Abstract / Povzetek predavanja

Week 4 ustekinumab serum concentration is associated with early and late endoscopic improvement in patients with ulcerative colitis – results from a prospective observational study

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BACKGROUND

Healing of colonic mucosa is an important goal of ulcerative colitis (UC) treatment.

Ustekinumab, an interleukin (IL)-12/23 inhibitor, is one of the therapeutic options for patients with moderate to severe UC. The exposure–response relationship between ustekinumab and endoscopic improvement is not well studied in real-life settings.

AIM

We studied the correlation between early ustekinumab serum concentrations and endoscopic improvement in UC.

MATERIAL AND METHODS

This was a prospective, observational, single-center study at the Department of Gastroenterology, University Medical Centre Ljubljana. UC patients initiating ustekinumab therapy had their serum ustekinumab concentrations measured at baseline (peak level after infusion), and then at weeks 2 and 4. Endoscopic activity was assessed at weeks 8 and 24 using the Mayo endoscopic subscore, with improvement defined as a score of ≤1 (assessed by a central reader blineded to clinical information). Patients who prematurely discontinued treatment due to loss of response before endoscopic assessment were classified as non-responders. Statistical analysis included the Mann–Whitney U test, Chi-square test, Fisher's exact test, and ROC curve analysis, as appropriate. A p-value of <0.05 was considered statistically significant.

RESULTS

We included 35 patients (19 males, 16 females; mean age: 42.03 ± 14.46 years). Serum ustekinumab concentrations were available for 34 patients at week 0, 30 patients at week 2, and 27 patients at week 4. Endoscopic evaluation was performed in 29 patients at both week 8 and week 24. Endoscopic improvement was observed in 11/35 (31.43%) patients at week 8 and in 19/35 (54.29%) patients at week 24. Median serum ustekinumab concentrations at week 0, week 2, and week 4 were 153.94 µg/mL (interquartile range (IQR): 132.13–175.51), 41.66 µg/mL (IQR: 33.52–46.40), and 19.91 µg/mL

Association between ustekinumab concentrations and endoscopic outcome at week 8

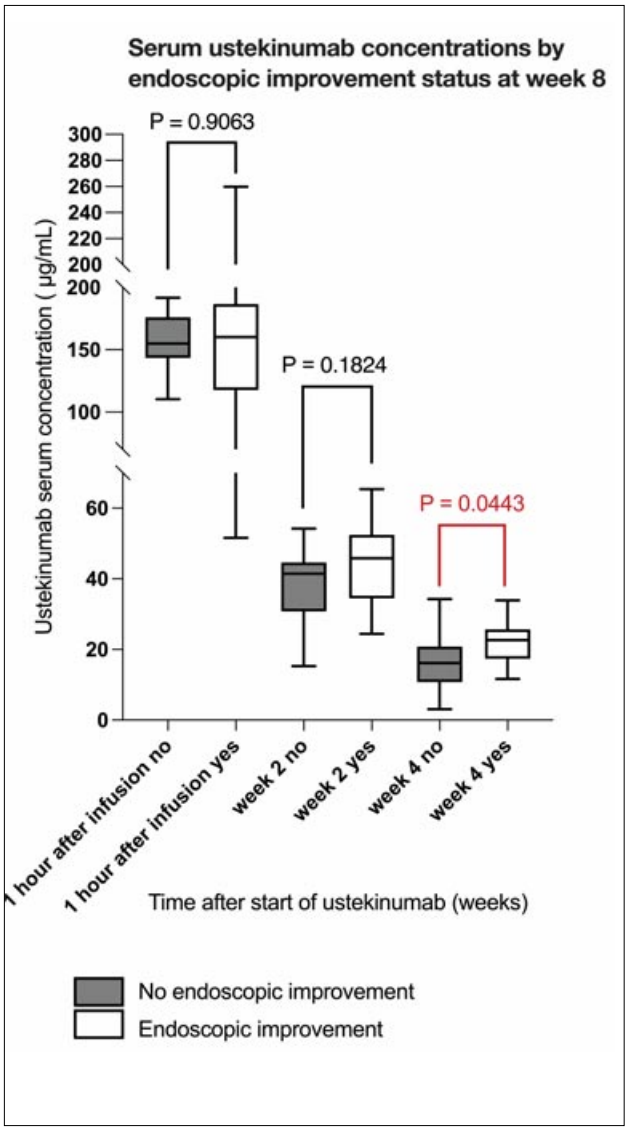

Figure 1. Serum ustekinumab concentrations at baseline (peak concentration), week 2, and week 4 in patients with and without endoscopic improvement at week 8.

Association between ustekinumab concentrations and endoscopic outcome at week 24

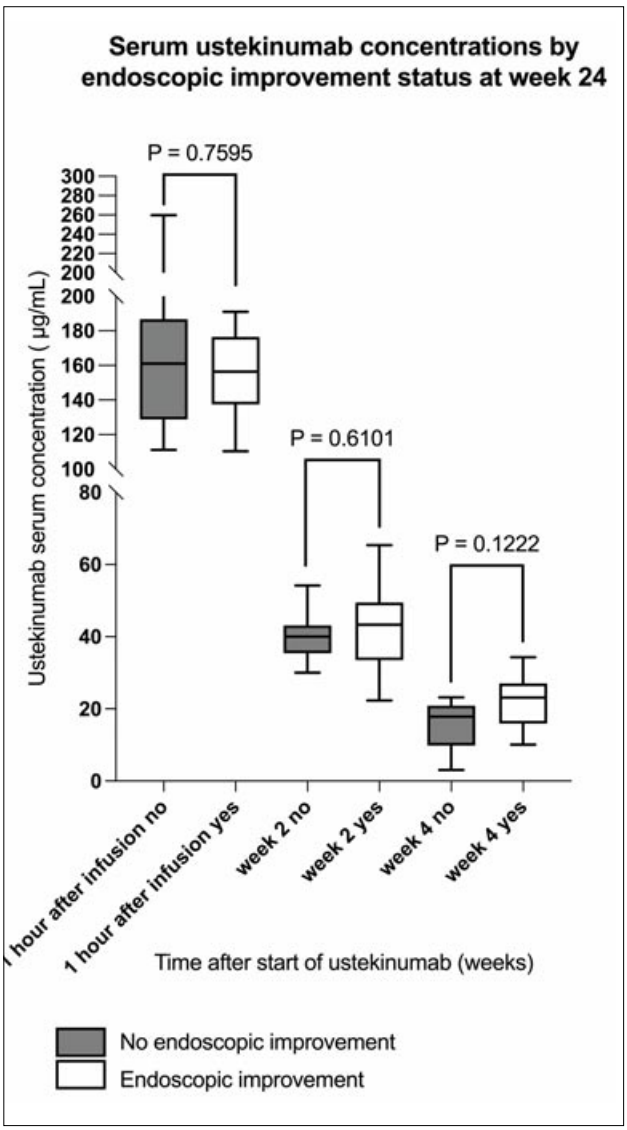

Figure 2. Serum ustekinumab concentrations at baseline (peak concentration), week 2, and week 4 in patients with and without endoscopic improvement at week 24.

(IQR: 14.49–23.18), respectively. Peak concentrations were similar between patients with endoscopic improvement and those without improvement. At week 2 and week 4, however, patients with endoscopic improvement at week 8 and 24, had higher serum concentrations than those without (Figure 1 and 2). We observed exposure-response correlation over increasing ustekinumab concentrations for both endoscopic timepoints (Figure 3).

For week 8 endoscopic improvement ROC analysis demonstrated an AUC of 0.754 (95% CI: 0.541–0.967, p = 0.019). The optimal cut-off concentration was 20.900 µg/mL, with a sensitivity of 70.0% and specificity of 83.3% (Figure 4). Endoscopic improvement at week 8 was achieved in 7/9 patients (77.78%) with ustekinumab concentrations ≥ 20.900 µg/mL, compared to 3/13 patients (23.10%) with concentrations below this threshold (p = 0.027; odds ratio: 3.462, 95% CI: 0.984–12.179).

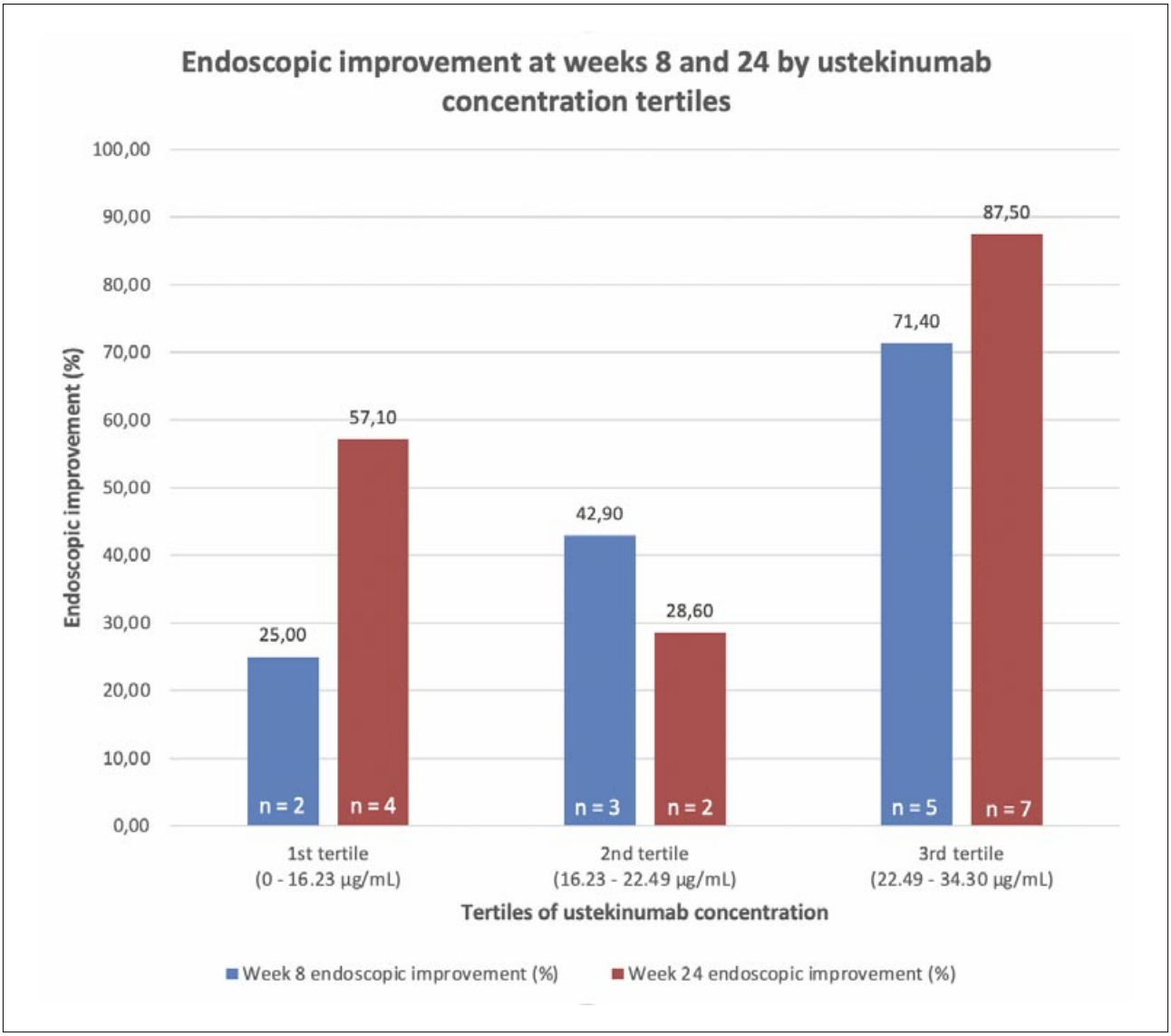

Figure 3. Proportion of patients with endoscopic improvement at weeks 8 and 24 across tertiles of week 4 ustekinumab serum concentrations.

For week 24 endoscopic improvement ROC analysis demonstrated an AUC of 0.701 (95% CI: 0.481–0.921, p = 0.073). The optimal cut-off concentration was 22.000 µg/mL, with a sensitivity of 53.80% and specificity of 88.90% (Figure 5). Endoscopic improvement at week 24 was achieved in 7/8 patients (87.50%) with week 4 ustekinumab concentrations ≥ 22.000 µg/mL, compared to 6/14 patients (42.86%) with concentrations below this threshold (p = 0.074; odds ratio: 4.571 (95% CI: 0.692–30.220).

CONCLUSIONS

In this prospective observational study we confirmed exposure–response relationship between ustekinumab concentrations at week 4 and endoscopic improvement in UC. A week 4 concentration above 20.900 µg/mL was associated with a high probability of endoscopic improvement. These results suggest that measuring week 4 ustekinumab concentrations could be clinically relevant for predictiong endoscopic response.

Predictive value of week 4 ustekinumab serum concentrations for endoscopic improvement at week 8

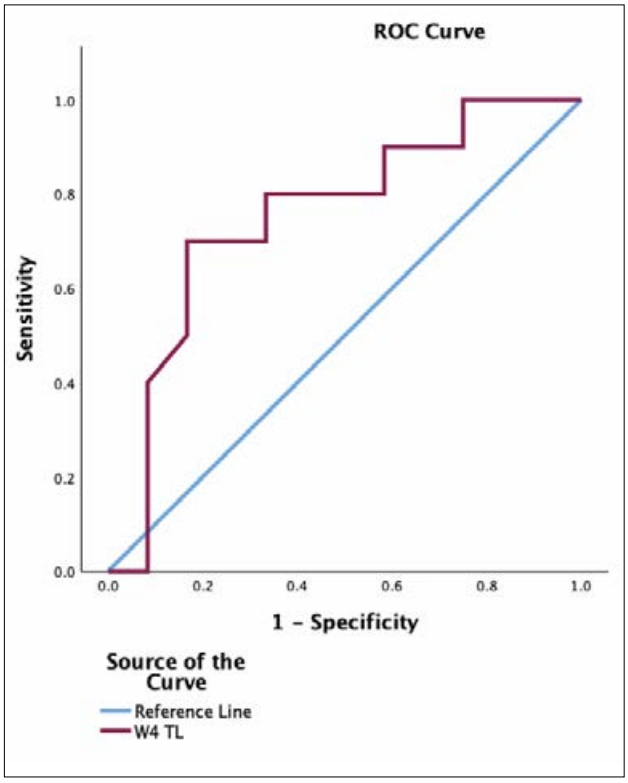

Figure 4: ROC curve of ustekinumab serum concentration at week 4 as a predictor of endoscopic improvement at week 8.

Predictive value of week 4 ustekinumab serum concentrations for endoscopic improvement at week 24

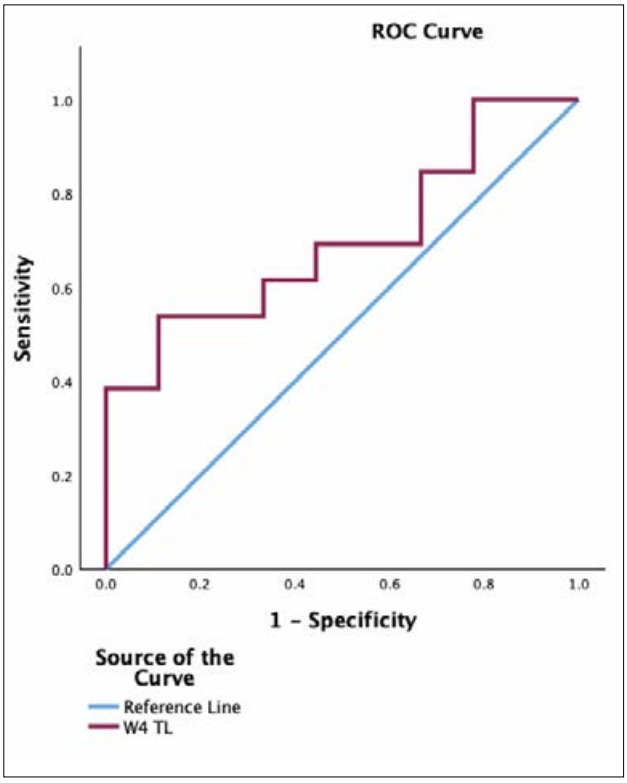

Figure 5. ROC curve of week 4 ustekinumab serum concentration for prediction of endoscopic improvement at week 24.