1.0 Abstract

Title

A Cohort Study to Evaluate the Effectiveness of Drug Concentrations in **P**redicting **R**ecapture of Response with Weekly **ADA**limumab in Crohn's Disease Patients with Secondary Loss of Response (**PRADA**)

Keywords

Adalimumab; Crohn's disease; observational; recapture of response; secondary loss of response

Rationale and Background

Up to 40% of patients with Crohn's disease (CD) who initially respond to a tumor necrosis factor (TNF)-antagonist may experience loss of response (LOR) within one year. Current publications on monitoring of trough serum adalimumab and anti-adalimumab antibody (AAA) concentrations have identified 3 categories of patients with CD with LOR: 1) those with undetectable drug concentrations and negative AAAs; 2) those with undetectable drug concentrations and positive AAAs; 3) those with therapeutic drug concentrations. While patients with undetectable drug concentrations and negative for AAAs are often treated with increased drug dosing, it is unclear whether there is a drug concentration above which no additional therapeutic benefit can be attained. Determining such a threshold concentration for adalimumab may reduce the occurrence of ineffective dose escalation or inappropriate switch.

Research Question and Objectives

The primary objective of this study was to explore the relationship between recapture of response with escalation to weekly adalimumab and trough adalimumab concentration before escalation in patients experiencing LOR. LOR was defined as the presence of active inflammation (confirmed with a C-reactive protein [CRP] $\geq$ 5 mg/L and/or a fecal calprotectin [FC] $\geq$ 250 μg/g). The threshold trough concentration of

adalimumab in patients with LOR that predicts non-recapture of response at Week 12 with weekly adalimumab was planned to be determined.

Study Design

This was a multi-center prospective observational cohort study.

Setting

A total of 100 patients experiencing LOR were planned to be recruited from approximately 30 investigative sites in Canada, where such therapeutic drug monitoring (TDM)/AAA testing at the point of patient LOR and pre-dose escalation to every week (EW) occurs. Gastroenterologists who treat patients with CD and who were able to appropriately conduct this study were selected to participate.

Patients and Study Size, Including Dropouts

The study population was to be adult patients (18 years of age or older) with a documented diagnosis of CD who had received treatment with adalimumab, for a minimum of 16 weeks, as per clinical practice, at a dose of 160 mg at Week 0, 80 mg at Week 2, and then 40 mg every other week (EOW) with a documented response as defined by the investigator. Patients were to have current evidence of active inflammatory disease/LOR, defined as the presence of active inflammation (confirmed with a CRP $\geq$ 5 mg/L and/or a FC $\geq$ 250 μg/g). Patients were able to participate fully in all aspects of this clinical trial and provided written informed consent.

A patient was not eligible for study participation if they were primary non-responders to 16 weeks of adalimumab therapy, if they had received any investigational drug within the 16 weeks of adalimumab therapy; had a serious underlying disease other than CD that, in the opinion of the investigator, may have interfered with the patient's ability to participate fully in the study; had a history of alcohol or drug abuse that, in the opinion of the investigator, may have interfered with the patient's ability to comply with the study procedures; or had stools positive for *Clostridium difficile*.

Variables and Data Sources

The endpoints to evaluate the effectiveness of drug concentrations in predicting recapture of response with weekly adalimumab in patients with CD with secondary LOR included:

- Primary endpoint: proportion of patients who did not respond to dose escalation (non-recapture of response) following escalation to weekly adalimumab and the relationship to baseline trough adalimumab concentration. Recapture of response was defined as a 50% decrease in either CRP or FC from screening and/or normalization of CRP (< 5 mg/L) or FC (< 150 μg/g) at Week 12.

- Secondary endpoints:

    1. Factors associated with non-recapture of response and baseline adalimumab trough concentrations. Baseline factors included sex, disease severity, baseline immunomodulator therapy, corticosteroids at baseline, body mass index, albumin, hemoglobin, and antibody status.

    2. Relationship between clinical response/remission endpoints at Week 12 and baseline adalimumab trough concentrations. Response/remission endpoints included clinical remission (2-Item Patient-reported Outcome [PRO2] <8), normalization of CRP (< 5 mg/L) or FC (< 150 μg/g), a substantial decrease (50% drop) from screening in CRP or FC, and *de novo* steroid therapy or additional therapy.

    3. Changes in CD markers and relationship to baseline adalimumab trough concentrations.

    4. Changes in CD markers and relationship to final adalimumab trough concentrations.

- Other endpoints: descriptive statistics for Harvey Bradshaw Index (HBI), PRO2, CRP, FC, albumin, and adalimumab concentrations at baseline and Week 12, along with the change from baseline.

Safety variables: serious adverse events (SAEs), any non-serious event of malignancy in patients 30 years of age and younger, adverse event leading to discontinuation of the prescribed treatment under observation, unusual failure in efficacy, and pregnancy.

Results

- A total of 97 patients were enrolled in the study and analyzed in the report as the intent-to-treat (ITT) population, which was defined as patients who received at least 1 dose of adalimumab.

- Half (49.5%) of patients with LOR at baseline recaptured response at Week 12 after an increase in the frequency of adalimumab to weekly dosing.

- In 49 (50.5%) patients who did not recapture response, there was no apparent relationship between baseline trough concentration and non-recapture of overall response (odds ratio [OR] 0.98; 95% confidence interval [CI]: 0.91, 1.06, P = .626). Similarly, for subgroups with CRP, or FC elevated at baseline, there was no apparent relationship with trough concentration and non-recapture of response.

- The observed increase in adalimumab trough levels, following dose escalation, was similar in both responders and nonresponders. For patients who did not recapture response, the mean change in adalimumab trough concentration from baseline to Week 12 was not statistically significantly associated with non-recapture of response.

- The threshold trough concentration level that predicts non-recapture of response at Week 12 was < 19.9 μg/mL, but with sensitivity and specificity of 100.0% and 0.0%, respectively, and a non-significant AUC value, for the overall non-recapture of response definition (neither CRP nor FC recaptured after either elevated at

baseline). The threshold trough concentrations that predict non-recapture of response for the CRP or FC definitions could not be determined.

- No statistically significant associations were found between baseline adalimumab trough concentration and clinical remission, CRP normalization, FC normalization, or substantial decrease in CRP or FC at Week 12.

- A statistically significant association between baseline adalimumab trough concentration and *de novo* steroid therapy at Week 12 was observed (OR 0.70; 95% CI: 0.56, 0.87 P = .002), suggesting that a higher baseline adalimumab trough level was associated with a lower chance of starting steroid therapy following dose escalation.

- There were no statistically significant correlations between baseline adalimumab trough concentrations and change in any of the clinical observations (PRO2, CRP, FC, or HBI).

- There were no statistically significant correlations between final adalimumab trough concentrations and change in the clinical observations (PRO2, FC, or HBI), with the exception of a small linear negative correlation between the change in CRP and the final trough concentration, suggesting a high final adalimumab trough concentration is associated with a lower CRP level.

- No new adalimumab safety signals were detected in the study.

Discussion

Study P15-770 was a real-world post-marketing observational study and intended to be descriptive. Limitations of observational studies, such as missing data, may have an impact on results. However, the overall completion rate in this study was high (n=85, 87.6%).

In this P15-770 study, after an increase to weekly dosing of adalimumab, it was observed that trough levels increase over time and that approximately half of patients

were able to recapture response. The observed increase in adalimumab trough levels, following dose escalation, was similar in both responders and nonresponders. This study did not show that we can predict which patients will be most likely to recapture response based on trough levels at the time of LOR, and the increase in trough levels with the dose escalation was not predictive of recapture of response.

As Study P15-770 was an observational study of less than 100 patients, the generalisability is limited. Discussion points follow:

- Duration of disease was not capped, so the population included patients with longstanding disease (up to 41 years).
- Some patients with LOR based on elevated inflammatory biomarker definition were only mildly symptomatic, clinically, highlighting the potential disconnect between symptoms and inflammation.
- There are known differences between assays and laboratories so absolute TDM values reported here may not reflect what would have been seen with other assays or laboratories.

Marketing Authorisation Holder(s)

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Names and Affiliations of Principal Investigators

The study investigators were from 22 Canadian centers. A list of physicians with site information is presented in the study report (see Section 3.0).