD); **Gastroenterology and Endoscopy, IRCCS Ospedale San Raffaele and Università Vita-Salute San Raffaele, Milan, Italy** (Prof S Danese MD); **Northwestern University Feinberg School of Medicine, Chicago, IL, USA** (Prof S B Hanauer MD); **Division of Gastroenterology, Department of Medicine, University Hospital, London, ON, Canada** (Prof V Jairath MD); **Division of Epidemiology and Biostatistics, Western University, London, ON, Canada** (Prof V Jairath); **Department of Internal Medicine, Gastroenterology, Diabetology, Hemato-Oncology, and**

Summary

Background Active-comparator trials are important to inform patient and physician choice. We aimed to evaluate the efficacy and safety of monotherapy with either ustekinumab or adalimumab in biologic-naive patients with moderately to severely active Crohn's disease.

Methods We conducted a randomised, double-blind, parallel-group, active-comparator, phase 3b trial (SEAVUE) at 121 hospitals or private practices in 18 countries. We included biologic-naive patients aged 18 years or older with moderately to severely active Crohn's disease and a Crohn's Disease Activity Index (CDAI) score of 220–450, who had not responded to or were intolerant to conventional therapy (or were corticosteroid dependent) and had at least one ulcer of any size at baseline endoscopic evaluation. Eligible patients were randomly assigned (1:1; via an interactive web response system) to receive ustekinumab (approximately 6 mg/kg intravenously on day 0, then 90 mg subcutaneously once every 8 weeks) or adalimumab (160 mg on day 0, 80 mg at 2 weeks, then 40 mg once every 2 weeks, subcutaneously) through week 56. Study treatments were administered as monotherapy and without dose modifications. Patients, investigators, and study site personnel were masked to treatment group assignment. The primary endpoint was the proportion of patients who were in clinical remission (CDAI score <150) at week 52 in the intention-to-treat population (ie, all patients who were randomly assigned to a treatment group). This trial is registered with ClinicalTrials.gov, NCT03464136, and EudraCT, 2017-004209-41.

Findings Between June 28, 2018, and Dec 12, 2019, 633 patients were assessed for eligibility and 386 were enrolled and randomly assigned to receive ustekinumab (n=191) or adalimumab (n=195). 29 (15%) of 191 patients in the ustekinumab group and 46 (24%) of 195 in the adalimumab group discontinued study treatment before week 52. There was no significant difference between the ustekinumab and adalimumab groups in the occurrence of the primary endpoint; at week 52, 124 (65%) of 191 patients in the ustekinumab group versus 119 (61%) of 195 in the adalimumab group were in clinical remission (between-group difference 4%, 95% CI −6 to 14; p=0·42). Safety for both groups was consistent with previous reports. Serious infections were reported in four (2%) of 191 patients in the ustekinumab group and five (3%) of 195 in the adalimumab group. No deaths occurred through week 52 of the study.

Interpretation Both ustekinumab and adalimumab monotherapies were highly effective in this population of biologic-naive patients, with no difference in the primary outcome between the drugs.

Funding Janssen Scientific Affairs.

Copyright © 2022 Elsevier Ltd. All rights reserved.

Introduction

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract that is characterised by mucosal ulcerations, diarrhoea, and abdominal pain.[1,2] Conventional treatments include corticosteroids and immunomodulators (eg, azathioprine, mercaptopurine, and methotrexate).[2,3] Tumour necrosis factor (TNF) antagonists, interleukin (IL)-12 and IL-23 inhibitors, or integrin inhibitors are recommended for use in patients who do not respond to or are intolerant to conventional therapy.[1–5]

Ustekinumab, a monoclonal antibody to the p40 subunit of IL-12 and IL-23, and adalimumab, an anti-TNF monoclonal antibody, are approved for use in the treatment of Crohn's disease.[6,7] In randomised controlled studies, both ustekinumab and adalimumab showed significantly higher rates of induction and maintenance of clinical remission in patients with Crohn's disease than did placebo.[4,8–10]

Although a network meta-analysis compared the safety and efficacy of biologics in Crohn's disease,[11] indirect comparisons across studies can be problematic due to

Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en junio 17, 2022. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2022. Elsevier Inc. Todos los derechos reservados.

Research in context

Evidence before this study

In addition to conventional Crohn's disease treatments (ie, corticosteroids and immunomodulators), several biologic agents have been approved for use. These agents include tumour necrosis factor (TNF) antagonists, interleukin (IL)-12 and IL-23 inhibitors, and integrin inhibitors. Ustekinumab, a monoclonal antibody to the p40 subunit of IL-12 and IL-23, and adalimumab, an anti-TNF monoclonal antibody, have both been approved for use in the treatment of Crohn's disease. We searched PubMed for articles published in English from database inception to Oct 13, 2021, with no restrictions for year of publication or article type, using the terms "Crohn's disease", "biologic", and "head-to-head". Our search yielded 46 articles on inflammatory bowel disease therapies, of which 40 were indirect comparisons, review articles, or commentaries, and six were observational, retrospective, or open-label studies.

Added value of this study

To our knowledge, this is the first randomised, active-comparator trial with a treat-through design to evaluate the efficacy and safety of two biologic agents in patients with moderately to severely active Crohn's disease. There was no significant difference in the primary endpoint of clinical remission at week 52, and both ustekinumab and adalimumab monotherapies were highly effective in this population of biologic-naive patients. Safety results were consistent with the known safety profiles of these two commonly used biologic agents.

Implications of all the available evidence

This study provides comparative efficacy and safety data for two biologic agents with different mechanisms of action in the treatment of biologic-naive patients with moderately to severely active Crohn's disease. The results validate the use of both mechanisms of action as first-line treatment for these patients.

differences in study designs, endpoints, populations, concomitant treatments, and the inability to adjust for patient-level confounders. Comparisons of maintenance data from randomised withdrawal studies are confounded by differential carryover effects in patients who had a response with induction treatment. Thus, although described as placebo, these maintenance groups are not truly common comparators, because they consist of patients who responded to active drug induction. Thus, active-comparator trials are needed to inform patient and physician treatment decisions.

We aimed to evaluate the efficacy and safety of monotherapy with either ustekinumab or adalimumab in biologic-naive patients with moderately to severely active Crohn's disease.

Methods

Study design and participants

We conducted a randomised, double-blind, parallel-group, active-comparator, phase 3b trial (SEAVUE) at 121 hospitals or private practices in 18 countries (appendix p 3). Patients aged 18 years or older were eligible for inclusion if they had moderately to severely active Crohn's disease for at least 3 months with a baseline Crohn's Disease Activity Index (CDAI) score of 220–450,[12,13] at least one ulcer of any size on baseline endoscopic evaluation (ie, a Simple Endoscopic Score for Crohn's Disease [SES-CD] ≥3 on ileocolonoscopy),[14] had not previously received biologic therapy, and had not responded to or were intolerant to conventional therapy or were corticosteroid dependent (appendix p 12).

Key exclusion criteria were pregnancy, confounding Crohn's disease complications or other confounding comorbidity, bowel resection within 6 months of randomisation, any intra-abdominal surgery or a hospitalisation for bowel obstruction within 3 months of randomisation, evidence of ongoing infection or malignancy, history of recurrent infection or serious opportunistic infection, and use of apheresis or total parenteral nutrition within 3 weeks of randomisation (appendix p 12).

Patients on oral corticosteroids were eligible, provided that they had been on a stable dose (prednisone-equivalent ≤40 mg/day or budesonide ≤9 mg/day) for at least 3 weeks before randomisation. Patients were required to have discontinued azathioprine, mercaptopurine, methotrexate, or intravenous corticosteroids at least 3 weeks before randomisation, and to have discontinued other immunosuppressants (eg, Janus kinase inhibitors, thioguanine, and cyclosporine) at least 4 weeks before randomisation.

The study was conducted in compliance with the Declaration of Helsinki, International Council for Harmonisation and Good Clinical Practice guidelines, and local country regulations. All participants provided written informed consent. The protocol was approved by the relevant institutional review boards or ethics committees at all sites.

Randomisation and masking

After a screening period (of ≤5 weeks), eligible patients were randomly assigned (1:1) via an interactive web response system to receive ustekinumab or adalimumab. Concealed allocation was done via computer-generated randomisation schedule, managed by an independent vendor under supervision by the study funder (Janssen). We used permuted block randomisation (with a block size

Palliative Medicine, Medius Clinic Nuertingen, Nürtingen, Germany (T Kuehbacher MD); **Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA** (Prof J D Lewis MD); **Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine and Science, Rochester, MN, USA** (Prof E V Loftus Jr MD); **Department of Internal Medicine and Hematology, Semmelweis University, Budapest, Hungary** (E Mihaly MD); **Inflammatory Bowel Disease Unit, Division of Gastroenterology and Hepatology, University of Calgary, Calgary, AB, Canada** (Prof R Panaccione MD); **Weill Department of Medicine, New York Presbyterian Hospital Weill Cornell Medicine, New York, NY, USA** (Prof E Scherl MD); **Division The City Center for IBD Diagnosis and Treatment, Saint Petersburg State Budgetary Health Institution, City Clinical Hospital 31, Saint Petersburg, Russia** (O B Shchukina MD); **Division of Gastroenterology, University of California San Diego, La Jolla, CA, USA** (Prof W J Sandborn MD)

Correspondence to:
Prof Bruce E Sands, Dr Henry D Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
bruce.sands@mssm.edu

See **Online** for appendix

Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en junio 17, 2022. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2022. Elsevier Inc. Todos los derechos reservados.

of four), stratified by baseline corticosteroid use (yes or no), baseline CDAI score (≤300 or >300), and the presence of ulcers greater than 5 mm diameter at baseline endoscopic evaluation (yes or no).

Patients, investigators, and study site personnel were masked to treatment group assignment. Placebo was administered as necessary so that all patients received the same number of infusions and injections at the same timepoints to maintain blinding. Ustekinumab and adalimumab syringes were not identical but were packaged identically, and study site personnel did not see syringes out of containers. At day 0 and 2 weeks, a non-masked site employee who was not part of the study team administered the study treatments and trained patients for at-home administration after week 2. Efficacy and safety assessments were done by masked study personnel.

Procedures

Patients assigned to the ustekinumab group received an intravenous weight-range-based dose of approximately 6 mg/kg on day 0 plus subcutaneous placebo on day 0 (four injections) and at 2 weeks (two injections), then 90 mg subcutaneous ustekinumab once every 8 weeks through week 56, with subcutaneous placebo once every 2 weeks (except for every 8th week when they received subcutaneous ustekinumab). Patients assigned to the adalimumab group received 160 mg subcutaneous adalimumab (four injections of citrate-free 40 mg per 0·4 mL formulation) plus intravenous placebo on day 0, 80 mg subcutaneous adalimumab at week 2 (in two injections), then 40 mg subcutaneous adalimumab once every 2 weeks through week 56. Dosing regimens were in accordance with prescribing information approved by the US Food and Drug Administration (FDA),[6,7] which did not incorporate alternative dosing (including dose escalation) for either therapy.

Corticosteroid doses were to remain stable through week 8; tapering was permitted starting at week 8 and was mandatory from week 16, per a recommended schedule (appendix p 12). If corticosteroids had to be reinitiated, tapering was resumed as soon as possible.

CDAI scores (from 0 to 600; higher scores indicate more severe disease)[12–14] were determined at randomisation and at 2, 8, 16, 24, 32, 40, 48, and 52 weeks. Endoscopic evaluations were recorded at screening and at 52 weeks or early termination. Endoscopic recordings were assessed by a masked central reader for SES-CD analyses (scored from 0 to 56, appendix p13).[14] Laboratory and safety evaluations were done throughout the study. Blood samples were collected before study drug administration for evaluation of serum drug concentrations and anti-drug antibodies at weeks 0, 8, 16, 32, 48, and 52, or at early termination.

Serum drug concentrations were determined using validated, sensitive methods.[15,16] The lower limit of quantitation was 0·17 µg/mL for ustekinumab and 1·00 µg/mL for adalimumab. Separate, drug-specific, drug-tolerant, electrochemiluminescent immunoassays on the Meso Scale Discovery platform,[15,17] developed and validated in accordance with FDA guidelines,[18] were used to detect and characterise antidrug antibodies. Serum trough drug concentrations were collected at weeks 16 and 52 for adalimumab and before each ustekinumab maintenance dose.

Outcomes

The primary endpoint was the proportion of patients who were in clinical remission (CDAI score <150) at week 52, which was also evaluated for prespecified subgroups (by baseline demographics and clinical disease characteristics, Crohn's disease medication use at baseline, baseline surgical history and endoscopy information, and previous history of Crohn's disease medications). Major secondary endpoints were corticosteroid-free remission (CDAI score <150 and no corticosteroids for at least the past 30 days) at week 52; clinical response (CDAI score decreased by ≥100 points from baseline or CDAI score <150) at week 52; PRO-2 symptom remission, defined using the CDAI patient-reported components of abdominal pain (mean daily score ≤1) together with stool frequency (mean daily score ≤3), at week 52; clinical remission at week 16; and endoscopic remission (SES-CD ≤3, or SES-CD 0 for patients with baseline SES-CD 3) at week 52. Additional secondary and other prespecified endpoints are listed in the appendix (pp 13–14). All analyses were prespecified except for time to treatment discontinuation and endoscopic response in subgroups based on baseline SES-CD.

Safety analyses included all safety data reported up to and including the week 52 visit for all patients who received at least one dose of study treatment. Medical Dictionary for Regulatory Activities (version 23.0) was used for reporting adverse events.

Statistical analysis

The study was powered to evaluate ustekinumab superiority over adalimumab for clinical remission at week 52. The proportion of patients in the ustekinumab group who would reach clinical remission at week 52 was assumed to be 56%, based on data from biologic-naive patients from phase 3 studies.[10] The proportion for the adalimumab group was assumed to be 41%, based on published phase 3/3b studies that had a sample and design that were similar to SEAVUE.[4,19,20] We estimated that a sample size of 175 patients per treatment group would provide 80% power to detect a 15% difference between the ustekinumab and adalimumab groups in the proportion of patients who were in clinical remission at week 52, using the two-sided Mantel-Haenszel test at a significance level of 0·05. Stratification factors were not included in the sample size calculation because published data were not available to make specific assumptions for all strata.

For the primary and secondary efficacy endpoints, the proportions of patients who reached each endpoint were compared between treatment groups using the

Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en junio 17, 2022. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2022. Elsevier Inc. Todos los derechos reservados.

two-sided Cochran-Mantel-Haenszel χ^2 test at a significance level of 0·05, with adjustment for randomisation stratification factors. Continuous variables were compared between treatment groups using an analysis of covariance on van der Waerden normal scores with baseline value and randomisation stratification factors, except for CDAI score change from baseline where the baseline CDAI score was used as a covariate instead of the baseline CDAI stratification factor. A hierarchical testing procedure was used to control inflation of the type I error due to multiple efficacy outcomes, with a two-sided significance level of 0·05 required to proceed to the next test.[21] If the primary endpoint did not show a significant difference between treatment groups, all subsequent major secondary endpoints were considered not significant, and p values were nominal. Remaining prespecified endpoints were not adjusted for multiplicity. Treatment retention was measured by post-hoc analysis of time to treatment discontinuation through week 52 using the Kaplan-Meier estimator and log-rank test.

Efficacy was analysed in the full analysis set of all patients who were randomly assigned to a treatment group, in accordance with the intention-to-treat principle. Patients who had a prohibited Crohn's disease-related surgery while on study, discontinued study treatment due to an adverse event of worsening Crohn's disease or absence of improvement, or had a prohibited change in concomitant medications (including initiating or increasing the dose of corticosteroids above the baseline dose) were deemed to have had treatment failure and to have not reached dichotomous efficacy endpoints from the time the treatment failure occurred (appendix p 12). For continuous efficacy endpoints, the baseline value was carried forward from the time the treatment failure occurred. Missing values were imputed as not having reached the endpoint for dichotomous outcomes or using the last observation carried forward approach for continuous outcomes.

Adverse events were analysed according to the treatment received in the safety population and were summarised descriptively.

Statistical analyses were done with SAS (version 9.4). This study is registered with ClinicalTrials.gov, NCT03464136, and EudraCT, 2017-004209-41.

Role of the funding source

The study was designed by the funder, in collaboration with the authors. Data were collected by study investigators. Statistical analyses were conducted by statisticians employed by the funder and results were reviewed by all authors.

Results

Between June 18, 2018, and Dec 12, 2019, 633 patients were assessed for eligibility and 386 were enrolled and randomly assigned to receive ustekinumab (n=191) or adalimumab (n=195; figure 1). All randomly assigned patients received at least one dose of assigned study treatment. 29 (15%) of 191 patients in the ustekinumab group and 46 (24%) of 195 in the adalimumab group discontinued study treatment before week 52. The most common reasons for treatment discontinuation were adverse events (11 [6%] of 191 patients in the ustekinumab group *vs* 21 [11%] of 195 in the adalimumab group), withdrawal of consent (11 [6%] *vs* ten [5%]), and absence of improvement (four [2%] *vs* ten [5%]). Treatment retention, as measured by time to treatment discontinuation, was longer in the ustekinumab group than in the adalimumab group (nominal p=0·047; appendix p 15).

Regarding all assigned study treatment injections, including placebo, six (3%) of 191 patients in the ustekinumab group and 15 (8%) of 195 in the adalimumab group missed one assigned injection, and four (2%) ustekinumab-treated patients and eight (4%) adalimumab-treated patients missed two or more injections. Baseline demographics and disease characteristics were balanced between treatment groups (table 1). 69 (18%) of 386 patients had been receiving immunomodulators at screening (these were discontinued before randomisation, per protocol).

There was no significant difference in the occurrence of the primary outcome between the ustekinumab and adalimumab groups; at week 52, 124 (65%) of 191 patients in the ustekinumab group versus 119 (61%) of 195 in the adalimumab group were in clinical remission (between-group difference 4%, 95% CI –6 to 14; p=0·42; figure 2A). Because there was no significant difference between

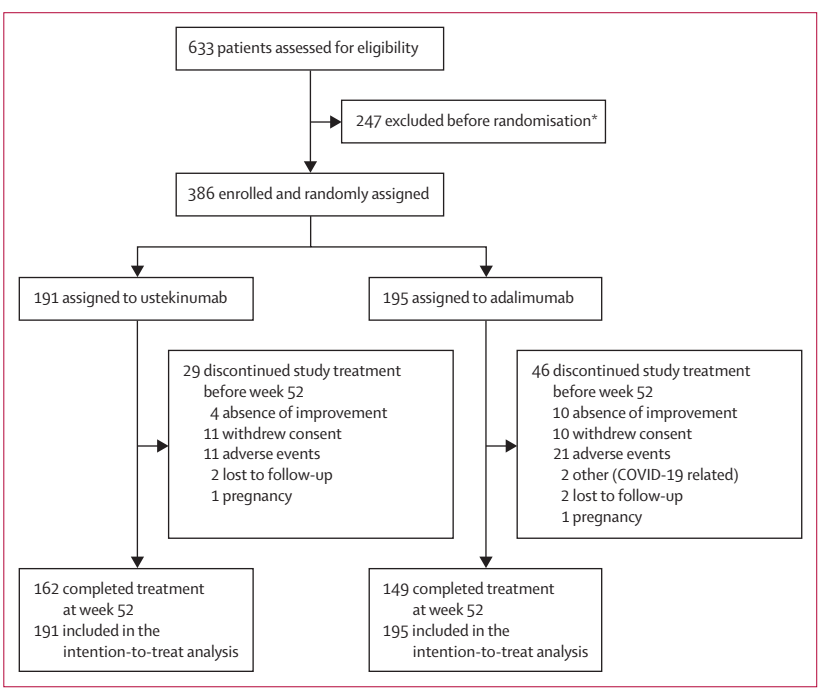

Figure 1: **Trial profile**
All randomised patients received at least one dose of study treatment. *Reasons are provided in the appendix (p 30).

Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en junio 17, 2022. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2022. Elsevier Inc. Todos los derechos reservados.

	Ustekinumab group (n=191)	Adalimumab group (n=195)
Age, years	37·0 (13·23)	37·4 (12·99)
Sex		
Female	101 (53%)	100 (51%)
Male	90 (47%)	95 (49%)
Race		
White	164 (86%)	181 (93%)
Asian	11 (6%)	6 (3%)
Black	8 (4%)	7 (4%)
Other, multiple, or unknown	8 (4%)	1 (1%)
Bodyweight, kg	72·7 (20·07)	70·5 (17·21)
Duration of disease, years	5·4 (8·36)	5·8 (7·09)
Median (IQR)	2·6 (0·7–5·8)	2·6 (0·9–8·6)
CDAI score	301·6 (61·58)	300·0 (55·99)
Median (IQR)	287·0 (253–348)	291·0 (257–330)
SES-CD*	9·9 (6·94)	9·8 (7·04)
Median (IQR)	7·0 (5·0–14·0)	8·0 (5·0–13·0)
C-reactive protein concentration, mg/L	14·5 (23·56)	11·9 (17·58)
Median (IQR)	6·2 (1·98–19·70)	5·5 (2·02–14·20)
Faecal calprotectin concentration, mg/kg	1392 (1771)	1272 (2209)
Median (IQR)	895 (238–1741)	546 (193–1533)
Gastrointestinal tract areas involved		
Patients assessed	189	195
Ileum only	60 (32%)	55 (28%)
Colon only	26 (14%)	34 (17%)
Ileum and colon	102 (54%)	103 (53%)
Proximal gastrointestinal tract	30 (16%)	17 (9%)
Perianal involvement	50 (27%)	41 (21%)
One or more fistulas (current)	17 (9%)	20 (10%)
Previous Crohn's disease-related surgery		
Previous intra-abdominal Crohn's disease-related surgery	29 (15%)	37 (19%)
Any other Crohn's disease-related surgery	6 (3%)	9 (5%)
Corticosteroids for Crohn's disease at baseline		
Corticosteroids including budesonide	70 (37%)	75 (39%)
Corticosteroid excluding budesonide	42 (22%)	46 (24%)
Corticosteroid dose, mg/day	20·0 (10·0–20·0)	20·0 (10·0–20·0)
Budesonide	28 (15%)	29 (15%)
Budesonide dose, mg/day	9·0 (6·0–9·0)	9·0 (6·0–9·0)
History of corticosteroid or immunomodulator treatment failure†‡	191 (100%)	194 (99%)
Corticosteroids only	84 (44%)	80 (41%)
Immunomodulators only	40 (21%)	36 (19%)
Corticosteroids and immunomodulators	67 (35%)	78 (40%)

Data are mean (SD), median (IQR), or n (%) unless otherwise stated. CDAI=Crohn's Disease Activity Index. SES-CD=Simple Endoscopic Score for Crohn's Disease. *187 patients assessed in the ustekinumab group, 186 in the adalimumab group. †Includes patients who did not respond to or became intolerant to corticosteroids or immunomodulators, or became dependent on corticosteroids. ‡Includes budesonide.

Table 1: **Baseline characteristics in the intention-to-treat population**

treatment groups in the primary endpoint, all major secondary endpoint p values were nominal and considered non-significant. Regarding the major secondary endpoints, 116 (61%) of 191 patients in the ustekinumab group and 112 (57%) of 195 in the adalimumab group had corticosteroid-free clinical remission at week 52, 138 (72%) in the ustekinumab group and 129 (66%) in the adalimumab group had clinical response at week 52, 108 (57%) in the ustekinumab group and 108 (55%) in the adalimumab group had PRO-2 symptom remission at week 52, and 109 (57%) in the ustekinumab group and 117 (60%) in the adalimumab group had clinical remission at week 16 (figure 2A). When the key patient-reported symptoms of abdominal pain and stool frequency were assessed at the time of the primary endpoint as continuous variables, the mean change from baseline to week 52 in the sum of the number of stools and abdominal pain scores in the previous 7 days was –29·6 (IQR –43·0 to –12·0) in the ustekinumab group and –25·1 (–39·0 to –10·0) in the adalimumab group (nominal p=0·013; figure 2B). Resolution of CDAI abdominal pain and diarrhoea through week 52 were similar between groups (appendix pp 15–16). Sensitivity analyses are reported in the appendix (pp 14–15).

When clinical remission and response were evaluated over time, the proportions of patients who reached each endpoint were similar for both treatment groups (figures 3A, B). Among patients who had clinical response after induction (at week 16), 124 (89%) of 140 patients in the ustekinumab group versus 110 (78%) of 141 in the adalimumab group showed maintenance of clinical response at week 52 (between-group difference 11%, 95% CI 2 to 19; nominal p=0·016). Among patients who were in clinical remission after induction, 94 (86%) of 109 patients in the ustekinumab group versus 94 (80%) of 117 in the adalimumab group showed maintenance of clinical remission at week 52 (between-group difference 7%, 95% CI –3 to 16; nominal p=0·19; figure 3C). Durable clinical remission and response at week 52 analyses are shown in the appendix (p 17). When the primary endpoint of clinical remission at week 52 was evaluated by prespecified subgroups, there were no clinically meaningful differences between treatment groups, including in areas of Crohn's disease involvement and endoscopic disease severity per SES-CD, except for among patients who did not respond to or were intolerant to immunomodulators at baseline (78 [73%] of 107 patients in the ustekinumab group *vs* 68 [60%] of 114 in the adalimumab group were in clinical remission at week 52; appendix pp 18–21).

Mean prednisone-equivalent dose decreased in both treatment groups after corticosteroid tapering became mandatory (week 16), and this decrease was maintained through week 52 (appendix p 21). At week 52, the mean daily prednisone-equivalent dose was 4·5 mg/day (decreased from 19·4 mg/day) in the ustekinumab group and 8·5 mg/day (decreased from 18·8 mg/day) in the adalimumab group (nominal p=0·15).

At week 52, 51 (29%) of 179 patients in the ustekinumab group and 55 (31%) of 179 in the adalimumab group had endoscopic remission, 75 (42%)

Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en junio 17, 2022. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2022. Elsevier Inc. Todos los derechos reservados.

and 66 (37%) had endoscopic response, and 92 (51%) and 75 (42%) had at least a 25% improvement in SES-CD from baseline (figure 4). When examined as a continuous variable, mean change in SES-CD from baseline to week 52 was –4·1 (SD 5·9) in the ustekinumab group and –3·1 (6·0) in the adalimumab group (nominal p=0·046).

Evaluation of endoscopic remission by baseline SES-CD showed that the proportion of patients reaching endoscopic remission declined with higher baseline SES-CD but remained similar between treatment groups. Endoscopic remission was reached in 23 (34%) of 67 patients with mild endoscopic disease severity (SES-CD 3–6) and six (17%) of 36 patients with severe endoscopic disease severity (SES-CD >16) in the ustekinumab group and in 25 (37%) of 67 patients with mild endoscopic disease severity and seven (21%) of 34 patients with severe endoscopic disease severity in the adalimumab group (appendix p 22). In the moderate and severe endoscopic disease subgroup (SES-CD >6), which corresponds more closely with enrolment criteria of other Crohn's disease clinical studies, endoscopic response (added as a post-hoc analysis) was reached by 51 (46%) of 112 patients in the ustekinumab group and 41 (37%) of 112 in the adalimumab group, and remission was reached by 28 (25%) of 112 in the ustekinumab group and 30 (27%) of 112 in the adalimumab group (appendix p 23).

Inflammatory Bowel Disease Questionnaire results are summarised in the appendix (pp 24–25), as well as change from baseline in C-reactive protein and faecal calprotectin results (appendix pp 25–26) and the proportions of patients who had clinical and biomarker remission through week 52 (appendix p 26). For these endpoints, results were similar between treatment groups.

Median serum trough steady-state concentration at the last dosing visit was 2·0 µg/mL (IQR 1·1–3·6) for ustekinumab (week 48) and 7·8 µg/mL (3·9–10·3) for adalimumab (week 52). The proportions of patients who reached clinical remission at week 52 were mildly higher with higher final serum trough steady-state drug concentrations in both groups (appendix p 27).

At week 16, three (2%) of 179 evaluable patients had anti-ustekinumab antibodies and 112 (63%) of 177 had anti-adalimumab antibodies. At week 52, three (2%) of 156 evaluable patients had anti-ustekinumab antibodies and 106 (74%) of 144 had anti-adalimumab antibodies. Through week 52, four (2%) of 190 evaluable patients in the ustekinumab group and 145 (74%) of 195 evaluable patients in the adalimumab group had anti-drug antibodies at one or more timepoints. Most patients (102 [70%] of 145) who were positive for anti-adalimumab antibodies through week 52 had low titres (<1:8). In patients with anti-adalimumab antibodies, serum trough steady-state concentrations were inversely associated with anti-adalimumab antibody status and titres (appendix p 28). However, proportions of patients in clinical remission at week 52 were not reduced in those with anti-adalimumab antibodies versus those without, regardless of titre (appendix pp 28–29). As only four patients were positive for anti-ustekinumab antibodies up to week 52, their effect on pharmacokinetics or efficacy could not be evaluated.

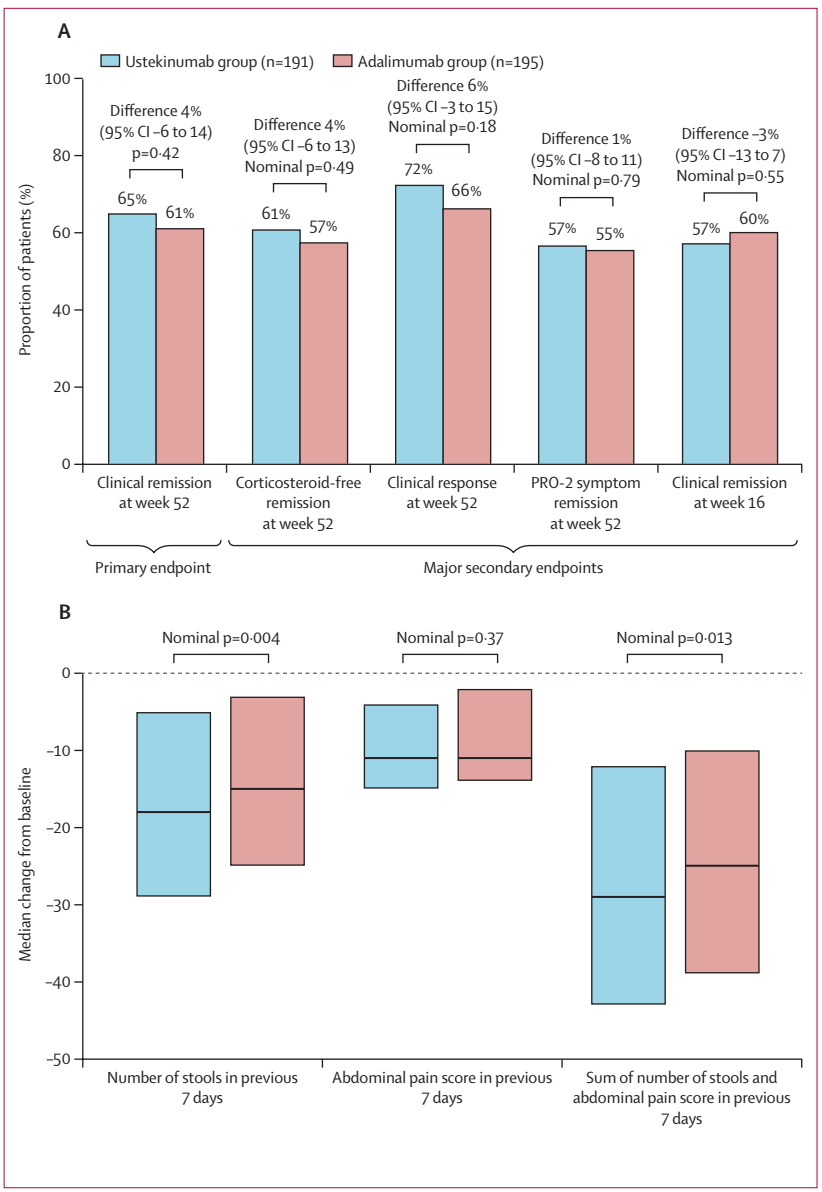

***Figure 2*: Primary and major secondary endpoints**
(A) Proportions of patients in clinical remission, corticosteroid-free remission, clinical response, or PRO-2 symptom remission at week 52 and in clinical remission at week 16; 95% CIs were based on the Wald statistic with Mantel-Haenszel weight. (B) Median change from baseline to week 52 in the number of stools, abdominal pain scores, and sum of stools and abdominal pain scores in the previous 7 days; bars show IQR. Nominal p values for dichotomous endpoints were based on the two-sided Cochran-Mantel-Haenszel χ^2 test at a significance level of 0·05. Treatment group differences and p values were adjusted for randomisation stratification factors. Nominal p values for continuous endpoints were based on an analysis of covariance on van der Waerden normal scores with adjustment for baseline value and randomisation stratification factors. PRO-2=patient-reported outcome-2.

Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en junio 17, 2022. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2022. Elsevier Inc. Todos los derechos reservados.

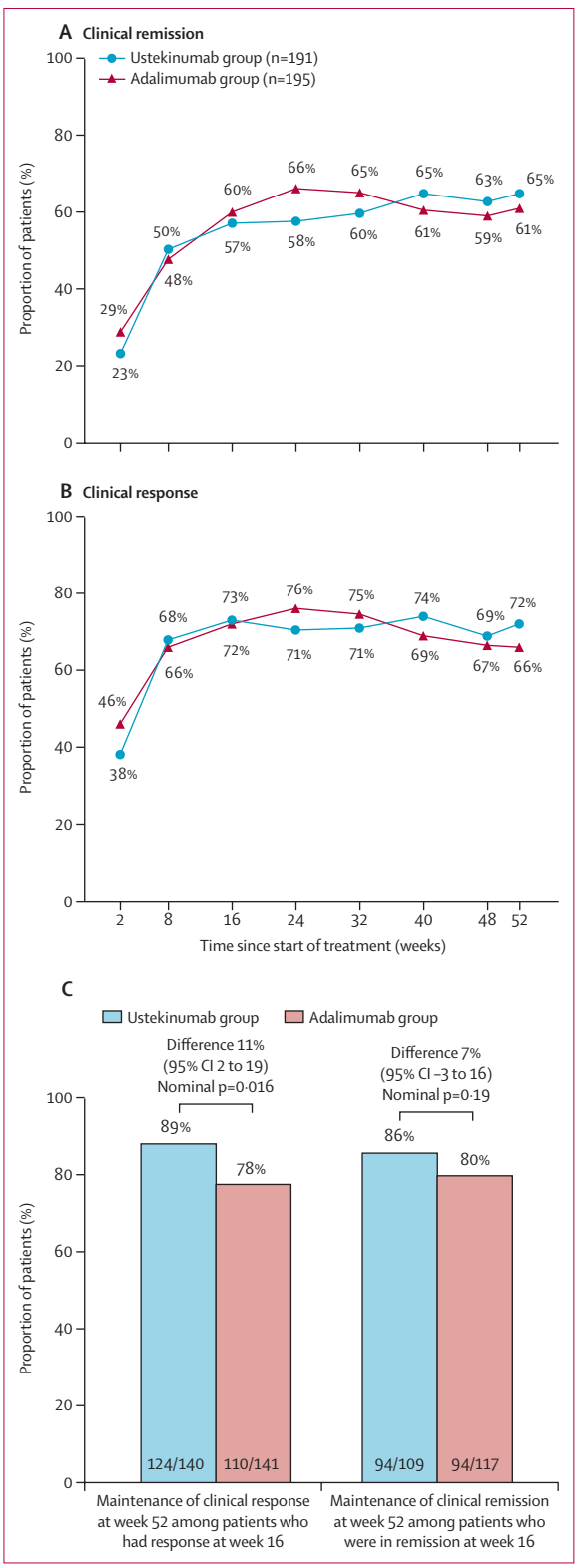

Figure 3: **Clinical efficacy over time**
(A) Proportions of patients in clinical remission through week 52. (B) Proportions of patients in clinical response through week 52. (C) Maintenance of clinical response and clinical remission at week 52 in patients who had clinical response or clinical remission at week 16. 95% CIs were based on the Wald statistic with Mantel-Haenszel weight. Nominal p values were based on the two-sided Cochran-Mantel-Haenszel χ^2 test at a significance level of 0·05. Treatment differences and p values were adjusted for randomisation stratification factors. CDAI=Crohn's Disease Activity Index.

Adverse events were reported in 153 (80%) of 191 patients in the ustekinumab group and 152 (78%) of 195 in the adalimumab group (table 2). 11 (6%) patients in the ustekinumab group and 21 (11%) in the adalimumab group had one or more adverse events that led to study treatment discontinuation (appendix p 29).

Serious adverse events were reported in 25 (13%) of 191 patients in the ustekinumab group and 32 (16%) of 195 in the adalimumab group (table 2). The most common serious adverse event was worsening of Crohn's disease (five [3%] patients in the ustekinumab group and 14 [7%] in the adalimumab group). Other serious adverse events of note included pneumonia (in two patients, both in the adalimumab group), thrombophlebitis (in one patient in the adalimumab group), unstable angina (in one patient in the ustekinumab group), and psoriasis (in one patient in the adalimumab group).

Infections were reported in 65 (34%) of 191 patients in the ustekinumab group and 79 (41%) of 195 in the adalimumab group. Serious infections were reported in four (2%) patients in the ustekinumab group (four events: *Paracoccidioides* infection, rectal abscess, urinary tract infection, and enterocolitis) and five (3%) in the adalimumab group (six events: pneumonia [n=2], appendicitis, pulmonary tuberculosis, anal fistula, and intestinal perforation). Opportunistic infections (two serious and one non-serious) occurred in three patients overall: the aforementioned *Paracoccidioides* infection in a patient in the ustekinumab group in Brazil, where this organism is endemic; active pulmonary tuberculosis in a patient in the adalimumab group in Poland; and disseminated herpes zoster virus in a patient in the adalimumab group. Oral or genital herpes simplex virus occurred in two (1%) patients in the ustekinumab group and 12 (6%) in the adalimumab group. Herpes zoster virus occurred in one (1%) patient in the ustekinumab group and three (2%) in the adalimumab group. One patient in the adalimumab group had multiple herpes viral adverse events (two oral herpes events and one herpes zoster event).

Injection-site reactions associated with active treatment occurred in two (1%) of 191 patients in the ustekinumab group and 20 (10%) of 195 in the adalimumab group (table 2). Infusion-related adverse events occurred in three (2%) patients in the ustekinumab group and six (3%) in the adalimumab group (placebo infusions). One malignancy event (basal cell carcinoma) occurred in the adalimumab group. No deaths occurred through week 52 of the study. One patient in the adalimumab group died suddenly at week 56, after discharge from a prolonged hospitalisation related to intestinal perforation and pulmonary embolism. Although no autopsy was performed, the investigator-suspected cause of death was pulmonary embolism.

Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en junio 17, 2022. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2022. Elsevier Inc. Todos los derechos reservados.

Discussion

Studies comparing biologic treatments are needed to inform clinician and patient decisions, including selection of first-line therapy in the treatment of Crohn's disease. Previous reports were indirect comparisons that relied upon randomised withdrawal studies of successfully induced patients during maintenance,[11] or retrospective, unblinded, non-randomised studies.[22–25] To our knowledge, this is the first clinical trial to directly and prospectively compare two approved biologic treatments for Crohn's disease, ustekinumab and adalimumab, in a randomised, double-blind, treat-through design.

Ustekinumab was not shown to be superior to adalimumab in the primary endpoint of proportion of patients in clinical remission at week 52 (between-group difference 4%, 95% CI −6 to 14; p=0·42). Clinical remission at week 52 was reached by most patients in both treatment groups. The treat-through study design accounted for all patients who received induction treatment, including patients with and without response. Clinical response and remission results continued to increase well beyond the originally studied induction periods (4–8 weeks). Efficacy was high in both treatment groups relative to previous studies that evaluated maintenance efficacy in patients with response after short induction periods. In the IM-UNITI ustekinumab maintenance study,[10] 52 (65%) of 80 biologic-naive patients who had clinical response 8 weeks after induction were in clinical remission at 1 year. In the CHARM adalimumab maintenance study,[4] 36 (42%) of 87 biologic-naive patients who had clinical response 4 weeks after induction were in clinical remission at week 56. Unlike these studies, SEAVUE did not have a placebo group. The absence of a placebo group could lead to higher efficacy when using symptom-based efficacy scales alone, because patients know they received active study treatment. Thus, SEAVUE might reflect effectiveness observed in clinical practice more closely than placebo-controlled studies.

The high clinical efficacy in this study is also, in part, a reflection of the study population, which comprised biologic-naive patients with short disease duration and evidence of active inflammation at baseline (not a feature of the original pivotal studies).[4,10] The median disease duration (2·6 years [IQR 0·7–7·3]) was similar to that in the SONIC study[19] of infliximab and azathioprine in patients who had not previously received biologic or immunosuppressive therapy (2·3 years), but shorter than in previous studies of biologics in patients who had received previous immunosuppressive therapy (6·4 years in UNITI-2,[10] 7·9 years [range 0·3–44·1] in CHARM[26]). Notably, in SEAVUE, the proportions of patients in clinical remission at week 24 (58% in the ustekinumab group and 66% in the adalimumab group) were similar to that of the infliximab plus azathioprine group in SONIC[19] at week 26 (102 [60%] of 169 patients; the time of the primary endpoint). Unlike this study, SONIC did not require evidence of active inflammation at baseline.

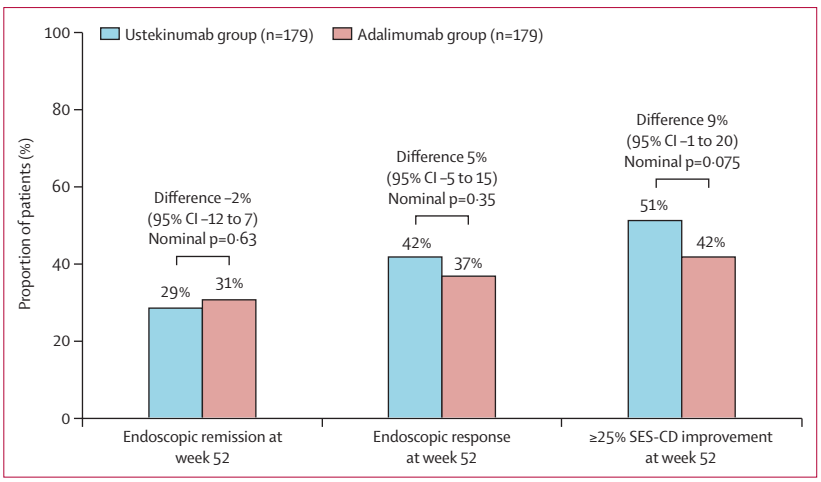

Figure 4: **Endoscopic remission, endoscopic response, and improvement from baseline in SES-CD at week 52**
95% CIs were based on the Wald statistic with Mantel-Haenszel weight. Nominal p values were based on the two-sided Cochran-Mantel-Haenszel χ^2 test at a significance level of 0·05. Treatment group differences and p values were adjusted for randomisation stratification factors. SES-CD=Simple Endoscopic Score for Crohn's Disease.

We observed rapid onset of clinical response and remission in both treatment groups as early as the first assessment point at week 2, and the proportions of patients with these outcomes increased even after week 16. High efficacy was shown without concomitant immunosuppression or dose adjustment. The treatment discontinuation rate was relatively low (15% in the ustekinumab group and 24% in the adalimumab group) compared with the original pivotal studies, which allowed for dose escalation, showing that efficacy might eventually be achieved when the original dose is maintained in this population. The FDA-approved dosages for each product do not indicate alternative doses. However, the European Medicines Agency have approved an adalimumab maintenance dosing interval of 1 week,[27] and the ustekinumab maintenance dosing interval has been shortened to 4 or 6 weeks in observational studies.[28,29] In the SERENE adalimumab study,[30] weekly dosing using serum drug concentrations did not result in superior efficacy compared with adjustment based on clinical parameters; however, a control group to evaluate whether dose adjustment was beneficial was not included. Our findings suggest that almost two-thirds of biologic-naive patients who receive ustekinumab or adalimumab will, in time, reach and maintain clinical remission without dose adjustment at least up to 1 year.

Both treatment groups showed robust and similar endoscopic response (42% of patients in the ustekinumab group *vs* 37% in the adalimumab group) and remission results (29% *vs* 31%) at week 52. To our knowledge, these are the first endoscopic data in Crohn's disease from a trial with treat-through design, which is reflective of real-world use.

Ustekinumab and adalimumab were administered as monotherapy. 18% of patients were receiving immunosuppressants before enrolment with active disease and

Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en junio 17, 2022. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2022. Elsevier Inc. Todos los derechos reservados.

	Ustekinumab group (n=191)	Adalimumab group (n=195)
Duration of follow-up, weeks		
Mean (SD)	47·6 (12·0)	45·8 (13·4)
Median (IQR)	52·1 (51·6–52·3)	52·1 (51·0–52·4)
Number of study treatment administrations		
Mean (SD)	29·0 (5·8)	28·0 (6·4)
Median (IQR)	31·0 (31·0–31·0)	31·0 (30·0–31·0)
Any adverse event	153 (80%)	152 (78%)
Serious or other clinically important events		
Discontinued study treatment because of adverse events	11 (6%)	21 (11%)
Discontinued study treatment because of Crohn's disease adverse events	5 (3%)	6 (3%)
Serious adverse events	25 (13%)	32 (16%)
Serious adverse events of worsening Crohn's disease	5 (3%)	14 (7%)
Death	0	0*
Adverse events of special interest		
Infections	65 (34%)	79 (41%)
Serious infections	4 (2%)	5 (3%)
Malignancies	0	1 (1%)†
Infusion-related adverse events	3 (2%)	6 (3%)‡
Injection-site reactions		
Active treatment injections	2 (1%)	20 (10%)
Placebo injections	4 (2%)§	NA
Most frequent treatment-emergent adverse events¶		
Crohn's disease event	22 (12%)	31 (16%)
Nasopharyngitis	14 (7%)	19 (10%)
Abdominal pain	24 (13%)	16 (8%)
Arthralgia	12 (6%)	16 (8%)
Upper respiratory tract infection	12 (6%)	15 (8%)
Headache	22 (12%)	13 (7%)
Injection-site erythema	3 (2%)	13 (7%)
Oral herpes	1 (1%)	11 (6%)
Urinary tract infection	8 (4%)	10 (5%)
Nausea	11 (6%)	9 (5%)
Vomiting	10 (5%)	4 (2%)
Diarrhoea	11 (6%)	2 (1%)

Data are n (%) unless otherwise stated. The citrate-free 40 mg/0·4 mL adalimumab formulation was used. NA=not applicable. *One sudden death, with pulmonary embolism as the suspected cause, occurred in the adalimumab group about 4 weeks after week 52. †Basal cell carcinoma. ‡Infusions in the adalimumab group were placebo. §One additional patient had a reaction to placebo who also had a reaction to ustekinumab; overall rate of injection-site reactions, combining both active treatment and placebo injections, was 3%. ¶Occurring in at least 5% of patients in either treatment group.

Table 2: **Safety summary at week 52 in the safety population**

discontinued them during the screening period; 57% of these patients had not had a response with these agents. Although the SONIC study[19] in immunosuppressive-naive patients showed a benefit of infliximab plus azathioprine over monotherapy, subgroup analyses from previous ustekinumab and adalimumab studies suggested that concomitant immunosuppression might not provide an efficacy benefit, although the studies were not designed to answer this question.[4,8–10] In the DIAMOND study[31] of adalimumab, concomitant immunosuppression was not clinically beneficial, although some endoscopic benefit was reported. Observational studies and a meta-analysis have also shown a potential benefit of adalimumab with concomitant immunosuppression.[32–35] However, our results show that, in biologic-naive patients, ustekinumab and adalimumab were highly efficacious through 1 year without concomitant immunosuppression.

Substantially higher proportions of patients who received adalimumab had anti-drug antibodies through week 52 than those who received ustekinumab (74% *vs* 2%, respectively). Anti-drug antibodies were detected using new-generation, high-sensitivity, drug-tolerant assays that were validated according to FDA guidelines.[18] Most patients with anti-adalimumab antibodies had low antibody titres. Although anti-adalimumab antibody titres were inversely related to steady-state trough serum concentrations, clinical remission at week 52 did not appear to be negatively affected by antibody positivity or titre. It is unclear if differences between groups might have emerged beyond 1 year, which is a limitation of these data. The number of patients with anti-ustekinumab antibodies (four of 191 patients) was too small for meaningful characterisation.

Treatment retention was greater in the ustekinumab group than in the adalimumab group, with discontinuation rates of 15% and 24%, respectively. This finding is consistent with observational studies and analyses of insurance claims databases.[24,36–39] The proportion of patients (11%) in the adalimumab group who discontinued study treatment because of an adverse event was about twice that of the ustekinumab group (6%).

Overall, safety was consistent with the known safety profiles of both treatments.[6,7] The proportions of patients in the ustekinumab group who had infections and serious adverse events of worsening Crohn's disease were numerically lower than in the adalimumab group, but overall adverse event frequencies were similar between groups. A greater proportion of patients in the adalimumab group than in the ustekinumab group had active-treatment injection-site reactions (10% *vs* 1%), despite the newer 40 mg per 0·4 mL citrate-free adalimumab formulation. No patients discontinued the study because of COVID-19, and the pandemic did not affect the study results.

This study has several limitations. The findings might not be applicable to patients with previous biologic therapy failure, without evidence of active inflammation, or longer disease history. The study also had a duration of only 1 year; longer-term follow-up would be needed to determine if efficacy is sustained similarly with each drug. Safety might not be extrapolatable to patients with previous biologic failure or concomitant use of

Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en junio 17, 2022. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2022. Elsevier Inc. Todos los derechos reservados.

immunomodulators. Efficacy findings in this treat-through study are not directly comparable to studies that included a placebo group or only evaluated maintenance treatment in patients who responded to induction. The sample size calculation did not consider the stratification factors that were used in the efficacy analysis. However, the study enrolled 386 patients, which was more than the target sample size (350 patients). Subgroup analyses were subject to sparse data bias. Finally, the intention-to-treat approach to the primary analysis is subject to measurement bias; however, the number of patients who discontinued or were non-compliant to the study protocol was low, so we do not believe that this bias affected the overall study conclusion.

In conclusion, both ustekinumab and adalimumab monotherapy resulted in high rates of clinical remission through 1 year of treatment in biologic-naive patients with moderately to severely active Crohn's disease, but ustekinumab did not meet significance for superiority versus adalimumab in the primary endpoint of clinical remission at week 52. Safety and immunogenicity results were consistent with the known profiles of these commonly used biologic agents. Further study is needed to determine whether the higher treatment retention and lower immunogenicity observed with ustekinumab could affect subsequent long-term efficacy. The results of this study support the use of safe and effective biologic agents for patients with moderately to severely active Crohn's disease early in the disease course and reinforce the need for direct active-comparator studies for inflammatory bowel disease treatment, rather than indirect comparisons.

Contributors

All authors met the International Committee of Medical Journal Editors criteria for authorship for this Article, take responsibility for the integrity of the work as a whole, were involved in drafting and critical review of the manuscript, and approved the final version for submission. All authors agree to be accountable for all aspects of the work and attest to the accuracy and integrity of the work. BES, PMI, TH, JLI, L-LG, CG, AG, MA, SD, SBH, TK, JDL, EVL, RP, ES, and WJS designed and conceived the study. BES, PMI, TH, JLI, L-LG, CG, AG, MA, SD, SBH, VJ, TK, JDL, EVL, EM, RP, ES, OBS, and WJS interpreted the data. BES, PMI, MA, SD, SBH, VJ, TK, JDL, EVL, EM, RP, ES, OBS, and WJS acquired the data. L-LG analysed the data. L-LG and TH accessed and verified the underlying data. All authors contributed to data interpretation and had access to the full datasets. Agreements between Janssen and the investigators included provisions relating to confidentiality of study data. All authors vouch for the accuracy and completeness of the data and analyses, as well as for the fidelity of this report to the study protocol, which is available from Janssen. All authors had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

BES reports consulting fees from 4D Pharma, AbbVie, Abivax, Allergan, Amgen, Arena Pharmaceuticals, Artugen Therapeutics, AstraZeneca, Baxalta Bioscience India, Boehringer Ingelheim, Boston Pharmaceuticals, Bristol Myers Squibb, Calibr, Capella Bioscience, Celltrion Healthcare, ClostraBio, Entera, Evommune, Ferring, Galapagos, Genentech, Gilead Sciences, GlaxoSmithKline, GossamerBio, Hoffmann-La Roche, HMP Acquisition, Immunic, InDex Pharmaceuticals, Innovation Pharmaceuticals, Inotrem, Ironwood Pharmaceuticals, Janssen, Johnson & Johnson, Kaleido, Kallyope, Lilly, Merck & Co, MiroBio, Morphic Therapeutic, Oppilan Pharma, OSE Immunotherapeutics, Otsuka, Palatin Technologies, Pfizer, Progenity, Prometheus Laboratories, Prometheus Biosciences IBD, Protagonist Therapeutics, Q32 Bio, Redhill Biopharma, Rheos Medicines, Salix Pharmaceuticals, Seres Therapeutics, Shire, Sienna Biopharmaceuticals, Sun Pharma, Surrozen, Takeda, TARGET RWE, Teva, TLL Therapeutics, USWM Enterprises, Viela Bio, Vivelix Pharmaceuticals; grants and consulting fees from Arena Pharmaceuticals, Celgene, and Theravance Biopharma; consulting fees and stock options from Ventyx Biosciences; and stock options from Vivante Health. PMI reports lecture fees from AbbVie, Celgene, Falk Pharma, Ferring, Janssen, MSD, Pfizer, Sapphire Medical, Sandoz, Shire, Takeda, Tillots, and Warner Chilcott; financial support for research from MSD, Pfizer, and Takeda; and advisory fees from AbbVie, Arena, Genentech, Gilead, Hospira, Janssen, Lilly, MSD, Pfizer, Pharmacosmos, Prometheus, Roche, Sandoz, Samsung Bioepis, Takeda, Topivert, VH2, Vifor Pharma, and Warner Chilcott. TH, JLI, L-LG, CG, and AG report employment with Immunology Global Affairs, Janssen Pharmaceutical Companies of Johnson & Johnson or Janssen Scientific Affairs, a wholly owned subsidiary of Johnson & Johnson, and stock ownership in Johnson & Johnson. MA reports consulting or lecture fees from AbbVie, Amgen, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Ferring, Genentech, Gilead, IQVIA, Janssen, Novartis, Pfizer, Roche, Takeda, and Tillots; and grant support from Innate Pharma, Janssen, Takeda, and Genentech/Roche. SD reports consulting or lecture fees from AbbVie, Alimentiv, Allergan, Amgen, AstraZeneca, Athos Therapeutics, Biogen, Boehringer Ingelheim, Celgene, Celltrion Healthcare, Enthera, Ferring Pharmaceuticals, Gilead Sciences, Hospira, Inotrem, Janssen, Johnson & Johnson, Lilly, MSD, Mundipharma, Mylan, Pfizer, Roche, Sandoz, Sublimity Therapeutics, Takeda, TiGenix, UCB, and Vifor International. SBH reports grant support and fees for consulting, lectures, and serving on an advisory board from AbbVie, Janssen, and Takeda; consulting or advisory board fees from Allergan, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Ferring, Genentech, Gilead, Merck, Novartis, Pfizer, Protagonist, Receptos, Salix, Samsung Bioepis, Seres Therapeutics, TiGenix, and Vhsquared; and grant support from AbbVie, Celgene, Boehringer Ingelheim, Gilead, Janssen, Pfizer, and Takeda. VJ reports consulting fees from AbbVie, Alimentiv, Arena Pharmaceuticals, Asahi Kasei Pharma, Asieris, Bristol Myers Squibb, Celltrion, Ferring, Fresenius Kabi, Galapagos, GlaxoSmithKline, Genentech, Gilead, Janssen, Lilly, Merck, Mylan, Pandion, Pendopharm, Pfizer, Protagonist, Reistone Biopharma, Roche, Sandoz, Second Genome, Takeda, Teva, and Topivert; and speaker's fees from AbbVie, Ferring, Galapagos, Janssen, Pfizer, Shire, and Takeda. TK reports lecture and consulting fees from AbbVie, Allmiral, Amgen, Arena, Bristol Myers Squibb, Celgene, Celltrion, Ferring, Falk, Gilead, Galapagos, Janssen, Merkle, Pfizer, Takeda, and Tillots. JDL reports consulting fees from Arena Pharmaceuticals, AbbVie, Bridge Biotherapeutics, Bristol Myers Squibb, Entasis Therapeutics, Gilead, Janssen, Lilly, Merck, Nestle Health Science, Pfizer, Protagonist Therapeutics, Samsung Bioepis, Scipher Medicine, and UCB; and research grants from AbbVie, Janssen, and Takeda. EVL Jr reports consulting fees from AbbVie, Amgen, Arena, Boehringer Ingelheim, Bristol Myers Squibb, Calibr, Celgene, Genentech, Gilead, Gossamer Bio, Iterative Scopes, Janssen, Lilly, Morphic, Ono Pharma, Pfizer, Protagonist, Scipher Medicine, Sun Pharma, Surrozen, Takeda, and UCB; and research support from AbbVie, Bristol Myers Squibb, Celgene, Genentech, Gilead, Gossamer Bio, Janssen, Pfizer, Receptos, Robarts Clinical Trials, Takeda, Theravance, and UCB. EM reports participation as an investigator in trials sponsored by Janssen. RP reports consulting fees from AbbVie, Abbott, Alimentiv, Amgen, Arena, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Celltrion, Cosmos Pharmaceuticals, Eisai, Elan, Ferring, Galapagos, Genentech, Gilead Sciences, GlaxoSmithKline, Janssen, Lilly, Merck, Mylan, Oppilan Pharma, Pandion Pharma, Pfizer, Progenity, Protagonist Therapeutics, Roche, Satisfai Health, Sandoz, Schering-Plough, Shire, Sublimity Therapeutics, Theravance, UCB, and Takeda; speaker fees from AbbVie, Arena, Celgene, Ferring, Gilead Sciences, Janssen, Lilly, Merck, Pfizer, Roche, Sandoz, Shire, and Takeda; research or educational support from AbbVie, Ferring, Janssen, Pfizer, and Takeda; and has served on advisory boards for AbbVie, Amgen, Arena, Bristol Myers Squibb, Celgene, Celltrion, Ferring, Galapagos, Genentech, Gilead Sciences, GlaxoSmithKline, Janssen, Lilly, Merck, Mylan, Oppilan Pharma,

Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en junio 17, 2022. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2022. Elsevier Inc. Todos los derechos reservados.

Pandion Pharma, Pfizer, Sandoz, Shire, Sublimity Therapeutics, Theravance, and Takeda. ES reports grant support from AbbVie, AstraZeneca, Celgene, Crohn's and Colitis Foundation, Genentech, Janssen Research & Development, New York Crohn's Foundation, Pfizer, Seres Therapeutics, and UCB; consulting fees from AbbVie, Abgenomics, Crohn's and Colitis Foundation, Evidera, GI Health Foundation, Janssen, Protagonist, Seres, and Takeda; stock ownership in Gilead; and speaker fees from GI Health Foundation and Prime Therapeutics. OBS reports participation as an investigator in trials sponsored by Janssen. WJS reports grants from AbbVie, Aviva, Arena Pharmaceuticals, Boehringer Ingelheim, Celgene, Genentech, Gilead Sciences, GlaxoSmithKline, Janssen, Lilly, Pfizer, Prometheus Biosciences, Seres Therapeutics, Shire, Takeda, and TheraVance Biopharma; consulting fees from AbbVie, Abivax, Admirx, Alfa sigma, Alimentiv, Alivio Therapeutics, Allakos, Allergan, Amgen, Applied Molecular Transport, Arena Pharmaceuticals, Avexegen Therapeutics, Bausch Health (Salix), BeiGene, Bellatrix Pharmaceuticals, Boehringer Ingelheim, Boston Pharmaceuticals, Bristol Myers Squibb, Celgene, Celltrion, Cellularity, Conatus, Cosmo Pharmaceuticals, Equillium, Escalier Biosciences, Ferring, Forbion, Genentech/Roche, Gilead Sciences, Glenmark Pharmaceuticals, Gossamer Bio, Immunic (Vital Therapies), Incyte, Index Pharmaceuticals, Intact Therapeutics, Janssen, Kyowa Kirin Pharmaceutical Research, Kyverna Therapeutics, Landos Biopharma, Lilly, Miraca Life Sciences, Nivalis Therapeutics, Novartis, Nutrition Science Partners, Oppilan Pharma (acquired by Ventyx Biosciences), Otsuka, Pandion Therapeutics, Paul Hastings, Pfizer, Progenity, Prometheus Biosciences, Prometheus Laboratories, Protagonists Therapeutics, Provention Bio, Reistone Biopharma, Ritter Pharmaceuticals, Seres Therapeutics, Shanghai Pharma Biotherapeutics, Shire, Shoreline Biosciences, Sienna Biopharmaceuticals, Sigmoid Biotechnologies, Sterna Biologicals, Sublimity Therapeutics, Surrozen, Takeda, Theravance Biopharma, Thetis Pharmaceuticals, Tigenix, Tillotts Pharma, UCB Pharma, Vendata Biosciences, Ventyx Biosciences, Vimalan Biosciences, Vivelix Pharmaceuticals, Vivreon Biosciences, and Zealand Pharma; stock or stock options from Allakos, BeiGene, Gossamer Bio, Oppilan Pharma (acquired by Ventyx Biosciences), Prometheus Biosciences, Prometheus Laboratories, Progenity, Shoreline Biosciences, Ventyx Biosciences, Vimalan Biosciences, and Vivreon Biosciences; and employment at Shoreline Biosciences.

Data sharing

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this website, requests for access to the study data can be submitted through the Yale Open Data Access project site at http://yoda.yale.edu.

Acknowledgments

The study was funded by Janssen Scientific Affairs. Holly Capasso-Harris (Certara Synchrogenix, Wilmington, DE, USA) provided writing and editorial assistance under the direction of the authors in accordance with Good Publications Practice guidelines. Writing assistance was funded by Janssen Scientific Affairs. Tony Ma (Janssen Scientific Affairs, Horsham, PA, USA) provided assistance with data analysis. Omoniyi J Adedokun (Janssen Research & Development, Spring House, PA, USA) provided assistance with data interpretation.

References

1 Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet* 2012; **380:** 1590–605.
2 Lichtenstein GR, Loftus EV Jr, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults. *Am J Gastroenterol* 2018; **113:** 481–517.
3 Sandborn WJ, Gasink C, Gao LL, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med* 2012; **367:** 1519–28.
4 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.
5 Feuerstein JD, Ho EY, Shmidt E, et al. AGA clinical practice guidelines on the medical management of moderate to severe luminal and perianal fistulizing Crohn's disease. *Gastroenterology* 2021; **160:** 2496–508.
6 Janssen Biotech. Stelara (ustekinumab) prescribing information. 2020. http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/STELARA-pi.pdf (accessed Oct 25, 2021).
7 AbbVie. Humira (adalimumab) prescribing information. 2021. https://www.rxabbvie.com/pdf/humira.pdf (accessed Oct 25, 2021).
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.
9 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:** 1232–39.
10 Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2016; **375:** 1946–60.
11 Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review and network meta-analysis: first- and second-line biologic therapies for moderate-severe Crohn's disease. *Aliment Pharmacol Ther* 2018; **48:** 394–409.
12 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.
13 Sandborn WJ, Feagan BG, Hanauer SB, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. *Gastroenterology* 2002; **122:** 512–30.
14 D'Incà R, Caccaro R. Measuring disease activity in Crohn's disease: what is currently available to the clinician. *Clin Exp Gastroenterol* 2014; **7:** 151–61.
15 Adedokun OJ, Xu Z, Gasink C, et al. Pharmacokinetics and exposure response relationships of ustekinumab in patients with Crohn's disease. *Gastroenterology* 2018; **154:** 1660–71.
16 Covance Laboratories. ELISA method for determination of adalimumab in human serum (ELISA-0682-006). Indianopolis: Covance Laboratories, 2021.
17 Covance Laboratories. Protocol on file for adalimumab assay. ECL method for the determination of antibodies to adalimumab in human serum (ECL-0424-002). Indianopolis: Covance Laboratories, 2021.
18 US Food and Drug Administration. Immunogenicity testing of therapeutic protein products—developing and validating assays for anti-drug antibody detection. 2019. https://www.fda.gov/media/119788/download (accessed Aug 27, 2021).
19 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.
20 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 Crohn's Colitis* 2013; **7:** 213–21.
21 Alosh M, Bretz F, Huque M. Advanced multiplicity adjustment methods in clinical trials. *Stat Med* 2014; **33:** 693–713.
22 Melsheimer R, Geldhof A, Apaolaza I, Schaible T. Remicade (infliximab): 20 years of contributions to science and medicine. *Biologics* 2019; **13:** 139–78.
23 Ahmed Z, Venkata K, Zhang N, Malik TA. Comparative effectiveness of ustekinumab versus adalimumab in induction of clinical response and remission in Crohn's disease: experience of a real-world cohort at a tertiary care inflammatory bowel disease referral center. *Gastroenterol Res* 2019; **12:** 245–51.
24 Manlay L, Boschetti G, Pereira B, et al. Comparison of short- and long-term effectiveness between ustekinumab and vedolizumab in patients with Crohn's disease refractory to anti-tumour necrosis factor therapy. *Aliment Pharmacol Ther* 2021; **53:** 1289–99.
25 Townsend T, Razanskaite V, Dodd S, et al. Comparative effectiveness of ustekinumab or vedolizumab after one year in 130 patients with anti-TNF-refractory Crohn's disease. *Aliment Pharmacol Ther* 2020; **52:** 1341–52.
26 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.
27 AbbVie. Humira (adalimumab); summary of product characteristics. 2008. https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_en.pdf (accessed July 7, 2021).

Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en junio 17, 2022. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2022. Elsevier Inc. Todos los derechos reservados.

28 Dalal RS, Njie C, Marcus J, Gupta S, Allegretti JR. Predictors of ustekinumab failure in Crohn's disease after dose intensification. *Inflamm Bowel Dis* 2021; **27:** 1294–301.

29 Haider SA, Yadav A, Perry C, et al. Ustekinumab dose escalation improves clinical responses in refractory Crohn's disease. *Therap Adv Gastroenterol* 2020; **13:** 1756284820959245.

30 D'Haens GR, Sandborn WJ, Loftus EV Jr, et al. Higher *vs* standard adalimumab induction dosing regimens and 2 maintenance strategies: randomized SERENE CD trial results. *Gastroenterol* 2022; published online Feb 3. https://doi.org/10.1053/j.gastro.2022.01.044.

31 Matsumoto T, Motoya S, Watanabe K, et al. Adalimumab monotherapy and a combination with azathioprine for Crohn's disease: a prospective, randomized trial. *J Crohn's Colitis* 2016; **10:** 1259–66.

32 Targownik LE, Benchimol EI, Bernstein CN, et al. Combined biologic and immunomodulatory therapy is superior to monotherapy for decreasing the risk of inflammatory bowel disease-related complications. *J Crohn's Colitis* 2020; **14:** 1354–63.

33 Cosnes J, Sokol H, Bourrier A, et al. Adalimumab or infliximab as monotherapy, or in combination with an immunomodulator, in the treatment of Crohn's disease. *Aliment Pharmacol Ther* 2016; **44:** 1102–13.

34 Targownik LE, Benchimol EI, Bernstein CN, et al. Upfront combination therapy, compared with monotherapy, for patients not previously treated with a biologic agent associates with reduced risk of inflammatory bowel disease-related complications in a population-based cohort study. *Clin Gastroenterol Hepatol* 2019; **17:** 1788–98.

35 Kopylov U, Al-Taweel T, Yaghoobi M, et al. Adalimumab monotherapy versus combination therapy with immunomodulators in patients with Crohn's disease: a systematic review and meta-analysis. *J Crohn's Colitis* 2014; **8:** 1632–41.

36 Obando C, Ding Z, Muser E, et al. Persistence, dose titration, and health care resource utilization among Crohn's disease patients treated with ustekinumab: a real-world analysis in the United States. *Adv Ther* 2020; **37:** 2127–43.

37 Teeple A, Sah J, Mallampati R, Adams C, Waters D, Muser E. Treatment patterns in biologic-experienced Crohn's disease patients using three large commercial claims databases in the United States. *Gastroenterol* 2021; **160:** S696–97.

38 Ko Y, Paramsothy S, Yau Y, Leong RW. Superior treatment persistence with ustekinumab in Crohn's disease and vedolizumab in ulcerative colitis compared with anti-TNF biological agents: real-world registry data from the Persistence Australian National IBD Cohort (PANIC) study. *Aliment Pharmacol Ther* 2021; **54:** 292–301.

39 Ding Z, Obando C, Muser E, Kozma C, Slaton T. Real-world persistence, maintenance dosing, and pre-post corticosteroid and opioid use among Crohn's disease patients with prescription claims for ustekinumab in the USA. *Drugs Real World Outcomes* 2021; **8:** 565–75.

Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en junio 17, 2022. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2022. Elsevier Inc. Todos los derechos reservados.