Association Between Ustekinumab Trough Concentrations and Clinical, Biomarker, and Endoscopic Outcomes in Patients With Crohn’s Disease

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BACKGROUND & AIMS: Ustekinumab, an inhibitor of the p40 subunit of interleukins 12 and 23, is an effective treatment for patients with Crohn’s disease (CD). Trough concentrations of tumor necrosis factor (TNF) antagonists and presence of anti-drug antibodies are associated with important clinical and endoscopic outcomes. We investigated associations between trough concentrations of ustekinumab and clinical, biomarker, and endoscopic outcomes of real-world patients with CD.

METHODS: We recruited 62 patients with CD who were either refractory or intolerant to TNF antagonists, treated with ustekinumab from April 2014 to September 2015. Patients received 90 mg of ustekinumab subcutaneously at weeks 0, 1, and 2 during induction and 90 mg every 4 or 8 weeks during maintenance. Clinical, biomarker, and endoscopic outcomes, trough concentrations of ustekinumab, and anti-drug antibodies were assessed at both week 10 postinduction therapy and at week 26 or later during maintenance therapy in a prospective longitudinal patient cohort or at week 26 or later during maintenance therapy in a cross-sectional patient cohort. Analysis was performed on data combined from both maintenance cohorts, which had similar outcomes at week 26 or later. A primary analysis determined if ustekinumab drug trough concentrations were associated with clinical response (reduction in Harvey Bradshaw Index score of 3 or greater), clinical remission (Harvey Bradshaw Index score < 5), steroid-free clinical remission, biomarker (serum level of C-reactive protein [CRP] or level of fecal calprotectin) reduction, biomarker normalization (serum level of CRP below 5 mg/L or level of fecal calprotectin below 200 μg/g), endoscopic response (simple endoscopic score for CD reduced by 50% or more), or endoscopic remission (simple endoscopic score for CD of 2 or less).

RESULTS: At week 26 or beyond, 80.7% of patients had a clinical response, 66.1% were in clinical remission, 50.0% were in steroid-free clinical remission, 58.9% had an endoscopic response, and 19.6% were in endoscopic remission. The mean trough concentration of ustekinumab at this time point was higher in patients with an endoscopic response (4.7 μg/mL) than without (3.8 μg/mL; P = .03). An optimal ustekinumab threshold trough concentration at week 26 or later was found to be 4.5 μg/mL (area under the curve, 0.67). A greater proportion of patients with trough concentrations of ustekinumab above 4.5 μg/mL at week 26 or later had an endoscopic response (75.9%) than did patients with trough concentrations below this level (40.7%; P = .008). Patients with trough concentrations of ustekinumab above 4.5 μg/mL at week 26 or later also had a lower mean level of CRP (12.6 mg/L) than did patients with trough concentrations below this level (mean level of CRP, 23.9 mg/L; P = .04). We did not detect antibodies against ustekinumab in any patient.

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Abbreviations used in this paper: CD, Crohn’s disease; CRP, C-reactive protein; FC, fecal calprotectin; HBI, Harvey Bradshaw Index; IBD, inflammatory bowel disease; IV, intravenous; Q4, every 4; Q8, every 8; SES-CD, Simple Endoscopic Score for Crohn’s Disease; SC, subcutaneous; TDM, therapeutic drug monitoring; TNF, tumor necrosis factor; UST, ustekinumab.
CONCLUSIONS:

Ustekinumab therapy was effective in patients with CD who had not responded to or were intolerant to treatment with a TNF antagonist. Maintenance trough concentrations of ustekinumab above 4.5 μg/mL at 26 weeks or later were associated with biomarker reduction and endoscopic response.

Keywords: Biologic; Inflammatory Bowel Disease; Therapeutic Drug Monitoring; UNITI.

Crohn’s disease (CD) is a chronic debilitating inflammatory bowel disease. In patients receiving anti–tumor necrosis factor (anti-TNF) medications, up to two-thirds have either primary nonresponse or secondary loss of response. Overexpression of the p40 subunits of proinflammatory cytokines interleukin 12 and interleukin 23 has been implicated in the pathogenesis of CD. Ustekinumab (UST) (Stelara; Janssen Biotech, Inc, Horsham, PA) is a fully human IgG1 monoclonal antibody that blocks the biologic activity of interleukin 12 and interleukin 23 through their common p40 subunit. UST was recently approved for the treatment of CD in the United States.

In a phase 2a placebo-controlled trial either subcutaneous (SC) (90 mg) or intravenous (IV) UST at weeks 0, 1, 2, and 3 induced clinical response at week 8. In a phase 2b placebo-controlled trial, IV (6 mg/kg) UST at weeks 0 and 8 induced greater clinical remission at week 8. In successfully induced patients, 90 mg SC every 8 (Q8) weeks achieved greater clinical response and remission during maintenance at 22 weeks. Antibody development to UST was rare (0.7%).

A retrospective observational study found UST 90 mg SC induction at weeks 0, 1, and 2, followed by maintenance UST 90 mg SC every 4 (Q4) or Q8 weeks was clinically effective for anti-TNF refractory, moderate to severe CD patients. Others have also demonstrated efficacy with SC UST as well as with intensification of therapy.

Two double-blind, phase 3 placebo-controlled studies investigated UST induction therapy for moderate-to-severe CD (Study to Evaluate the Safety and Efficacy of Ustekinumab in Patients With Moderately to Severely Active Crohn’s Disease, UNITI). These studies were conducted in anti-TNF refractory or intolerant patients (UNITI-1) and anti-TNF naïve patients (UNITI-2). UST 130 mg IV and UST 6 mg/kg IV, in both trials, demonstrated greater clinical response and remission at weeks 3, 6, and 8. In IM-UNITI, a phase 3 maintenance trial, moderate-to-severe CD patients with clinical response in the UNITI-1 and UNITI-2 studies were randomized to receive UST 90 mg SC or placebo Q8 or Q12 weeks. Treatment groups had greater continued clinical response and remission at week 44. In a UNITI substudy, maintenance Q8 week UST demonstrated endoscopic response at week 44.

Anti-TNF trough and anti-drug antibody concentrations are associated with important outcomes in inflammatory bowel disease (IBD). The UNITI-1, UNITI-2, and IM-UNITI trial pharmacokinetic data demonstrated a drug concentration dose response with clinical remission rates at 1 year. Antibodies to UST were rare (2.3%) at 1 year. Biomarker and endoscopic pharmacokinetic data are currently unavailable.

Our study aimed to investigate the relationship between UST trough concentrations and anti-UST antibodies with clinical, biomarker, and endoscopic outcomes in a real-world setting.

Methods

Patients

Consecutive adult moderate-to-severe CD patients who were anti-TNF refractory or intolerant were assessed. Patients initiating or already being treated with UST were recruited from April 2014 to September 2015 at the McGill University Health Centre and the Jewish General Hospital, in Montreal, Canada.

Study Design

Two patient cohorts were analyzed. A longitudinal cohort prospectively received UST 90 mg SC induction at weeks 0, 1, and 2, followed by UST 90 mg SC maintenance Q8 weeks. After week 10, treating physicians were permitted to escalate the frequency to Q4 weeks if inadequate clinical response was seen. Baseline, week 10, and week 26 clinical outcomes (Harvey Bradshaw Index [HBI]), C-reactive protein (CRP), and fecal calprotectin (FC) were assessed. Patients had routine endoscopic assessment prior to treatment and after week 26, using the Simple Endoscopic Score for Crohn’s Disease (SES-CD). Mean time of endoscopy was 18.4 ± 18.4 weeks prior to UST initiation and 30.9 ± 9.4 weeks after UST initiation. Blood sample collection blinded to clinical activity at baseline, week 10, and week 26 assessed UST trough and anti-UST antibody concentrations prior to injection.

A cross-sectional cohort, already on UST ≥26 weeks (mean 63 ± 34.9 weeks), at a 1-time visit, had clinical (HBI) and biomarker (CRP/FC) assessment completed. Baseline (prior to treatment) and post-treatment clinical, biomarker, and endoscopic data were extracted from electronic medical records. Mean time of endoscopy was 22.9 ± 31.2 weeks prior to treatment and 71.8 ± 33.2 weeks after UST initiation. Blood samples were collected for UST trough and anti-UST antibody concentrations at this visit.