P551
6-Thioguanine nucleotide levels are associated with mucosal healing in patients with Crohn’s disease: A multi-centre, international study

R. Mao1, J. Guo1, R. Luber2, B.J. Chen1, Y. He1, Z.-t. Zeng1, S. Ben-Horin3, M. Sparrow2, R. Xavier4, M.-h. Chen1
1First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, 2The Alfred Hospital, Melbourne, Australia, 3Sheba Medical Center, Tel Aviv, Israel, 4University Hospital Saint Etiene, Saint Etiene, France

Background: The level of 6-thioguanine nucleotides (6-TGN) has been reported to be associated with clinical remission in patients with Crohn’s disease (CD) receiving maintenance treatment with thiopurines. Whether 6-TGN levels are associated with mucosal healing (MH) has seldom been investigated. We aimed to assess the correlation between 6-TGN levels and MH in patients with CD.

Methods: This was a retrospective cross-sectional observational multi-centre study of 119 patients with CD treated with thiopurines in three IBD referral centres (France, Australia and China) between June 2012 and April 2016. Established CD patients who underwent ileocolonoscopy during thiopurine treatment were included. MH was defined as simple endoscopic score-CD <3. Univariate and multivariable regression analyses were used to evaluate variables associated with MH.

Results: The mean concentration of 6-TGN in MH group was higher compared with that in non-MH group (359.0 ± 226.7 pmol/8 × 108 RBC vs. 277.1 ± 170.5 pmol/8 × 108 RBC) (p = 0.017). The cut-off 6-TGN concentration of 397.3 pmol/8x108 RBC was 86.7% specific for MH, with a sensitivity of 35.3% and area under curve (AUC) of 0.631 (p = 0.010). On multivariate analysis, 6-TGN levels were associated with MH (odds ratio [OR] 3.287, 95% confidence interval [CI] 1.348–8.017; p = 0.004). Fewer than 50% of patients with MH were reported hospitalisation when treated with VDZ (39% UC-related and 52% all-cause) vs. IFX (45% UC-related and 57% all-cause). Flares were reported by 52% and 53% of VDZ and IFX initiators, respectively. Among patients with an event, median times to event for VDZ vs. IFX initiators were: 159 days vs. 36 days (p = 0.34; Figure 1a) for UC-related hospitalisation; 159 days vs. 36 days (p = 0.20) for all-cause hospitalisation; and, 203 days vs. 42 days (p = 0.56; Figure 1b) for first flare. Corresponding event rates (all per 100 PY) for VDZ vs. IFX initiators were: 50.4 vs. 72.9 for UC-related hospitalisation; 72.8 vs. 108.1 for all-cause hospitalisation; and, 68.9 vs. 88.9 for flare.

Conclusions: Higher 6-TGN levels are independently associated with a reduced rate of endoscopically active disease and a higher rate of mucosal healing in CD patients. Prospective studies of adequate sample size are required to confirm these findings.

P552
Early use of vedolizumab vs. infliximab in biologic-naive patients with ulcerative colitis: A real-world analysis of healthcare utilisation

H. Patel1*, J.M. Khalid1, S. Shah2, R. Shah1, A. Berger2
1Takeda Development Centre Europe Ltd., Evidence and Value Generation, London, UK, 2Evidera, Real World Evidence, Waltham, MA, USA

Background: Early use of biologics may be an effective strategy to reduce the risk of bowel damage in ulcerative colitis (UC), thus potentially changing the course of disease. In this study, we compared outcomes in biologic-naive patients who initiated vedolizumab (VDZ), a gut-selective humanised monoclonal antibody that binds to α4β7 integrin, or infliximab (IFX), a systemic tumour necrosis factor antagonist, as their first biologic within 2 years of UC diagnosis.

Methods: This retrospective, observational study used electronic medical records from the Explorys Universe database. Patients included in this analysis were biologic-naive, had initiated VDZ or IFX therapy within 2 years of UC diagnosis, had completed induction therapy (≥3 infusions ≥98 days after index) and were receiving maintenance therapy (≥1 infusions ≥90 days after third infusion), with ≥188 days of follow-up (from May 20, 2014 to October 25, 2017). Weighted Kaplan–Meier plots were used to describe times to outcomes (UC-related hospitalisation, all-cause hospitalisation and flare). Incidence rates were calculated by dividing the number of events by the corresponding number of patient-years (PY), and are expressed as events per 100 PY.

Results: Data from 150 patients (VDZ n = 33; IFX n = 117) were analysed. Median times from diagnosis to initiation of biologic therapy were 0.6 years vs. 0.7 years (VDZ vs. IFX; p = 0.67). Fewer patients reported hospitalisation when treated with VDZ (39% UC-related and 52% all-cause) vs. IFX (45% UC-related and 57% all-cause). Flares were reported by 52% and 53% of VDZ and IFX initiators, respectively. Among patients with an event, median times to event for VDZ vs. IFX initiators were: 159 days vs. 36 days (p = 0.34; Figure 1a) for UC-related hospitalisation; 159 days vs. 36 days (p = 0.20) for all-cause hospitalisation; and, 203 days vs. 42 days (p = 0.56; Figure 1b) for first flare. Corresponding event rates (all per 100 PY) for VDZ vs. IFX initiators were: 50.4 vs. 72.9 for UC-related hospitalisation; 72.8 vs. 108.1 for all-cause hospitalisation; and, 68.9 vs. 88.9 for flare.

Conclusions: Early use of biologics may be an effective strategy to reduce the risk of bowel damage in ulcerative colitis (UC), thus potentially changing the course of disease. In this study, we compared outcomes in biologic-naive patients who initiated vedolizumab (VDZ), a gut-selective humanised monoclonal antibody that binds to α4β7 integrin, or infliximab (IFX), a systemic tumour necrosis factor antagonist, as their first biologic within 2 years of UC diagnosis.

Figure 1. Outcomes in biologic-naive patients with UC treated with vedolizumab or infliximab as initial biologic therapy.
Conclusions: Initiation of VDZ within 2 years of UC diagnosis was associated with nominal reductions in hospitalisations and flares over a 1-year follow-up period, compared with IFX. These results were based on relatively small patient numbers and need to be confirmed in larger cohorts; however, these findings suggest that early use of VDZ may lead to lower levels of healthcare resource utilisation compared with IFX.

P553
Development of an enzyme-linked immunosorbent assay for therapeutic drug monitoring of golimumab
C. Berger1,2, A. Pilch1, J. Ruppert1, E.P. Armbruster1, J. Stein1,2, K. Farrag1,2
1Immundiagnostik AG, Bensheim, Germany, 2Interdisciplinary Crohn Colitis Centre Rhein-Main, Frankfurt/Main, Germany, 3DGD Clinics Sachsenhausen, Frankfurt/Main, Germany

Background: Golimumab is a therapeutic anti-TNF monoclonal antibody approved for use in moderate-to-severe ulcerative colitis (UC). The PURSUIT trials showed a significant exposure-response relationship of golimumab in UC. Interindividual differences in response to golimumab treatment may be explained in part by interindividual variability in pharmacokinetics. The aim of this work was to develop and validate an enzyme-linked immunosorbent assay (ELISA) to measure golimumab drug concentrations.

Methods: Samples diluted at 1:100 were added to microtiter plates coated with recombinant human TNFα for binding. Mouse anti-human immunoglobulin G1 (HRP-anti h IgG1) was used to detect bound golimumab. Assay performance characteristics were determined according to the European in-vitro diagnostic devices directive 98/79/EC.

Results: The measuring range of the assay was determined to be 0.415–22.5 µg/ml, and the limit of detection (LoD) for golimumab measurement in human serum samples was 3.56 ng/ml. Intra-assay variation (n = 19) was ≤6.6%, while inter-assay variation (n = 11) was ≤5.3%. Linearity testing was performed by analysing three serially diluted samples spiked with golimumab; golimumab concentrations measured by the new assay were within 98–129% of the expected concentrations. The assay detected no false-positive signals from the samples of untreated patients. Since TNF-α was used as a capture reagent, other TNF-α blockers were detected.

Conclusions: This newly developed ELISA offers a fast and accurate test with reproducible results. The specificity of the assay could be improved by the use of monoclonal antibodies to golimumab. This ELISA has potential utility in therapeutic drug monitoring of patients receiving golimumab, and additionally in pharmacokinetic/pharmacodynamic studies of the drug.

P554
Incidence and impact of immunogenicity in a randomised, double-blind phase III study comparing a proposed infliximab biosimilar (PF-06438179/GP1111) with reference infliximab
R. Palapathy1, S. Schmitt2, M.I. Rehman1, C.-H. Cai1, K. Wang1, O. von Richter2
1Pfizer Inc., Biosimilars Development, New York, USA, 2Global Clinical Development, Biopharmaceuticals, Hexal AG (a Sandoz company), Holzkirchen, Germany, 3Pfizer Inc., Andover, USA

Background: Anti-drug antibodies (ADAs) have the potential to impact the pharmacokinetics (PK), efficacy and safety of biologic treatments, such as infliximab. With the recent availability of biosimilars, it is important to establish that immunogenicity and any associated impact is similar to that of the reference medicine.

Methods: A multi-national, randomised, double-blind, parallel-group study compared the efficacy, safety and immunogenicity of the proposed infliximab biosimilar, PF-06438179/GP1111, with the European reference infliximab (IFX-EU) in adult patients with moderate-to-severe active rheumatoid arthritis (RA) on a stable dose of methotrexate. Patients received 3 mg/kg IV dose of study treatment at Weeks 0, 2, 6 and then every 8 weeks, with a dose escalation to 5 mg/kg allowed from Week 14 for inadequate responders. The primary endpoint was a ≥20% improvement in American College of Rheumatology response (ACR20) at Week 14. Subgroup analyses by ADA status were conducted at Weeks 14 and 30. Serum PK samples were assayed using a validated ELISA. Blood samples were collected and assayed for ADA and neutralising antibodies (NAbs).

Results: Six hundred and fifty patients were randomised (PF-06438179/GP1111, n = 324; IFX-EU, n = 326). ADAs were observed in 48.6% (n = 157) of patients with PF-06438179/GP1111 and 51.2% (n = 167) with IFX-EU throughout 30 weeks, and NAbs were present in 79% (n = 124) and 85.6% (n = 143) of these patients, respectively. ACR20 response rates at Weeks 14 and 30 were similar between treatments regardless of ADA status.

Table. ACR20 response rates and risk differences at Week 14 and Week 30 by ADA and NAb status

<table>
<thead>
<tr>
<th>Week</th>
<th>ADA positive</th>
<th>ADA negative</th>
<th>NAb positive</th>
<th>NAb negative</th>
<th>Risk difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 14</td>
<td>PF-06438179/GP1111</td>
<td>IFX-EU</td>
<td>PF-06438179/GP1111</td>
<td>IFX-EU</td>
<td>1.1–(12.3, 15.2)</td>
</tr>
<tr>
<td>ADA positive</td>
<td>51.0</td>
<td>49.5</td>
<td>1.5–(12.3, 15.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADA negative</td>
<td>69.1</td>
<td>71.2</td>
<td>-2.1–(10.6, 6.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAb positive</td>
<td>50.0</td>
<td>45.7</td>
<td>4.3–(11.4, 20.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAb negative</td>
<td>67.5</td>
<td>70.5</td>
<td>-3.0–(12.2, 5.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 30</td>
<td>ADA positive</td>
<td>ADA negative</td>
<td>NAb positive</td>
<td>NAb negative</td>
<td>Risk difference (%)</td>
</tr>
<tr>
<td>ADA positive</td>
<td>58.0</td>
<td>56.3</td>
<td>1.7–(9.1, 12.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADA negative</td>
<td>65.0</td>
<td>72.8</td>
<td>-7.8–(27.8, 23.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAb positive</td>
<td>55.2</td>
<td>54.6</td>
<td>1.1–(10.9, 13.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAb negative</td>
<td>65.3</td>
<td>72.4</td>
<td>-7.1–(16.4, 2.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Serum concentrations of PF 06438179/GP1111 and IFX-EU were expectedly lower in patients with ADAs compared with those without. Importantly, serum concentrations were similar between treatment groups in ADA-positive patients. In each treatment group, n = 83 patients underwent dose escalation during the first 30 weeks of treatment and, in these patients, the ADA rates at Week 30 were similar (PF 06438179/GP1111, 45.8% vs. IFX-EU, 38.6%) and comparable to those patients not undergoing dose escalation (40.8% and 46.1%, respectively). Up to Week 30, infusion-related reactions (IRRs) occurred in 5.9% (n = 19 of 321) patients with PF 06438179/GP1111 and 6.4% (n = 21 of 326) with IFX-EU. In patients with ADAs, IRRs occurred in 7% (n = 11 of 157) with PF 06438179/GP1111 and 8.4% (n = 14 of 167) with IFX-EU.

Conclusions: Immunogenicity occurred at a similar frequency and had a similar impact on efficacy, PK and IRRs with PF 06438179/ GP1111 compared with IFX EU in patients with moderate-to-severe active RA.