DOP057

The influence of anti-adalimumab antibodies on adalimumab trough levels, TNF-α levels and clinical outcome

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Background: There is increasing evidence on the role of low trough levels and the development of anti-TNF-α antibodies for the occurrence of lack/loss of response to Infliximab (IFX) therapy in patients with Crohn's Disease (CD). Therefore, several recent papers and guidelines suggested the need for dosing IFX concentrations and anti-IFX antibodies in order to treat better CD patients. To date, there are limited data on the role of adalimumab (ADA) through levels and anti-ADA antibodies (AAA) for the management of CD patients.
Aim: We assessed the role of AAA on ADA trough levels, TNF-α concentrations, PCR value and clinical outcome.
Methods: In this prospective observational cohort study, performed at a single tertiary referral center, 23 [14M/9F; mean age 41 (range 21–66)] infliximab-naïve patients with CD achieving disease remission and in maintenance treatment with ADA were included in a follow-up program. Blood samples were drawn at standardized time points (i.e. at 6, 12, 18, 24 months and in case of relapse) just before ADA injection. Trough serum concentration and antibodies against ADA were measured using an homogenous mobility shift assay (HMSA; Prometheus Lab, San Diego, United States). Blood samples were considered positive for they presence if AAA were >1.7 U/mL and for ADA through levels if they levels were more than >5 μg/ml. Disease activity was assessed at the same points by means of routine biochemistry and the Harvey–Bradshaw Index (HBI, remission <5, mild disease 5–7, moderate disease 8–16, severe disease >16).
Results: We have data from 189 blood samples. AAA were observed in 42/189 (22.2%) samples, and 16/42 (38.1%) had levels of AAA >1.7 U/mL. ADA through levels were found in 183/189 (96.8%) samples, and 168/183 (91.8%) had a value of drug levels >5 μg/ml. Overall, 5/23 (21.7%) patients had AAA and 22/23 (95.6%) were positive for ADA levels. Blood samples with AAA had lower ADA trough levels [7.54 (0–26.49) vs. 9.45 (0.14–23.62); p = 0.002] and higher TNF-α concentrations [5.9 (4.1–11.5) vs. 3.6 (0–27.2); p = 0.0007] than blood samples without evidence of AAA. Moreover, patients with blood samples positive for AAA reported HBI values higher compared to patients without evidence of AAA [10 (3–17) vs. 5 (2–17); p < 0.0001]. Finally, no differences were found in terms of mean PCR values between patients with AAA and those without [8.1 (3–76.4) vs. 5.2 (2.6–56); p = 0.39].
Conclusions: Development and presence of AAA influence ADA trough levels and TNF-α concentrations in CD patients during maintenance treatment with ADA, thus favoring clinical relapse as demonstrated by the increased values of HBI scores.

DOP058

Pharmacokinetic and pharmacodynamic relationship and immunogenicity of vedolizumab in adults with inflammatory bowel disease: Additional results from the GEMINI 1 and 2 studies

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Background: Vedolizumab (VDZ) is a humanised monoclonal antibody in development for treating ulcerative colitis (UC) and Crohn's disease (CD). Efficacy and pharmacokinetic (PK) profiles of VDZ in patients with UC and CD have been previously reported (GEMINI 1 [NCT00783718] and 2 [NCT00783692]). Here the PK/pharmacodynamic (PD) relationship and immunogenicity of VDZ are described.
Methods: Both GEMINI studies had a 6-week induction phase, wherein patients received 2 intravenous infusions of placebo or VDZ 300 mg (weeks 0, 2) and were assessed at week 6. VDZ-treated patients who had a clinical response at week 6 (intention-to-treat [ITT] population) were randomised to receive placebo or VDZ 300 mg every 4 weeks (Q4W) or every 8 weeks (Q8W) during the 46-week maintenance phase. VDZ induction nonresponders (non-ITT population) received open-label VDZ 300 mg Q4W; patients who received placebo during induction continued on placebo. At prespecified times, blood samples were collected for determination of VDZ levels, PD assessment ($alpha_4beta_7$ [receptor] saturation via MAdCAM-1-Fc binding interference assay), and anti-VDZ antibody (AVA) assessment. Study data were examined separately for each disease and also pooled for VDZ PK/PD and AVA analyses. Receptor saturation plots were generated for each dose group.
Results: VDZ Q4W or Q8W led to median serum VDZ levels ⩾10 mcg/mL in both ITT and non-ITT UC and CD patients at steady state during maintenance. Complete receptor saturation was observed by week 6 and maintained until week 52 in both VDZ dose groups. Among pooled UC and CD patients, 4% (56/1434) tested positive for AVAs at any time during continuous VDZ therapy and 10% (32/320) tested positive off drug (5 VDZ half-lives after last dose). In patients with an investigator-defined infusion-related reaction, 5% (3/61) tested persistently (⩾2 consecutive visits) AVA positive; these persistently AVA-positive patients generally had lower serum VDZ trough levels than did the general study population. In the combined ITT and non-ITT VDZ group, the percentage of AVA-positive patients was similar between those with (3% [5/161]) and without (4% [51/1273]) concomitant immunomodulator use. In patients randomised to placebo, however, the impact was greater where AVA positive rates were 3% (1/32) and 18% (44/247) in those with and without concomitant immunomodulator use, respectively.
Conclusions: Median VDZ serum levels ⩾10 mcg/mL were maintained when VDZ 300 mg was administered (Q8W or Q4W) to patients with UC or CD, resulting in complete receptor saturation. The PK profile and immunogenicity during continuous treatment with VDZ were similar in patients with UC and CD.

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Table 1 (abstract DOP059)

	Laquinimod				Pooled placebo
	0.5 mg (n = 29)	1.0 mg (n = 30)	1.5 mg (n = 29)	2.0 mg (n = 29)	(n = 63)
Proportion of patients in clinical remission at Week 8*	48%	27%	14%	17%	16%
Proportion of Responders 100 at Week 8*	55%	40%	28%	28%	32%
Proportion of Responders 70 at Week 8*	62%	53%	31%	28%	35%
Patients with fecal calprotectin level ⩾250 μg/g at baseline (% of treatment arm)	18 (62%)	18 (60%)	15 (51.7%)	11 (37.9%)	44 (69.8%)
Reduction of calprotectin**	7 (38.9%)	7 (38.9%)	4 (26.7%)	4 (36.4%)	6 (13.6%)
Reduction of calprotectin and clinical remission**	5 (27.8%)	3 (16.7%)	1 (6.7%)	2 (18.2%)	1 (2.3%)
Reduction of calprotectin and Response 100**	5 (27.8%)	3 (16.7%)	3 (20.0%)	4 (36.4%)	3 (6.8%)
Reduction of calprotectin and Response 70**	6 (33.3%)	5 (27.8%)	2 (20.0%)	4 (36.4%)	4 (9.1%)

*Proportion of patients per treatment arm and **proportion of patients per treatment arm with fecal calprotectin concentrations ⩾250 μg/g at baseline.

DOP059

Reduction of fecal calprotectin levels and relationship to clinical parameters in the phase 2 study of laquinimod for the treatment of active moderate to severe Crohn's disease

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Background: Laquinimod is an oral therapy in development for the treatment of Crohn's disease (CD). An exploratory multi-center double-blind dose-ranging phase 2 study (NCT00737932) found that laquinimod at doses of 0.5 mg and 1.0 mg safely induced clinical remission in patients with active moderate-to-severe CD. The study also explored whether laquinimod which has been shown to have anti-inflammatory properties in other disease states, reduced fecal calprotectin concentrations, an objective measure of intestinal inflammation in patients with CD in addition to improving clinical symptoms.
Methods: Patients (N = 180) with active moderate-to-severe CD were randomly assigned to one of 4 laquinimod doses (0.5, 1.0, 1.5, 2 mg/day, n = 29 or 30 per dose) or placebo (n = 16 per dose) in sequential dose-escalating cohorts. Treatment was administered for 8 weeks with a 4-week follow-up visit. Stable concomitant therapies and prior anti-TNF medications were allowed. Efficacy analyses included the proportions of patients in clinical remission (CDAI < 150 and no treatment failure [TF]) and with a clinical response (70 or 100 point CDAI reduction or remission and no TF) and measures of fecal calprotectin. Patients with fecal calprotectin concentrations ⩾250 μg/g at baseline were assessed to determine if there was a shift in fecal calprotectin levels to <250 μg/g and reduction by at least 50%.
Results: Doses of 0.5 mg and 1.0 mg laquinimod increased the proportion of patients in clinical remission and with clinical response 100 and 70. There were increased proportions of patients with reduced fecal calprotectin levels for all laquinimod dose groups compared to the pooled placebo group at Week 8. Likewise, the proportions of patients who showed both a reduction in fecal calprotectin and an improvement in clinical remission or response were greater in the laquinimod dose groups than in the pooled placebo group (Table 1).
Conclusions: This dose-ranging study suggests that laquinimod at the lower doses of 0.5 mg and 1.0 mg improved clinical symptoms in patients with CD. All doses of laquinimod were found to have an effect on reducing intestinal inflammation using the threshold of ⩾250 μg/g fecal calprotectin levels as a marker of inflammation in active CD. The lowest dose of laquinimod 0.5 mg appears to have the most robust and consistent effect on reducing inflammation and improving clinical symptoms relative to the higher laquinimod doses and to placebo.

DOP060

CD62L (L-selectin) shedding for assessment of functional blockade of TNF alpha in anti-TNF treated inflammatory bowel disease patients: clinical feasibility and perspectives

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Background: Tumor necrosis factor (TNF) inhibition is central to the therapy of inflammatory bowel diseases (IBD). However, loss of response (LOR) is frequent and additional tests to help decision making with costly anti-TNF Therapy are needed.
Methods: Consecutive IBD Patients receiving anti-TNF therapy (Infliximab (IFX) or Adalimumab (after IFX LOR) from Bern University Hospital were identified and followed prospectively. Patient whole blood was stimulated with a dose-titration of two triggers of TLR receptors human: TNF and LPS. Median fluorescence intensity of CD62L on the surface of granulocytes was quantified by surface staining with specific antibodies (CD33, CD62L) and flow cytometry and logistic curves to these data permits the calculation of EC50 or the half maximal effective concentration TNF concentration to induce shedding [1]. A shift in the concentration were CD62L shedding occurred was seen before and after the anti-TNF agent administraion which permits to predict the response to the drug. This predicted response was correlated to the clinical evolution of the patients in order to analyze the ability of this test to identify LOR to IFX.
Results: We collected prospective clinical data and blood samples, before and after anti-TNF agent administration, on 33 IBD patients, 25 Crohn's disease and 8 ulcerative colitis patients (45% females) between June 2012 and November 2013. The assay showed a functional blockade of IFX (PFR) for 22 patients (17 CD and 5 UC) whereas 11 (8 CD and 3 UC) had no

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