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Concentrations of Ustekinumab During Induction Therapy Associate With Remission in Patients With Crohn's Disease

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Abbreviations: Crohn’s disease: CD; Area under the receiver operating characteristic curve: AUROC; Figure: Fig; Week: W; Anti-Tumor Necrosis Factor: Anti-TNF; C-reactive protein: CRP; Harvey-Bradshaw index: HBI; Sensitivity: Sen; Specificity: Spe; Positive predictive value: PPV; Negative predictive value: NPV; Interquartile range: IQR.

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Introduction

Ustekinumab is approved for treatment of Crohn's disease (CD) (1,2). Few data are available to assess the usefulness of monitoring inflammatory biomarkers and therapeutic drug monitoring (TDM) to predict response to ustekinumab. We conducted a prospective study to assess the relationships between these parameters and the clinical outcome at week (W) 16 in active CD patients under ustekinumab.

Methods

Fifty-one active luminal CD patients who had failed anti-TNF (100%) and vedolizumab (71%) were prospectively included. Patients had a Harvey-Bradshaw Index (HBI) > 5 with CRP > 5 mg/L and/or fecal calprotectin (fCal) > 250 µg/g of stools. All patients received an initial intravenous infusion of ustekinumab at W 0 according to the body weight followed by subcutaneous injections of 90 mg ustekinumab every W 8. At W 0, 4, 8 and 16 disease activity assessed by the HBI was recorded and blood and stool samples were collected. Ustekinumab serum trough levels (TL) were measured by a commercially bridging ELISA assay (LISA-TRACKER, Theradiag, France) and fCal by a commercially available ELISA assay (Bühlmann, Switzerland). Patients who failed to achieve a steroid-free clinical and biochemical remission (HBI ≤ 4 points with CRP < 5mg/L and fCal < 250 µg/g) at W 16 were considered as primary non-responders (PNR). W 16 was chosen to assess the outcome of ustekinumab induction since it included also the delayed responders to ustekinumab, as previously demonstrated in the IM-UNITI trial (3). Quantitative data were expressed as medians and interquartile ranges (IQR). Comparisons of CRP, fCal and ustekinumab concentrations over time were analyzed with a one-way analysis of variance. A receiver operating characteristic (ROC) curve analysis was performed to calculate the sensitivity, specificity and the area under the ROC curve (AUROC). The best cutoff value was generated according to the maximal value of sensitivity plus specificity.

Results

At W 16, 32 patients (63%) achieved a steroid-free clinical and biochemical remission. The median ustekinumab TL were 10.0 µg/mL [IQR₂₅₋₇₅: 7.9-22.0], 5.0 µg/mL [IQR₂₅₋₇₅: 1.3-7.7] and 1.6 µg/mL [IQR₂₅₋₇₅: 0.9-5.1] at W 4, 8 and 16, respectively. At W 8, median ustekinumab TL became significantly higher in responders compared with PNR (6.0 µg/mL [IQR₂₅₋₇₅: 3.1-8.0] vs 1.3 µg/mL [IQR₂₅₋₇₅: 0.9-5.6] p=0.03). Trough concentrations of ustekinumab of 2.0 µg/mL or greater at W 8 were associated with response to induction therapy. fCal dropped significantly over time exclusively in responders: at W 0, 4, 8 and 16 median fCal levels were respectively 1612 µg/g of stools [IQR₂₅₋₇₅: 333-5828], 374 µg/g [IQR₂₅₋₇₅: 131-1002], 339 µg/g [IQR₂₅₋₇₅: 218-870] and 224 µg/g [IQR₂₅₋₇₅: 112-835] (p=0.006) in responders, and 1102 µg/g [IQR₂₅₋₇₅: 390-2222], 984 µg/g [IQR₂₅₋₇₅: 263-1490], 814 µg/g [IQR₂₅₋₇₅: 309-1658] and 437 µg/g [IQR₂₅₋₇₅: 179-805] (p=0.36) in PNR. In contrast, CRP did not change significantly from W 0 to W 16 in both responders and PNR. Monitoring CRP and fCal in addition with ustekinumab concentrations did not provide an added value to predict response to induction therapy. The respective performances (AUROC) of CRP, fCal and ustekinumab TL over time to predict response to induction therapy, as well as their sensitivities, specificities, positive and negative predictive values according to the optimal cutoff points are reported in Table.

Discussion

As previously showed in a cross-sectional and a longitudinal cohort study (4) and in pivotal induction and maintenance studies (5), the present real-life study reports a positive relationship between ustekinumab TL and disease outcomes during ustekinumab therapy. The optimal drug trough concentrations > 2.0 µg/mL measured at W 8 enabled to predict response to induction therapy at W 16. Our findings differ from those found in previous studies in which the optimal thresholds were higher than 4.5 µg/mL at W 26 or later for achieving endoscopic response (4) and 3.3 µg/mL at W 8 for achieving remission (5). Distinct time points of drug and disease outcome assessments, different assays of measuring ustekinumab, distinct patient population, and finally the lack of endoscopic data in our cohort (even if fCal monitoring was available) may explain such differences. We also acknowledge that the relative small sample size and the short period of follow-up represent substantial limitations. In

addition, the fast and early (as soon as W 4) drop of fCal only in responders to ustekinumab during induction regimen confirms the value of this biomarker, as previously demonstrated in inflammatory bowel disease with anti-TNF (6-8).

In conclusion, TDM is useful to identify early PNR CD patients during ustekinumab induction therapy. The benefit of ustekinumab dose escalation in these patients warrants to be further investigated in dedicated studies.

Table. Areas under the receiver operating characteristic curves, sensitivities, specificities, positive and negative predictive values of serum C-reactive protein, fecal calprotectin and ustekinumab trough levels over time at weeks 4, 8 and 16 after ustekinumab infusion to distinguish between primary non-responders and responders to ustekinumab induction therapy. Serum and fecal samples were available for analysis in all patients (n=51) at each time point.

		AUROC	CI 95 %	<i>P</i> values	Optimal cutoff	Sen (%)	Spe (%)	PPV (%)	NPV (%)
CRP	Week 4	0.55	0.36-0.74	0.53	3.9 mg/mL	51	58	46	77
	Week 8	0.64	0.44-0.83	0.18	5.4 mg/mL	55	77	28	47
	Week 16	0.51	0.28-0.73	0.90	9.5 mg/mL	58	50	31	61
fCal	Week 4	0.62	0.41-0.84	0.24	250 µg/g	41	75	50	72
	Week 8	0.57	0.34-0.80	0.50	250 µg/g	33	81	43	77
	Week 16	0.55	0.25-0.85	0.42	250 µg/g	53	80	33	90
Ustekinumab TL	Week 4	0.62	0.39-0.85	0.25	13.0 µg/mL	66	63	59	35
	Week 8	0.75	0.53-0.96	0.04	2.0 µg/mL	87	66	82	75
	Week 16	0.77	0.57-0.98	0.03	1.4 µg/mL	77	75	90	66

Abbreviations: CRP, C-reactive protein; fCal: fecal calprotectin; Ustekinumab TL: ustekinumab trough levels; ROC:

receiver operating characteristic; AUROC: Area under the ROC curve; CI 95%: Confidence interval 95%; Sen: Sensitivity; Spe: Specificity.

p values compared to baseline

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