Higher anti-TNF serum levels are associated with perianal fistula closure in Crohn’s disease patients

A. Strik1*, M. Löwenberg2, C. Ponsioen1, K. Gece2, C. Buskens1, W. Benelman3, G. D’Haens1

1Academic Medical Center, Gastroenterology and Hepatology, Amsterdam, The Netherlands, 2Academic Medical Center (AMC), Department of Gastroenterology and Hepatology, Amsterdam, The Netherlands, 3Academic Medical Center (AMC), Department of Surgery, Amsterdam, The Netherlands

Background: Anti-tumour necrosis factor (anti-TNF) agents are effective agents to treat perianal Crohn’s disease (CD). Recent evidence suggests that CD patients with perianal fistulas need higher serum concentrations of infliximab (IFX) compared with patients without perianal CD in order to achieve disease control.

Methods: We performed a retrospective survey of all CD patients receiving active treatment with IFX or adalimumab (ADL) at our centre with available serum concentrations of IFX and ADL in CD patients with perianal fistulas. Fistula closure was defined as absence of drainage at physical examination and/or fistula healing on magnetic resonance imaging. Anti-TNF serum concentrations were compared among patients with active and closed perianal fistulas. Only patients with an interval between physical fistula examination/imaging and serum anti-TNF serum level measurement not exceeding 4 weeks were included in the analysis. Patients who underwent surgical interventions (i.e. ligation of intersphincteric fistula tract surgery or faecal diversion procedure) between physical examination and serum anti-TNF serum level measurement and patients with internal fistulas were excluded.

Results: Of 352 CD patients receiving IFX or ADA, 67 had a history of perianal fistula. Forty-seven out of 67 were treated with IFX. Median IFX serum concentrations at trough ([interquartile range]) were significantly higher in patients with closed fistula (n = 32) compared with patients with active fistula (n = 15): 6.0 µg/ml [5.4–6.9] vs. 2.3 µg/ml [1.1–4.0], respectively (p < 0.001). A similar outcome was seen in 19 of 67 patients treated with ADL (13 with closed fistula and 6 with active fistula) with median serum concentrations of 7.4 µg/ml [6.5–10.8] vs. 4.8 µg/ml [1.7–6.2] respectively; p = 0.003. There were no differences seen in IFX and ADL dose and intervals between patients with active draining fistula and closed fistula.

Conclusions: We report an association between anti-TNF serum concentrations and fistula closure in CD patients. Dose reduction of anti-TNF in CD patients with perianal disease is contraindicated, despite quiescent luminal disease.

Apremilast for active ulcerative colitis: a phase 2, randomised, double-blind, placebo-controlled induction study

S. Danese1*, M. Neurath1, A. Kopon1, S. Zakkou1, T. Simmons1, R. Fogel1, J. Maccarone1, X. Zhan2, K. Usiskin3, D. Chitkara2

1Instituto Clinico Humanitas, Milan, Italy, 2University Erlangen, Nurnberg, Germany, 3Torunskie Centrum Gastrologiczne Gastromed, Torun, Poland, 4Connecticut Clinical Research Foundation of Bristol Hospital, Bristol, USA, 5West Gastroenterology Medical Group, Los Angeles, USA, 6Clinical Research Institute of Michigan, Chesterfield, USA, 7Celgene Corporation, Summit, USA

Background: Apremilast is an oral small-molecule inhibitor of phosphodiesterase 4 that works intracellularly to modulate a wide array of pro- and anti-inflammatory mediators in ulcerative colitis (UC).

Methods: Patients with active UC (defined as a total Mayo score [TMS] of ≥6 to ≤11, with a Mayo endoscopic score [MES] of ≥2) who failed at least one conventional therapy for UC and were naïve to biologic therapy were randomised in a 1:1:1 ratio to receive apremilast 30 mg BID (APR30), apremilast 40 mg BID (APR40), or placebo (PBO) for up to 12 weeks. The primary endpoint of the study was TMS clinical remission at Week 12. Endoscopy was read centrally by independent experts blinded to treatment allocation and time point.

Results: A total of 170 patients were randomised to PBO (n = 58), APR30 (n = 57), or APR40 (n = 55). There were no differences in baseline disease characteristics, and mean baseline TMS and OP006

Figure. Apremilast serum concentrations productive vs. closed fistula.

Figure. Apremilast serum concentrations productive vs. closed fistula.

Figure. IFX serum concentrations productive vs. closed fistula.

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MES were 8.3 and 2.6, respectively. A significantly higher proportion of patients treated with APR30 achieved TMS clinical remission (Δ18%) and modified Mayo score (MMS) clinical remission (Δ25%) compared with PBO. A higher proportion of patients treated with APR30 and APR40 achieved a clinical response at Week 12 compared with PBO, but the result was only significant for the APR40 treatment group. At Week 12, a significantly higher proportion of patients treated with APR30 achieved a decrease of at least one point from baseline MES (Δ32%) and an MES ≤1 (Δ32%) compared with PBO. Both APR30 and APR40 treatment groups showed a trend for a higher proportion of patients achieving histological remission, defined as a Geboes score <2, compared with the PBO group. A significantly higher proportion of patients treated with APR30 achieved mucosal healing (MES ≤1 with Geboes score <2) (Δ18%) compared with PBO. Patients treated with APR30 achieved significant improvements in percent changes from baseline in hsCRP at Weeks 4, 8, and 12 and faecal calprotectin at Weeks 2, 4, and 8 compared with PBO. A similar safety profile was seen in patients treated with APR30 and APR40.

Conclusions: In this 12-week, phase 2 study, patients with active UC treated with APR30 had clinically meaningful improvements in symptoms, endoscopy, biomarkers, and mucosal healing compared with PBO. The observed adverse events were consistent with those expected in UC patients and were also consistent with the known safety profile of apremilast.

**OP007**

Detection of mucosal healing with a serum marker panel in adalimumab-treated patients with ulcerative colitis

M. de Bruyn1,2, R. Ringold3, E. Martens2, M. Ferrante3,4, G. Van Assche1,4, G. Opdenakker2, A. Dukler1, S. Vermeire1,4
1Translational Research Center for Gastrointestinal Disorders (TARCID), Chronic Diseases, Metabolism and Ageing (CHROMETA), Leuven, Belgium, 2Rega Institute for Medical Research, Microbiology and Immunology, Leuven, Belgium, 3Kepler Diagnostics, Inc., Simi Valley, USA, 4University Hospitals Leuven, Gastroenterology and Hepatology, Leuven, Belgium

Background: Surrogate markers that accurately detect mucosal healing (MH) in patients with ulcerative colitis (UC) are urgently needed. After infliximab therapy, neutrophil gelatinase B-associated lipocalin in complex with matrix metalloproteinase-9 (NGAL-MMP-9), cathelicidin LL-37 and chitinase 3-like 1 (CHI3L1), together with C-reactive protein (CRP) and neutrophil count were significantly associated with MH. We investigated whether these five markers were also associated with MH after treatment with adalimumab (ADM).

Methods: Serum samples were obtained from 31 UC patients (58% female, median age 35.6 years) both at baseline and after a median (IQR) of 14 (10–25) weeks. All patients had endoscopic disease activity prior to treatment (Mayo endoscopic subscore/MES ≥2) and MH was defined at follow-up endoscopy as MES ≤1. NGAL-MMP-9, LL-37, and CHI3L1 were measured with ELISA. Binary logistic regression analysis was used to combine multiple markers. ROC analysis was used to test the performance of individual and combined markers. Non-parametric tests were performed, and p-values of <0.05 were considered significant.

Results: Twenty-one patients (68%) achieved MH with ADM therapy. Compared with baseline, NGAL-MMP-9 levels significantly decreased in patients with MH (96.9 vs. 214.1 ng/ml, p = 0.002), whereas patients without MH had similar levels. Neutrophil count was significantly lower after ADM compared with baseline in patients with MH only (3.6 vs. 6.3 109/l, p = 0.023). CRP levels significantly decreased after ADM in patients with MH (15 to 1.1 mg/l, p = 0.008) and were higher at baseline in patients with MH compared with without MH (15 vs. 2.4 mg/l, p = 0.004). LL-37 levels significantly increased in patients without MH post-ADM compared with baseline (29 vs. 19.3 ng/ml, p = 0.034) and were significantly higher compared with patients with MH post-ADM (29 vs. 18.7 ng/ml, p = 0.031). CHI3L1 levels significantly decreased after ADM in patients with MH only (47.4 to 21.6 pg/ml, p = 0.049). The performance of NGAL-MMP-9 (AUC=0.70), neutrophil count (AUC=0.58), CRP (AUC=0.56), LL-37 (AUC=0.79), and CHI3L1 (AUC=0.69) to discriminate MH post-ADM significantly increased when all markers were combined (AUC=0.86). The 5-marker panel was discriminative for MH with 75% sensitivity, 89% specificity, 67% positive predictive value, and 92% negative predictive value.

Conclusions: Neutrophil-related markers (NGAL-MMP-9, LL-37, and CHI3L1) as well as CRP and neutrophil count were significantly associated with MH after treatment with ADM. These data are in concordance with our previous findings in infliximab-treated patients. We therefore suggest a broad clinical utility of this panel for monitoring MH in UC patients under anti-TNF treatment.

**OP008**

α4β7 Integrin-dependent gut homing of non-classical monocytes is essential for intestinal wound healing mediated by M2 macrophages

L. Schleier1, M. Wiendli1, M.-T. Binder1, R. Atreya1, A. Watson1, C. Neufert1, I. Atreya1, M.F. Neurath1, S. Zundler1*
1University of Erlangen-Nuremberg, Department of Medicine I, Erlangen, Germany, 2University of East Anglia, Norwich Medical School, Norwich, UK

Background: The anti-α4β7 integrin antibody Vedolizumab is successfully used for the treatment of IBD. Mechanistically, it is well established that it inhibits α4β7 integrin-dependent gut homing of pathogenic T lymphocytes to the inflamed gut. However, the impact of anti-α4β7 treatment on monocyte gut homing, which differentiates to macrophages regulating intestinal inflammation and tissue remodelling, has not been investigated so far.

Methods: Expression of gut homing integrins on peripheral blood monocyte and intestinal macrophage subsets from IBD patients and controls was analysed by flow cytometry and immunohistochemistry, respectively. Dynamic adhesion assays were used to investigate