At risk: 130	117	78	35	14	1	0
134	52	32	14	3	2	0

Sa1882

INFLIXIMAB CONCENTRATION THRESHOLDS DURING MAINTENANCE THERAPY VARY BASED ON THE THERAPEUTIC OUTCOME OF INTEREST IN INFLAMMATORY BOWEL DISEASE

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Background and aim Several therapeutic drug monitoring (TDM) exposure-response relationship studies have shown a positive correlation between anti-TNF trough concentration (TC) and favorable therapeutic outcomes in inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC). However, TC cut-offs may vary depending on the assay used and the outcome. The aim of our study was to investigate whether infliximab concentration thresholds differ depending on the therapeutic outcome of interest including biologic, endoscopic, and histologic remission in IBD during maintenance therapy. **Methods** We performed a single-center, cross-sectional study including all consecutive IBD patients treated with infliximab maintenance therapy who underwent either proactive or reactive TDM between January 2010 and June 2016. Primary non-responders to adalimumab and patients with ostomy or an ileal pouch-anal anastomosis were excluded. Biologic remission was defined as CRP ≤ 5 mg/L. Endoscopic remission was defined as absence of any ulceration or erosion for CD, a Rutgeerts score of i0 for CD patients with an ileocolonic resection and a Mayo endoscopic score of 0 for patients with UC. Histological remission was defined as absence of any sign of active inflammation. Infliximab TC was evaluated in serum samples using either the ELISA or the homogenous mobility shift assay (after July 2012) developed by Prometheus. Optimal thresholds were chosen using the Youden index, which maximizes the sum of the sensitivity (SN) and specificity (SP) of the receiver operating characteristic (ROC) curve. **Results** 104 patients [71 (68%) with CD; 95 (91%) naive to anti-TNF therapy] were included. Infliximab TC (median [interquartile range-IQR]) was significantly higher in patients with biologic (6.7 [4.2-10.9] vs 3.5 [0-10.4] $\mu\text{g/mL}$, $p=0.028$), endoscopic (10.2 [6.6-11.8] vs 8.2 [2.8-11.3] $\mu\text{g/mL}$, $p=0.033$) or histological (10.3 [6.4-12.7] vs 8.4 [2.3-11.3] $\mu\text{g/mL}$, $p=0.031$) remission compared with patients who did not achieve the outcome, respectively. A ROC analysis identified an infliximab TC threshold of 3.3 (area under the ROC curve [AUROC]: 0.639; SN: 0.84; SP: 0.48), 9.9 (AUROC: 0.630; SN: 0.54; SP: 0.71) and 9.9 $\mu\text{g/mL}$ (AUROC: 0.637; SN: 0.56; SP: 0.69) associated with biologic, endoscopic and histological remission, respectively. **Conclusion** This study showed that infliximab maintenance TC threshold to target varies depending on the therapeutic objective outcome of interest in IBD. The TC appears to be higher for achieving endoscopic or histological remission than biological remission. *Equal contribution for the first two authors

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ANTIBODIES TOWARDS VEDOLIZUMAB APPEAR FROM WEEK 2 ONWARDS AND DISAPPEAR UPON TREATMENT

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Background: Vedolizumab (VDZ), a monoclonal antibody (MA) that specifically binds to $\alpha_4\beta_7$ integrin, has demonstrated efficacy in patients with moderate-to-severe Crohn's disease (CD) and ulcerative colitis (UC). VDZ trough concentrations (TC) are typically >30 $\mu\text{g/mL}$ during induction and >10 $\mu\text{g/mL}$ during maintenance therapy, making it challenging for immunogenicity assays to detect anti-VDZ antibodies (AVA). The GEMINI trials reported AVA at ≥ 2 consecutive time points in 0.4% and 1% of patients with CD and UC, respectively. **Methods:** We developed a drug-resistant AVA assay in which AVA are complexed with an excess of VDZ followed by VDZ/AVA complex precipitation, acidification of the precipitate, coating and detection of released AVA using biotinylated VDZ. MA-VDZ19C11, a MA towards VDZ, was validated as calibrator. Drug resistance was examined by determination of the recovery of MA-VDZ19C11 in the presence of 3 different concentrations of VDZ. The cut-off was determined using 20 VDZ naive patients. Cross reactivity with serum from 2 anti-infliximab antibody and 2 anti-adalimumab antibody positive patients, as well as with serum containing high concentration of rheumatoid factor (150 U/mL) was determined. The assay was subsequently applied to serum samples from 75 VDZ-treated patients (46 CD, 29 UC) taken at trough during induction (w6) and maintenance (w22). VDZ TC, AVA and CRP were determined in all available sera of patients positive for AVA at w6/w22. **Results:** MA-VDZ19C11 yielded dose-response curve ranging from 25-1600 ng/mL in 1/125 diluted serum allowing detection of AVA concentrations up to 200 $\mu\text{g/mL}$ equivalents. Spiking 1, 10 and 100 $\mu\text{g/mL}$ of VDZ to 40 $\mu\text{g/mL}$ MA-VDZ19C11 yielded recoveries of $89 \pm 7\%$ (mean $\pm$ SD, $n=3$), $90 \pm 11\%$ and $82 \pm 5\%$, respectively, confirming the complete drug resistance of the AVA assay. Cut-off for quantification was determined to be 1.1 $\mu\text{g/mL}$ MA-VDZ19C11 equivalents and none of the sera tested revealed cross-reactivity. Among the 75 VDZ-treated patients, 1 patient (1.3%) had AVA antibodies at w6 determined by a classical drug-sensitive bridging assay whereas 4 patients (5.3%) were AVA positive on ≥ 2 time points using the drug-resistant AVA assay. AVA antibodies appeared from w2 onwards but disappeared over time (Figure 1). None of the 4 ADA-positive patients required VDZ intensification. **Conclusion:** Using a drug-resistant AVA assay, AVA are detected in 5.3% of patients. Antibodies appear from w2 onwards and disappear upon time indicating their transient character.

Figure1: VDZ TC (dashed line), AVA concentrations (solid line) and CRP levels (below graph) of the 4 AVA positive patients at consecutive time points during VDZ therapy.

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APPLICATION OF DRIED BLOOD SPOTS FOR PHARMACOKINETIC PROFILING OF GOLIMUMAB-TREATED PATIENTS WITH ULCERATIVE COLITIS

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Background Preventing loss of response to golimumab, an anti-tumour necrosis factor (TNF) biologic, is a challenge for clinicians treating patients with ulcerative colitis (UC). Although drug serum concentrations and anti-drug antibody serum concentrations have suggested an association between golimumab exposure and clinical outcome, detailed information on absorption, distribution and elimination of the drug in a real-life cohort of patients is lacking. Dry blood spot (DBS) sampling involves a finger prick to apply whole blood to a sampling paper after which drug is extracted. We wanted to study if golimumab efficacy can be increased by exploring its full pharmacokinetic (PK) profile in UC patients by intensive sampling via DBS. **Methods** First, DBS were obtained through spotting of different volumes of golimumab (0.2-20 $\mu\text{g/mL}$) or anti-golimumab antibody (20-200 ng/mL) spiked in whole citrated blood, to a filter paper (Figure 1). After punching, DBS were extracted and DBS extracts were analysed on both the MA-GOM171D8/MA-GOM159B8-HRP ELISA and the MA-GOM159B8 bridging ELISA. Extraction efficacy, accuracy, imprecision, sensitivity and robustness were determined as well as the impact of anti-golimumab antibodies on the detection of golimumab (and vice versa). Second, DBS were obtained by spotting blood obtained through a finger prick of eight golimumab-treated patients with UC (six females, mean (SD) age of 43 (16) years and median [IQR] duration under golimumab of 100 [72-114] weeks) of whom serum was taken simultaneously by venepuncture, allowing the calculation of a real-life conversion factor between golimumab serum concentration and DBS extract. **Results** The selected extraction condition yielded an average extraction efficiency of 54% and 53% for golimumab and anti-golimumab determination, respectively. Overall-assay accuracy and imprecision were between 80-120% and $<15\%$, respectively, for each concentration analysed. Storing the sampling papers at room temperature for one month or the extracts at -20°C for three months did not impair DBS recovery. The presence of golimumab hampered the detection of anti-golimumab and vice versa. A real-life conversion factor of 3.8 ± 0.3 ($n=6$) from DBS to serum was calculated. The blood volume per spot did not influence the results if it had at least a diameter of six mm, which was not the case in two out of eight patients and is the main drawback of this method. **Conclusion** The described DBS method is robust and can be used as a patient friendly and inexpensive