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Predictors and outcomes of ustekinumab dose intensification in ulcerative colitis: a multicenter cohort study

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Keywords

ulcerative colitis; inflammatory bowel disease; ustekinumab; LOR; dose escalation; optimization

Introduction

Ustekinumab has been shown to be effective for the treatment of ulcerative colitis (UC), however >40% of patients have suboptimal clinical response after induction and maintenance dosing every 8 weeks (q8w).[1, 2] The best management approach for these patients is unclear. Many undergo empiric dose intensification to q4w or q6w, a non-standardized decision due to limited data supporting therapeutic drug monitoring of ustekinumab.[3] In Crohn's disease (CD), approximately 50% of patients undergo ustekinumab dose intensification, which appears to be effective based on prior work from our group and others.[4–8] However, similar data in UC is lacking. In this real-world multicenter cohort study, we sought to identify predictors and outcomes of ustekinumab dose intensification in UC.

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Methods

Study design

This retrospective cohort study included adults with UC (ICD-10-CM 51x) initiating ustekinumab at Brigham and Women's Hospital, Massachusetts General Hospital, or the University of North Carolina, Chapel Hill between 1/1/2016–11/1/2020. Patients with prior colectomy or those treated primarily for non-UC indications were excluded. Electronic health records were reviewed for clinical data. Disease activity was documented using either the simple clinical colitis activity index (SCCAI) or partial Mayo score. (Supplementary Methods).

Independent variables

Independent variables included demographics, UC duration, extraintestinal manifestations, substance use, endoscopic extent/severity, prior/current UC medications, primary documented justification for intensification, intravenous (IV) reinduction, dose interval, and the most recent body mass index, albumin, C-reactive protein, and bowel frequency recorded within 12 weeks prior to intensification (Supplementary Methods).

Outcomes

The primary outcome was corticosteroid-free clinical remission (i.e. "remission," SCCAI/Mayo < 3 points and no oral/IV corticosteroid use for ≥4 weeks) at evaluation 12–16 weeks after intensification. Secondary outcomes were clinical response (i.e. "response," reduction in SCCAI/Mayo by ≥3 points from baseline) at 12–16 weeks and time-to-intensification. See Supplementary Methods for additional endpoints.

Statistical analysis

Logistic and Cox Proportional Hazards regression were used to identify variables associated with remission and time-to-intensification, respectively. Variables with $p<0.10$ on univariable analysis were included in multivariable analyses. Covariates with $p<0.05$ on multivariable analysis were considered significant (Supplementary Methods).

Results

A total of 108 patients with UC initiated ustekinumab: 56.5% were female, 91.7% had prior anti-TNF exposure, 39.8% had >2 prior biologic exposures, and 57.4% were taking oral corticosteroids (Supplementary Table 1). Among these, 39.6% (40/101 with SCCAI/Mayo data) achieved remission 12–16 weeks after induction.

42.6% (46/108) required intensification to q4w (n=33) or q6w (n=13) after a median of 95 days (IQR 65–208 days) primarily for no/minimal response to induction (22/46) or loss of response (LOR; 20/46) (Figure 1A). IV reinduction doses were administered to 4/46 preceding intensification. At 12–16 weeks after intensification, 55.0% (22/40 with SCCAI/Mayo data) achieved remission and 67.5% (27/40) achieved response. 30.0% (12/40) had drug discontinuation or colectomy within 16 weeks after intensification (Figure 1B). Among these, 10/12 had no/minimal response to induction and 2/12 had LOR. Over a median

follow-up of 230 days (IQR 137–623 days) after intensification, 56.3% (9/16 with pre/post-intensification data) had improvement in endoscopic inflammation and fecal calprotectin (Supplementary Table 2A), 10.0% (4/40) had IBD-related hospitalization, and 5.0% (2/40) had adverse events (urinary tract infection and *C. difficile* infection).

After multivariable analysis, no/minimal response to induction (OR 0.2, 95% CI 0.04–0.7) was inversely associated with remission after intensification. Bowel frequency (HR 1.1, 95% 1.02–1.2) and >2 prior biologic exposures (HR 2.5, 95% 1.1–5.8) were associated with time-to-intensification (Supplementary Table 2B).

Discussion

Nearly 40% of UC patients in our multicenter study achieved remission after ustekinumab induction. However >40% required intensification, which was associated with higher daily bowel frequency and >2 prior biologic exposures. Similar to our findings in CD[6], >50% of dose-intensified patients achieved corticosteroid-free remission, however patients with minimal/no response to induction had lower odds of remission after intensification. We observed no significant differences between q4w and q6w dosing, however larger studies are needed for this comparison.

The strengths of the study include utilization of an entire multicenter cohort of ustekinumab users to assess both predictors and comprehensive outcomes of dose intensification. Limitations include a small sample of dose-intensified patients precluding subgroup analyses. The variability in timing of colonoscopies also limits conclusions regarding endoscopic response. Long-term outcomes are lacking, which is largely due to the recent FDA approval of ustekinumab for UC in October 2019.

In summary, ustekinumab dose intensification appears to be safe and effective for patients with UC. This strategy may be more effective among patients with LOR to q8w dosing rather than those with no response after induction. Prospective studies may identify specific subpopulations that would benefit from different optimization strategies of ustekinumab in UC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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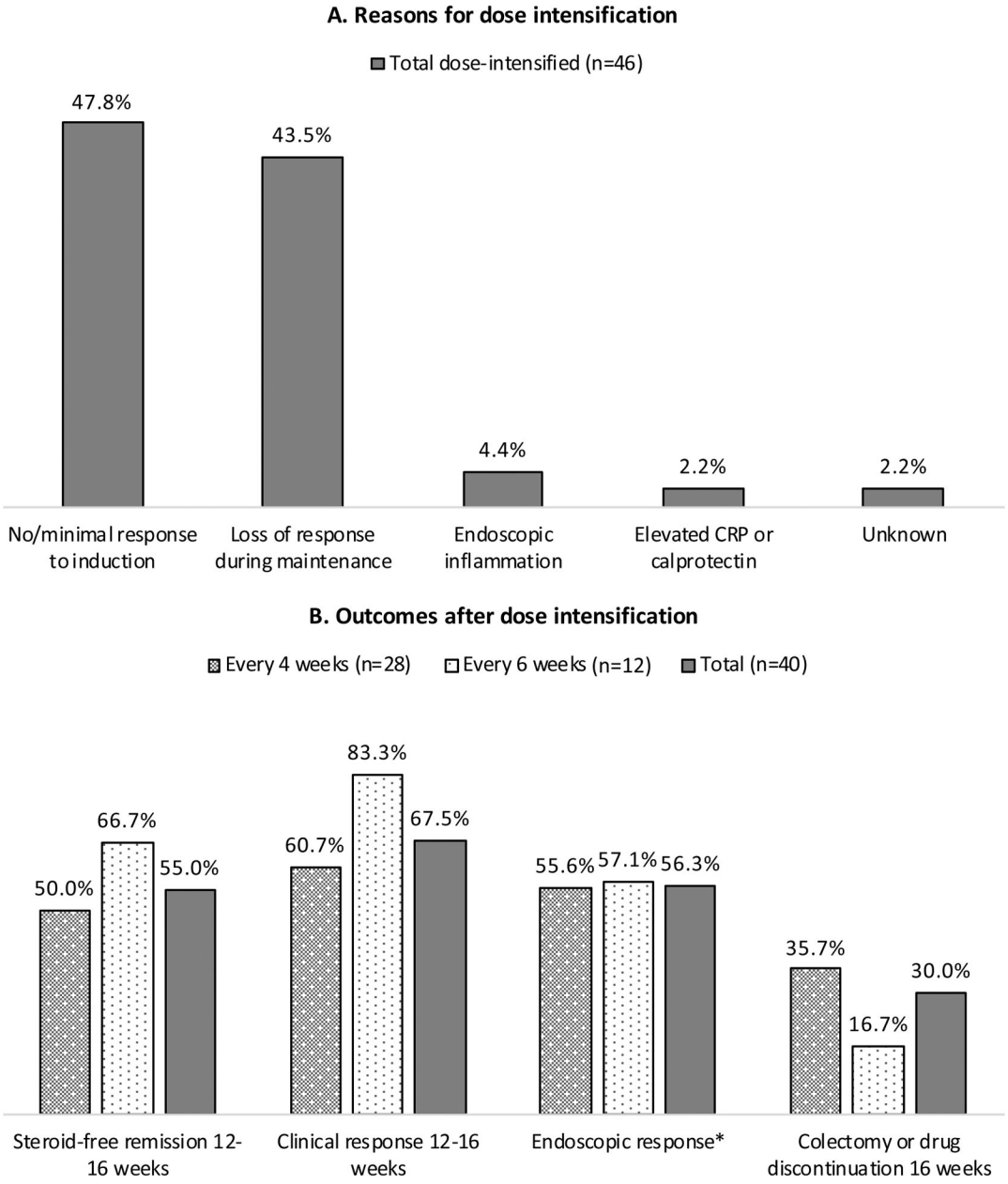

Figure 1. Reasons for dose-intensification (A) and outcomes after dose-intensification (B)

Clinical follow-up data after dose-intensification was available for 40/46 patients.

There were no significant differences between q4w and q6w outcomes using $p<0.05$ by Fisher's exact test

*Post-intensification endoscopic data was available for n=9 for q4w, n=7 for q6w.