DOP Session 6: Optimisation of biologic therapies

DOP046

Higher serum concentrations of vedolizumab are associated with superior endoscopic outcomes in Crohn's disease: data from the LOVE-CD trial

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Background: Vedolizumab (VDZ) is an anti-α4β7 integrin registered for treatment of moderate to severe Crohn's disease (CD). Prospective data on mucosal healing in CD and the association with VDZ serum concentrations are lacking. We report a first analysis of the ongoing LOVE-CD trial (NCT02646683).

Methods: Patients with moderate–severe CD based on Crohn's Disease Activity Index (CDAI) 220–450 and the presence of ulcers at baseline endoscopy received 300 mg VDZ at Week 0, 2, and 6 with additional w10 infusion in the absence of clinical response, followed by 300 mg VDZ every 8w. CDAI, C-reactive protein (CRP) and VDZ concentrations were measured before every infusion. Endoscopies were performed at baseline and w26 and scored with the Simple Endoscopic Score for CD (SES-CD). Clinical remission was defined as CDAI<150, endoscopic remission as SES-CD ≤3 and endoscopic response as SES-CD reduction ≥50% compared with baseline. Quartile analysis was performed in the per protocol population (patients who reached w26 and had two endoscopies).

Results: A total of 110 CD (70% female) patients were included, with median ([interquartile range, IQR]) age 36 years [28–46], median disease duration 12 years [6–16]. All patients had failed conventional therapy and 88% failed prior anti-TNF therapy. Median baseline SES-CD was 11 [7–17], median CDAI 263 [238–313], median CRP: 9 [4-22]. At week 26, 76 patients (69%) were still on VDZ and 74/76 patients underwent w26 endoscopy. Endoscopic response was observed in 43/110 (39%), endoscopic remission in 33/110 patients (30%) and clinical remission in 37/110 patients (34%). Patients with endoscopic response at w26 had higher median VDZ concentrations compared with endoscopic non-responders at w6, 10, 14, and 22 (Table 1). Higher proportions of patients achieved endoscopic remission at w26 with higher VDZ quartiles compared with lower quartiles at w6, 10, and 22 (Figure 1). CRP concentrations were inversely correlated with VDZ concentrations (p-value =.001).

Table 1. Vedolizumab serum concentrations (μg/ml).

	Endoscopic reponders week 26 (median [inter-quartile range])	Endoscopic non-responders (median [inter-quartile range])	*P*-value
Week 2	27 [25–33]	26 [20–33]	0.19
Week 6	31 [24–37]	23 [16–34]	0.02
Week 10	31 [26–39]	25 [14–31]	0.006
Week 14	26 [14–38]	13 [5–30]	0.007
Week 22	15 [11–24]	9 [4–14]	0.0003

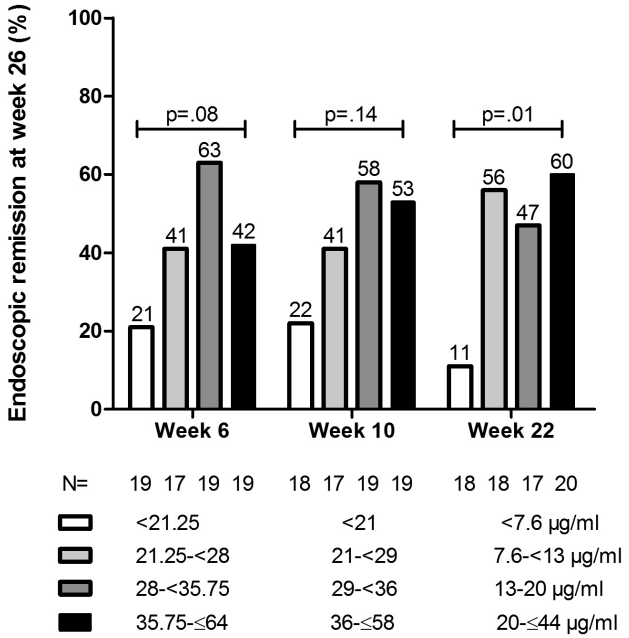

Figure 1. Vedolizumab quartiles and endoscopic remission at week 26.

Conclusions: This is the first prospective trial showing endoscopic response and remission rates with VDZ in CD. VDZ concentrations were significantly higher in patients with an endoscopic response compared with non-responders. The study was support provided by Takeda.

DOP047

Infliximab exposure predicts superior endoscopic outcomes in patients with active Crohn's disease: pharmacokinetic–pharmacodynamic analysis of TAILORIX

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Background: In the TAILORIX study, "proactive" dose escalation based on infliximab (IFX) serum concentrations (TDM groups) had no added value to "reactive" dose escalation based on symptoms

(TDM groups and control group).[1] In patients randomised to TDM groups, reactive dose escalation was only allowed in the presence of elevated serum CRP (>5 mg/l) and/or faecal calprotectin (FC, >250 µg/g). We explored the value of pharmacokinetic (PK) and pharmacodynamic (PD) monitoring of IFX therapy in patients with Crohn's disease (CD) in TAILORIX.

Methods: We studied associations between PK markers (IFX concentrations), PD markers (CD activity index or CDAI, CRP and FC) and the endoscopic remission (CD endoscopic index of severity, CDEIS <3), using prospectively collected data from 122 patients with CD in TAILORIX.

Results: During induction therapy, IFX trough concentrations (TC) were significantly higher in patients achieving endoscopic remission by w12 compared with patients who did not (Table 1). An IFX TC ≥23.1 µg/ml at w2 and ≥10.0 µg/ml at w6 predicted endoscopic remission by w12 (p = 0.002 and p = 0.013) (Figure 1). Also, FC ≤250 µg/g at w2 and w6 was associated with 69% and 68% endoscopic remission by w12, while only 44% and 26% of the patients with FC >250 µg/g demonstrated endoscopic remission by w12 (p = 0.021 and p = 0.0002). During maintenance therapy, FC was significantly lower in patients achieving endoscopic remission by w54 (p < 0.0001). Using classification tree analysis, endoscopic remission at w12 and w54 was found to be best predicted by FC. Overall, the strongest PK-PD correlation was found between IFX concentrations and FC at the same time point. IFX concentrations were significantly higher when FC was ≤250 µg/g (p < 0.0001). Out of 43 dose escalation opportunities based on CDAI in the TDM groups, 23 (53%) were avoided per protocol as biomarkers were not elevated. This additional biomarker criterion did not apply to the control group, where normal CRP and/or FC was observed in nine out of 15 (60%) of the CDAI based dose escalation events.

Table 1. Summary statistics of PK and PD markers during IFX induction therapy for patients with CD achieving endoscopic remission by week 12 or not. Differences were evaluated using the Mann–Whitney U test.

	Endoscopic remission at week 12 (n = 52)	No endoscopic remission at week 12 (n = 54)	P value
Week 2: IFX	26.5 [23.8–34.9] µg/ml	22.5 [17.8–27.9] µg/ml	0.002
Week 2: CDAI	159 [109–215]	194 [145–241]	0.056
Week 2: FC	218 [100–716] µg/g	768 [171–1729] µg/g	0.001
Week 2: CRP	2 [1–6] mg/l	3 [2–6] mg/l	0.079
Week 6: IFX	19.4 [14.8–26.3] µg/ml	15.6 [8.5–21.3] µg/ml	0.013
Week 6: CDAI	122 [72–198]	138 [73–186]	0.455
Week 6: FC	116 [100–289] µg/g	447 [194–934] µg/g	<0.0001
Week 6: CRP	1 [1–4] mg/l	3 [1–7] mg/l	0.123

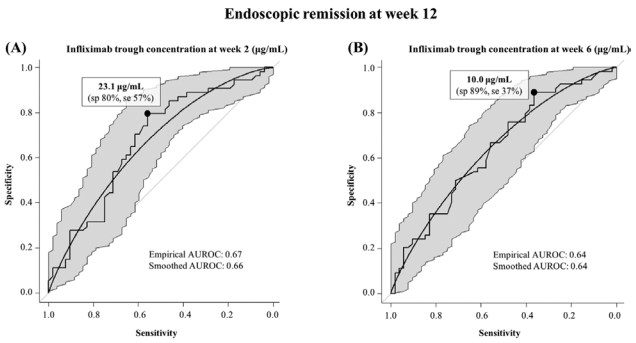

Figure 1. Receiver operating characteristic (ROC) curves of infliximab trough concentrations at (A) week 2 and (B) week 6 as a predictor of endoscopic remission at week 12. se: sensitivity; sp: specificity; AUROC: area under the ROC curve.

Conclusions: In TAILORIX, a clear exposure-response relation was observed during IFX induction therapy. The additional value of IFX concentration-based dose escalation during maintenance therapy might be blurred due to CDAI based dose escalations that increased the background IFX exposure and response.

Reference

1. D'Haens G, Vermeire S, Lambrecht G, *et al.* 692 Drug-level based dosing versus symptom-based dose adaptation in patients with Crohn's disease: a prospective, randomised multicenter study (TAILORIX). *Gastroenterology*, 2016:S143, http://www.gastrojournal.org/article/S0016-5085(16)30583-2/abstract.

DOP048

Vedolizumab levels during induction are associated with long-term clinical and endoscopic remission in patients with inflammatory bowel disease

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Background: Cross-sectional serum vedolizumab (VDZ) levels (SVL) have been associated with disease activity in Crohn's disease (CD) or ulcerative colitis (UC) but the role of therapeutic drug monitoring (TDM) early in the course of therapy is unknown. The aim of this study was to assess the association of serum vedolizumab (VDZ) levels (SVL) during induction and remission in CD and UC after 52 weeks (52w) of therapy. We also sought to assess predictive variables associated with SVL through the first 22w of therapy.

Methods: Prospective cohort study including patients with active UC and CD starting standard therapy with VDZ. Predictive variables included demographics, pre-infusion SVL measured using a validated drug-tolerant assay at weeks 2, 6, 14 and 22 (Anser® VDZ), C-reactive protein (CRP), albumin level, feacal calprotectin (FC), Harvey–Bradshaw index (HBI) in CD and Mayo Clinical Score (MCS) in UC, Simple endoscopic score-CD (SES-CD) in CD and Mayo endoscopic score (MES) in UC. Primary outcome was deep remission at 52W, defined as HBI<5 (in CD)/MCS<3 (in UC), and SES-CD≤2 (in CD) or MES≤1 (in UC). Secondary outcome was discontinuation of VDZ due to non-response.

Results: Of the 53 patients in the study population, 28 (53%) had UC. Twenty-one (40%) achieved deep remission by week 52. These patients had higher SVL at weeks 2, 6, 14 and 22 of therapy vs. those that did not, but only the differences at Weeks 2 and 6 achieved statistical significance (Figure 1).

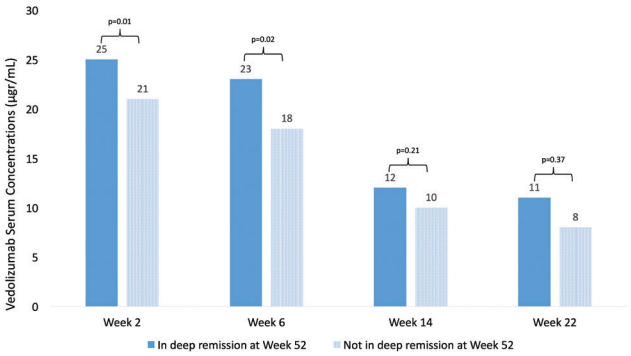

Figure 1. Differences in Vedolizumab Levels at Several Time-points Between those that did and did not achieve remission by week 52 of therapy (*) Statistically significant.