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P0356 - A PROACTIVE INFLIXIMAB DRUG MONITORING STRATEGY IMPROVES OUTCOMES IN PATIENTS WITH CROHN´S DISEASE

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Introduction: There is increasing evidence supporting the use of therapeutic drug monitoring (TDM) of anti-TNF therapies in Crohn´s disease (CD) following loss of response. However, the potential benefit of proactive TDM is still unknown [1-4]

Aims and Methods:

To study the pharmacokinetics and clinical benefits associated with a proactive TDM strategy in CD.Patients completing Infliximab (IFX) induction were assigned to a proactive TDM protocol (pTDM). Before the 4th infusion and before every 2 infusions, IFX drug levels and anti-drug antibodies were measured using a drug sensitive assay (Theradiag®, Lisa Tracker). Treatment was proactively escalated aiming at a trough level of 3-7 ug/ml. A retrospective cohort of patients treated with IFX but without TDM was used as a control group (noTDM). Endpoints included the need for IBD-related surgery and hospitalization, treatment discontinuation, and mucosal healing (absence of ulceration in non-operated patients or Rutgeerts score < i2 in operated patients) at 2 years of follow-up. Patients with major bowel surgery, drug holiday and primary IFX non-response were excluded

Results:

185 patients were included in the study (35 in the pTDM and 150 in the noTDM group); Baseline characteristics were non-significant between groups. A median (range) of 3 (1-7) drug/anti-drug measurements were collected in the pTDM group over the 2-year period. The median (range) IFX trough levels and anti-drug antibodies were 5.80 µg/ml (0.03-16.4) and 0 U/mL (0-200.0), respectively. Pharmacokinetic analysis showed a significant correlation between IFX trough levels and C-reactive protein (ρ= -0.197, P= 0.01), fecal calprotectin (ρ= -0.344, P= 0.004) and anti-drug antibodies (ρ= -0.220, P= 0.003). Higher trough levels were associated with higher rates of mucosal healing (7.25 µg/ml (1.9-14) vs 2.9 µg/ml (0.03-7); P= 0.02, AUROC= 0.83), magnetic resonance enterography normalization (7.25 µg/ml (3.75-14) vs 2.14 µg/ml (0.03-7); P< 0.001, AUROC= 0.92) and transmural healing (7.5 µg/ml (3.75-14) vs 2.6 µg/ml (0.03-7.66); P= 0.015, AUROC= 0.88). After 2 years of follow-up, pTDM patients presented higher rates of treatment escalation (74.3% vs 20.7%, P< 0.001) and mucosal healing (77.1% vs 46.7%, P= 0.01), but similar rates of hospitalization (P= 0.534), surgery (P= 0.241) and treatment discontinuation (P= 0.212). pTDM patients were less likely to reach any of the former outcomes (66.0% vs 45.7%, P= 0.033). In regression analysis only proactive TDM (OR 0.44 95%CI 1.52-8.54; P= 0.04) and immunomodulation (OR 0.35 95%CI 1.17-4.63; P= 0.016) were independently associated with mucosal healing. Immunomodulation did not influence IFX trough levels (P= 0.456) and anti-drug antibodies (P= 0.150), and was not associated with improved rates of mucosal healing (P= 0.182) in the pTDM group.

Conclusion:

Higher IFX trough levels were associated with lower inflammatory biomarkers and higher rates of endoscopic and radiologic healing. In comparison with a cohort under conventional management, proactive TDM was unable to show a difference in the rates of surgery, hospitalization and treatment discontinuation but significantly improved the rates of mucosal healing at 2-years. As several studies have shown that mucosal healing reduces the rates of

surgery and hospitalization in the long-term, we hypothesize that a longer follow-up would significantly improve our results.

In conclusion, improved IFX pharmacokinetics were associated with better disease control. Proactive TDM was associated with higher rates of mucosal healing than a conventional non-TDM based management.

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Disclosure: Nothing to disclose

P0401 - LONG-TERM OUTCOMES OF INFLIXIMAB THERAPY FOR PATIENTS WITH CROHN'S DISEASE AT DIFFERENT TIMES OF INITIATION OF INFLIXIMAB ADMINISTRATION: A SINGLE-CENTRE COHORT STUDY IN JAPAN

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Introduction:

In Japan, infliximab was first approved for patients with Crohn's disease as an induction therapy in 2002. Subsequently, it was approved for maintenance therapy and dose escalation in 2007 and 2011, respectively. However, the comparative long-term effectiveness of infliximab treatments in patients with Crohn's disease at different times of initiation of infliximab administration is not fully established.

Aims and Methods:

The aim of this study was to compare the rates of dose escalation of infliximab, intestinal resection and retention of infliximab among patients with Crohn's disease at different times of initiation of infliximab administration. Data for 338 patients with luminal Crohn's disease who were treated at our hospital with infliximab (5 mg/kg) for ≥14 weeks between January 2003 and May 2017 were retrospectively reviewed. The cumulative rate of the dose escalation of infliximab from 5 mg/kg to 10 mg/kg, the rate of intestinal resection and the rate of retention of infliximab following the initial infliximab administration were estimated using the Kaplan-Meier method. Patients were categorised into three groups according to the time of initiation of the infliximab therapy [A, 2003-2006 (n = 83); B, 2007-2010 (n = 146) and C, 2011-2017 (n = 109)]. Patient characteristics and the rates of dose escalation of infliximab, intestinal resection and retention of infliximab were compared among the three groups. Prognostic factors related to the outcomes were evaluated using the log-rank test

Results:

 Of the 338 patients (median age, 29.7 years; 85 females), the median duration of the disease at initiation of infliximab therapy was 4.3 years. Of the total patients, 201 patients had ileocolitis, 75 had ileitis and 62 had colitis. In addition, 145 patients were diagnosed with non-stricturing, non-penetrating disease, 145 with stricturing disease and 48 with penetrating disease. Perianal disease was diagnosed in 156 patients. The median C-reactive protein was 1.01 mg/dL. Prior to initiation of the infliximab therapy, 108 patients had undergone at least one intestinal resection and 11 had been previously exposed to adalimumab. Concomitant treatment with immunomodulators (azathioprine or 6-mercaptopurine) and prednisolone was administered to 248 and 36 patients respectively. The 1-, 3-, 5- and 10-year cumulative rates of dose escalation of infliximab, intestinal resection and retention of infliximab in all 338 patients were 16.2%, 33.7%, 42.3% and 52.2%, 3.4%, 9.8%, 13.8% and 21.3% and 98.2%, 93.5%, 89.8% and 80.1%, respectively. Patients in group C had significantly shorter disease durations (P = 0.029) and higher rates of concomitant treatment with immunomodulators (P < 0.001) than those in group A. The 5-year cumulative rates of dose escalation of infliximab, intestinal resection and retention of infliximab were 54.2%, 17.1% and 88.5% in group A; 46.8%, 16.6% and 89.1% in group B and 27.3%, 6.5% and 92.2% in group C, respectively. The rates of dose escalation of infliximab (P < 0.001) and intestinal resection (P = 0.043) in group C were significantly lower than those in groups A and B.

Conclusion:

The rates of dose escalation of infliximab and intestinal resection of patients with Crohn's disease who were administered infliximab after 2011 were lower than those of patients who were administered infliximab before 2010. Early induction of infliximab and a combined therapy with infliximab and immunomodulators in the 2011-2017 period may have contributed to the reduction in the rates of dose escalation of infliximab and intestinal resection.

Disclosure:

P1046 - ARE CUT-OFF RANGES OF INFLIXIMAB SERUM LEVELS IN CROHN´S DISEASE ALWAYS THE SAME IN CLINICAL PRACTICE?

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Introduction:

It has been seen that 30-40% of patients treated with Infliximab (IFX) who achieve an initial response to induction therapy lose this response over time with maintenance treatment. Therapeutic drug monitoring (TDM) could be used to optimize management in such situations. However, IFX serum levels are not well defined. The aim of the study was to find our cut-off range of Infliximab serum levels in Crohn´s disease (CD) patients in remission in clinical practice.

Aims and Methods:

An observational retrospective study was developed from 1st February, 2016, to 30th November, 2017, in our hospital. Patients with established CD who had been on maintenance dosing schedule of IFX were included.

IFX and antibody to IFX levels were measured before each infusion at least twice and after 6 months of treatment in all patients. All the tests were performed using enzyme linked immunosorbent assay (ELISA) with Progenika kits (PROMONITOR®). Clinical remission was defined using Harvey Bradshaw Index (HBI≤4). The interpretation of data was by cluster analysis (Silhouette measure of cohesion and separation: cluster quality >0.5**).

Results:

105 CD patients were included in the study, 57.1% men, with a mean age of 39 (DE±12.9). The median (range) time of the disease was 11 years (7-15). The median (range) time of follow-up was 32 months (22-38).

Montreal phenotypes were: 76% A2, 35.2% L2 and 53.3% B1. Perianal disease was present in 51.4%. 265 IFX levels were measured during the follow-up.

Patients who achieved remission had IFX serum levels between 4.26 - 8.26 ug/ml versus 0.06 - 1.43 ug/ml in patients who did not achieve remission (silhouette 0,72) the first time; and 2.84 - 7.75 ug/ml versus 0.05 - 2.69 ug/ml in patients who achieved remission versus those who did not achieve remission respectively the second time (silhouette 0,78) (Fig 1-2). 4,26- 7,75 ug/ml were the best cut-off range for remission (Table 1) We found that perianal disease does not have any influence on IFX serum levels for achieved remission.

Time 1	Time 2	Most Restrictive interval	
0.06-1.43	0.05-2-69	0.06-1.43	No Remission
1.43-4.26	2.69-2.84	1.43-4.26	Uncertainly zone
4.26-8.26	2.84-7.75	4.26-7.75	Remission

[Crohn's Disease]

Conclusion:

In our practice the best value to predict remission status in patients undergoing IFX TDM was 4 - 8 ug/ml, which was higher than in other studies.

References:

** Kaufman, L., Rousseeuw, P. J. (1990). Finding groups in data. An introduction to cluster analysis. New York: John Wiley & Sons. doi: https://doi.org/10.1002/9780470316801.

Disclosure:

Nothing to disclose

P1048 - INFLIXIMAB LEVELS & ANTIBODIES IN IBD- RELATED PERIPHERAL ARTHRALGIA

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Introduction:

Extra-intestinal manifestations (EIM) are common in inflammatory bowel diseases (IBD) and may affect up to 50% of the patients during the course of the disease. Peripheral arthralgia (PA) is by far the most common EIM. To date, TNF-alpha inhibitors are the most established treatment for EIMs in IBD. Infliximab (IFX) trough levels (TL) and anti-IFX antibodies (ATI) are correlated with multiple outcomes in IBD such as clinical response and remission, mucosal healing, fistular healing and more. To date, a correlation between IFX TL\ATI and PA has not been evaluated.

Aims and Methods:

This retrospective study included IBD patients followed by gastroenterology departments of Sheba Medical Center and Saint Etienne Medical Center. Patients with active peripheral arthralgia at onset of IFX treatment were included. IFX TL and ATI were evaluated at week 6, 14 and 26 and correlated with PA persistence.

Results:

Forty-nine patients (42 CD, 7 UC) with IBD associated arthralgia were included. The overall prevalence of arthralgia was 59.2% (29/49), 44.9% (22/49) and 53.1% (26/49) after 6, 14 and 26 weeks respectively. At 14 and 26 weeks of treatment, arthralgia was less prevalent in clinical responsive patients than in patients who didn't respond to IFX (8.8% vs 66.7%, p=0.004 and 35% vs 70.6%, p=0.031, respectively). IFX TL were not associated with PA at week 14 (median, 4.5 vs 3.15 ug/ml, p=0.26) and at week 26 (median, 3.9 vs 3.6 ug/ml, mean, p=0.84) however detectable ATI were significantly more prevalent in patients with PA than in patients without PA at week 26 (46.2% vs 13.6%, p=0.015)

Conclusion:

In patients with IBD-related PA, IFX ATI are associated with an increased risk of persistence of arthralgia. No direct correlation was demonstrated between IFX TL and persistence of arthralgia.

Disclosure:

Szántó K.[1], **Farkas K.**[2], **Kata D.**[3], **Tóth V.**[1], **Balint A.**[2], **Milassin Á.**[2], **Fabian A.**[2], **Bor R.**[2], **Rutka M.**[1], **Szepes Z.G.**[2], **Soós I.**[2], **Nagy F.**[4], **Földesi I.**[3], **Molnár T.**[1] [1]University of Szeged, 1st Dept. of Internal Medicine, Szeged, Hungary, [2]University of Szeged, 1st Dept. of Medicine, Szeged, Hungary, [3]University of Szeged, Institute of Laboratory Medicine, Szeged, Hungary, [4]SZTE ÁOK I. sz. Belgyógyászati Klinika, 1st Dept. of Medinine, Szeged, Hungary

Introduction:

Recent studies have demonstrated that proactive therapeutic drug monitoring (TDM) with drug titration to a target trough concentration is associated with better clinical outcomes. Moreover, dose intensification strategy based on the parallel assessment of clinical symptoms, serum and fecal biomarkers and serum infliximab (IFX) concentration may further increase therapeutic response.

Aims and Methods:

 The aim of this study is to evaluate the outcome of IFX optimisation based on proactive drug monitoring in combination with the assessment of clinical activity and biomarkers using rapid assays.
This is a prospective study of consecutive Crohn's disease (CD) and ulcerative colitis (UC) patients on IFX maintenance therapy. Blood and fecal samples were obtained from the patients at the day when subsequent IFX infusion was scheduled. C-reactive protein (CRP) and hematocrit levels were measured. Serum IFX and fecal calprotectin (FC) concentrations were benchmarked with rapid, lateral flow-based assays. Clinical activity indices were calculated. On the basis of all data, patients were assigned to 4 groups: no intervention (NI), dose increased (DI), stopping (ST) or switch. After optimisation, patients are followed for 6 months with determining all the above mentioned parameters retrospectively at every 2 months.

Results:

Twenty-six CD and 21 UC patients were enrolled. On the basis of the rapid tests, DI was performed in 14 CD and 11 UC patients, NI in 8 CD and 7 UC patients, and ST in 4 CD and 2 UC patients. One UC patients was switched from IFX to adalimumab. In DI CD group, serum level of IFX increased, CDAI decreased significantly compared to the baseline. Level of CRP and FC did not change significantly at month 2, but CRP decreased significantly at month 4. Twelve CD patients stayed in remission in the DI group; two relapses were observed, one patient was switched to ustekinumab and one patient received corticosteroid. In DI UC group IFX level increased significantly, CRP, pMayo and FC decreased compared to baseline. Seven patients in NI CD group and 3 patients in the NI UC group remained in remission till the end of the follow up. None of the examined parameters, except for serum IFX level at month 4 changed significantly. One patient in the ST group required reintroduction of therapy with adalimumab at month 2. Serum IFX concentration and FC level measured with the rapid, lateral flow-based assay and ELISA kits are correlated (r=0.69, p=0.0012).

Conclusion:

Change in therapy was performed in 32 cases on the bases of benchmarked concentrations of serum IFX and FC levels. Our results suggest benefit of using rapid tests in daily practice. Results of rapid, lateral flow-based assays and ELISA kits are correlated.

P1116 - MANAGEMENT AND OUTCOMES OF ANTI-DRUG ANTIBODIES TO INFLIXIMAB, A LONG-TERM OBSERVATIONAL STUDY

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Introduction:

Secondary loss of response (LOR) to Infliximab (IFX) occurs in up to 40% of IBD patients. One of the causes of LOR is the development of anti-drug antibodies (ADAs) which neutralize IFX. At present, evidence regarding the optimal management of ADAs is lacking.

Aims and Methods:

This is a long-term retrospective observational study of adult patients receiving IFX who developed ADAs >8mg/L over a study period of 3 years. This study reviewed the optimisation of Infliximab therapy and subsequent outcomes in patients who developed ADAs. The primary aim of this study is to identify the best practice of management of ADAs to IFX to avoid discontinuation of therapy/LOR and to identify predictors of development of ADAs. Secondary aims include review of adverse outcomes following development of ADAs.

Results:

 132 patients with IBD and 1 patient with collagenous colitis are included in the study. Baseline characteristics include 54% male, mean age of 39.4, mean IFX drug trough level 4.7 mg/L, mean ADA level 103 mg/L, 25% were on a previous biologic and 26% were on combination therapy prior to the development of ADAs.
52% of patients discontinued IFX- 72% due to LOR, 16% due to clinical remission, 12% due to infusion reaction.
Both an increase in IFX and adjustments to combination therapy (increase in IFX + addition/increase in immunomodulator) were associated with lower rates of discontinuation of treatment vs no intervention (P-Value < 0.001, P-Value < 0.001 respectively). No difference was seen with adjustment of immunomodulator therapy alone (P-Value= 0.62). An increase in IFX resulted in a significant difference in ADAs and IFX trough levels pre and post intervention (P-Value < 0.001, P-Value = 0.032).
There was a significant reduction in ADAs overtime for the entire cohort (Mean of 103 mg/L vs mean of 55 mg/L on follow-up, P-Value= 0.008) and a correlation was noted with ADAs and low drug trough levels (P-Value= 0.056). No significant correlation was found between the presence of ADAs and CRP, fecal calprotectin or serum albumin. 15% were admitted to hospital, 11% underwent surgery, 19% required steroids. 32% switched to another biologic- 63% of patients were switched to Adalimumab.

Conclusion:

A high percentage of patients who develop ADAs to IFX experience LOR. A reduction in ADA levels was seen due to proactive drug monitoring. Both escalation of IFX alone and combination therapy resulted in lower rates of LOR. Our most common practice post LOR due to ADAs was to switch within drug class.

P1135 - THERAPEUTIC DRUG MONITORING SUPPORTS CLINICAL DECISION MAKING WHEN EMPLOYED BEFORE AND AFTER BIOSIMILAR INFLIXIMAB SWITCHING

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Introduction:

Therapeutic drug and anti-drug antibody monitoring (TDM) of infliximab (IFX) is used with increasing regularity as a tool to optimize outcomes in inflammatory bowel disease (IBD). Trough levels (TL) of 2-8 mcg/ml are recommended during maintenance IFX treatment. The introduction of biosimilar infliximab (BI) in 2015 lead to widespread switching of patients from originator infliximab (OI) to BI. The value of TDM when switching to BI has not been defined. This study aimed to assess the impact of TDM testing before and after a managed switch to BI.

Aims and Methods:

Individuals with IBD treated with OI and demonstrating a satisfactory response to treatment, were entered in to BI switch programme in Dec 2016. Pre-switch information was provided to patients, virtual or face to face clinical assessment was undertaken and it was recommended that all patients had pre-switch TDM performed. After switching patients returned to routine clinical care. Further TDM was performed at clinician discretion with recommendation to follow published TDM testing guidance (1). Virtual review of all patients was undertaken 2 years post-switch. Demographics, pre and post switch TDM data, OI and BI dosing regimens and other IBD related medications were recorded along with clinical outcome data. Comparative analysis of pre-switch and most contemporary TDM results was performed.

Results:

76 individuals considered to be clinically responding to OI were entered in to the BI switch programme. 70/76 (92%) had TDM at < 3 months pre-switch. OI was discontinued prior to switch in 2 patients. 74 people were switched from OI to BI. 52/74 (70%) were on 5mg/kg 8 weekly OI pre-switch, 38 (51%) were on immunomodulators.
Of 69/74 with pre-switch TDM, 32/69 (46%) had subtherapeutic TLs (< 2mcg/ml). Median pre-switch TL was 2.2 mcg/ml (IQR 1.1-3.4 mcg/ml). Pre-switch TL review lead to 37/74 (50%) receiving an increased dose of BI at switch. In total 47/74 had ≥1 dose escalation at the time of or subsequent to switch.
58/74 (78%) had TDM testing in the 2 years after switch (median no. tests 2; range 1 - 5) at which point 54/74 (73%) remained on BI with sustained clinical response. 49 out of 54 still on BI had both pre and post switch TDM with results demonstrating a statistically significant increase in mean TLs (2.1 vs 6.3 mcg/ml; p< 0.001); only 6% had persisting sub-therapeutic TLs.

Conclusion:

High rates of sustained clinical response were observed to occur following a BI switch supported by the use of pre and post switch TDM. TDM dose escalation resulted in a statistically significant increase in TLs, this may account for the rates of continued clinical response.

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Disclosure: Nothing to disclose

OP165 - EARLY CLINICAL RESPONSE AND REMISSION WITH VEDOLIZUMAB VERSUS ADALIMUMAB IN ULCERATIVE COLITIS: RESULTS FROM VARSITY

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Introduction:

VARSITY is the first head-to-head trial comparing the efficacy and safety of 2 biologic therapies, vedolizumab (VDZ) and adalimumab (ADA), in patients with moderately to severely active ulcerative colitis (UC). We previously reported significantly higher rates of clinical remission (31.3% vs 22.5%; p=0.0061) and endoscopic improvement (39.7% vs 27.7%; p=0.0005) at Week 52 with VDZ vs ADA.[1] Here we report data on early response and remission within the first 14 weeks, as well as durable clinical remission.

Aims and Methods:

VARSITY was a phase 3b, randomised, double-blind, double-dummy, active-controlled study (NCT02497469; EudraCT 2015-000939-33). As predefined, exploratory endpoints, we examined early clinical response and remission, along with the durability of remission. Clinical response was defined as reduction in complete Mayo score of ≥3 points and ≥30% (or partial Mayo score reduction of ≥2 points and ≥25% from baseline if sigmoidoscopy was not performed), with a decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point. Clinical remission was defined as complete Mayo score of ≤2 (or partial Mayo score ≤2 points if sigmoidoscopy was not performed) and no individual subscore >1 point. Patients who were in clinical remission at Week 14 and Week 52 were considered as having achieved durable clinical remission.

Results:

A total of 769 patients received ≥1 dose of VDZ (n=383) or ADA (n=386). Baseline characteristics were comparable between the 2 groups. A trend for separation in clinical response started to emerge at Week 6 favouring VDZ vs ADA. Clinical response at Week 14 favoured VDZ vs ADA (257 [67.1%] vs 177 [45.9%]; treatment difference 21.2%). A greater number of patients achieved clinical remission at Week 14 on VDZ vs ADA (102 [26.6%] vs 82 [21.2%]; treatment difference 5.3%). Patients on VDZ achieved higher rates of durable clinical remission (70 [18.3%] vs 46 [11.9%]); laboratory results correlated with these findings. Post-hoc analyses showed a larger mean (standard deviation) change of C-reactive protein (CRP) from baseline to Week 14 (-32.88 [155.77] nmol/L VDZ vs -3.35 [260.82] nmol/L ADA) and to Week 52 (-50.87 [174.76] nmol/L VDZ vs -37.21 [169.17] nmol/L ADA) in favour of VDZ. Greater mean declines in faecal calprotectin (FCP) levels were seen in patients on VDZ compared to ADA (Week 14: -1,551.3 [6,236.70] mg/kg VDZ vs -1,167.6 [4,647.67] mg/kg ADA; Week 52: -2,187.3 [7,440.42] mg/kg VDZ vs -1,846.6 [4,560.55] mg/kg ADA).

Conclusion:

Patients on VDZ had numerically higher rates of both clinical response and clinical remission by Week 14 compared with ADA. Those patients on VDZ also achieved higher rates of durable clinical remission compared with ADA. CRP and FCP results correlated with these findings. These data on early clinical response and clinical remission, as well as durable remission, further support the use of VDZ over ADA in patients with moderately to severely active UC.

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1. Schreiber S, et al. J Crohns Colitis. 2019;13(suppl 1):S612-S613. Abstract OP34.

Disclosure:

OP216 - HIGH VERSUS STANDARD ADALIMUMAB INDUCTION DOSING REGIMENS IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS: RESULTS FROM THE SERENE-UC INDUCTION STUDY

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Introduction:

Adalimumab (ADA) is effective and well tolerated in inducing and maintaining clinical remission in adult patients (pts) with ulcerative colitis (UC).[1-3] We report results from the 8 wks induction

period of SERENE-UC (NCT02065622), comparing two ADA dosing regimens: a higher induction dosing regimen (HIR) and a standard induction dosing regimen (SIR).

Aims and Methods:

SERENE-UC is a Phase 3, double-blind, randomized multicenter study of higher versus standard ADA dosing regimens for induction and maintenance therapy in adult pts with moderately to severely active UC. Pts were randomized 3:2 to receive either the HIR (160 mg at Wks 0, 1, 2, and 3, followed by 40 mg at Wks 4 and 6) or the SIR (160 mg at Wk 0 and 80 mg at Wk 2, followed by 40 mg at Wks 4 and 6) of ADA. At randomization, pts were stratified by baseline corticosteroid use and previous infliximab (IFX) use. All pts who entered the study on oral corticosteroids were mandated to begin steroid taper at Wk 4. The primary efficacy endpoint for the induction study was the proportion of patients in the intent to treat population achieving clinical remission, defined as full Mayo Score ≤2 with no subscore >1, at Wk 8. The endoscopic component of the Mayo Score was scored via a central reading protocol. ADA trough serum concentrations were measured at Wks 2, 4, and 8. Exposure-response (ER) modelling was performed using NONMEM 7.3 for the overall population and the ER relationship (ERR) was compared with the ULTRA 2 study.[3] Non-responder imputation was used for missing values. Safety assessment included collection of adverse events (AEs), vital signs, and laboratory data.

Results:

In total, 852 pts were randomized, 512 and 340 into the HIR and the SIR, respectively. Baseline demographics were generally balanced across the two treatment groups; overall, mean UC disease duration was 7.2 (7.1) years, 87.1% of pts were biologic-naïve (12.9% had prior IFX experience with initial response and subsequent inadequate response or intolerance), and 58.7% of pts were receiving corticosteroids. There was no significant difference in clinical remission rate at Week 8 between the HIR and SIR (13.3% vs 10.9%, respectively; p=0.273). The Table displays results for secondary efficacy endpoints. ADA trough concentrations were higher in the HIR versus the SIR (mean [SD] = 39.2 [20.7] and 10.8 [5.2] µg/mL at Wk 4 and 19.3 [9.5] and 8.0 [4.9] µg/mL at Wk 8, respectively) and the levels for the SIR were comparable to those previously reported in ULTRA 2. Higher ADA concentrations were associated with higher clinical remission rate; however, modeling results indicated shallower ERR in this study compared with ULTRA 2. The observed safety profile was similar between the HIR and SIR groups, including AEs of special interest (< 1% across both groups).

Endpoints (Wk 8), n (%)	Adalimumab HIR (n=512)	Adalimumab SIR (n=340)	p-value
1. Endoscopic improvement[a] (endoscopic subscore of 0 or 1)	159 (31.1)	92 (27.1)	0.182
2. Fecal calprotectin < 150 mg/kg	115 (22.5)	67 (19.8)	0.283
3. IBDQ response (increase of IBDQ ≥ 16 from BL)	342 (66.8)	207 (60.9)	0.063
4. Clinical response per full Mayo Score[a,b]	241 (47.1)	136 (40.0)	0.034*
5. Endoscopic remission[a] (endoscopic subscore of 0)	67 (13.1)	34 (10.0)	0.162

*Nominal p-value < 0.05. [a]Endoscopy scored via a central reading protocol. [b]Clinical response per full Mayo Score: Decrease from baseline in the full Mayo Score ≥ 3 points and ≥ 30% from baseline, plus a decrease in RBS ≥ 1 or an absolute RBS ≤ 1. BL, baseline; HIR, higher induction dosing regimen; IBDQ, Inflammatory Bowel Disease Questionnaire; RBS, rectal bleeding score; SIR, standard induction dosing regimen

Conclusion:

In SERENE-UC, there was no additional benefit of the HIR at Wk 8 beyond the approved SIR. Both induction dosing regimens of ADA demonstrated similar clinical and endoscopic efficacy. Both dosing regimens were generally safe and well tolerated. The maintenance portion of the study is ongoing.

References: 1. Reinisch W et al. Gut 2011;60:780-7. 2. Reinisch W et al. Inflamm Bowel Dis 2013;19:1700-9. 3. Sandborn WJ et al. Gastroenterology 2012;142:257-65.

Disclosure:

P1773 - INCREASED ADALIMUMAB LEVELS ARE ASSOCIATED WITH CLINICAL, BIOLOGICAL AND ENDOSCOPIC REMISSION, AND LOWER DISEASE-RELATED COMPLICATIONS RATE IN PATIENTS WITH IBD

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Introduction:

Retrospective and prospective treat-to-target studies have shown biological and endoscopic remission are superior to clinical remission in achieving improved long-term clinical outcomes in patients with inflammatory bowel diseases (IBD). Stricter, more rigorous therapeutic targets may require higher drug levels.

Aims and Methods:

We aimed to study whether higher maintenance adalimumab drug levels are associated with clinical, biological and endoscopic remission. Demographic, clinical, laboratory and endoscopic data were collected retrospectively from 66 consecutive IBD patients treated with adalimumab who had a C-reactive protein (CRP) and/or stool calprotectin measured and endoscopic evaluation within 12 weeks of adalimumab serum trough levels. We defined clinical remission as HBI< 5 or MAYO < 2 for Crohn´s disease (CD) and ulcerative colitis (UC), respectively; biologic remission as CRP < 0.5 mg/dL and/or calprotectin < 250; endoscopic remission as SESCD ≤3 (for ileal disease) or SESCD ≤4 for a more extensive CD or endoscopic Mayo ≤1 for UC. Data was analyzed using STATA statistical analysis software. This study was approved by the local IRB.

Results:

Sixty-six consecutive patients were included in our study. Median age was 37 years (range 20 to 79), 50% were male, most patients (86%) had CD. Patients who achieved clinical, biologic and endoscopic remission had higher serum trough adalimumab levels (ug/mL±StdErr, 8.9±0.9 Vs. 5.7±1, p=0.016; 8.2±0.8 Vs. 6.6 ±1.1, p=0.023; 9.2±1.0 Vs. 6.1±0.7, p=0.019, respectively) . Increased levels of adalimumab were required to reach deeper levels of remission, reaching significance comparing clinical and deep (clinical, biologic and endoscopic) remission (ug/mL±StdErr, 5.9±1 Vs. 11.7±1.5, p=0.04).
Patients who achieved remission had lower odds ratio of developing disease-related complications (OR=0.4, p=0.04). Lower complications rate was also associated with higher maintenance adalimumab serum trough levels (8.4±0.8 Vs. 5.7±0.9, p=0.04).

Conclusion:

Higher adalimumab trough levels may be required to achieve better disease control. This study provides additional data to guide therapeutic drug monitoring with adalimumab.

Disclosure:

Nothing to disclose

P1795 - REAL LIFE EXPERIENCE OF FIRST LINE ANTI-TNF IN CROHN´S DISEASE PATIENTS IN SPAIN: DO WE HAVE DATA TO CHOOSE BETWEEN INFLIXIMAB AND ADALIMUMAB?

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Introduction:

Anti-TNFs represent a key treatment strategy for the management of IBD. However, it would be important to have more data about their use with the aim of facilitating the right choice in clinical practice. One of the aims of this study was to learn about the patterns of use of two anti-TNFs, adalimumab and infliximab, when used in biologic-naïve patients for the treatment of Crohn's disease (CD)

Aims and Methods:

This was a retrospective, observational study, conducted in 24 hospitals in Spain. IBD patients who started first anti-TNF treatment between June 2011 and June 2013 were included consecutively in the participating centres. Data about anti-TNF management were collected. Kaplan Meier analyses were used to evaluate time to treatment intensification and time to discontinuation in CD with adalimumab and infliximab. Data are presented descriptively

Results:

One hundred and ninety-four CD patients were included (n=85 treated with infliximab and n=109 treated with adalimumab). Median age was 43.0 years (range: 20.0-74.0) and most patients presented ileum and colon (L3=44.6%) or terminal ileum location (L1=37.3%). The most common disease behaviour was inflammatory (B1=44.6%). Median follow up time (from treatment initiation until informed consent signed) was 59.7 (range: 43.5 - 76.2) and 60.2 (range: 45.3 - 74.9) months for adalimumab and infliximab respectively. Dose intensification was recorded in 29.4% of patients treated with adalimumab and 28.2% of patients treated with infliximab. Median time to first dose intensification was similar with adalimumab, 15.1 months (range 1.3-61.8) and infliximab, 14.1 months (range 0.2-59.5).
Regarding treatment discontinuation, it occurred in 56.0% of patients treated with adalimumab, and in 63.5% with infliximab. Median time to treatment discontinuation was 27.4 months (range 0.9-66.9) with adalimumab, and 23.0 months with infliximab (range 0.0-58.9).
Concomitant use of corticosteroids at any time during maintenance was similar with adalimumab (31.2%) compared with infliximab (28.2%) being the mean number of cycles needed was similar (adalimumab 1.5, SD 0.8 vs infliximab 1.2, SD 0.5). The use of immunosuppressants at any time during maintenance was similar among the two products (adalimumab: 60.5% vs infliximab: 76.5%) being the mean number of required cycles was also comparable (adalimumab 1.3, SD 0.9 vs infliximab 2.2, SD 8.4).

Conclusion:

Similar proportions of patients with CD received dose intensification with infliximab and adalimumab, and the discontinuation rates with both anti-TNFs were also similar.
Dose intensification with both anti-TNFs was required in around one in every three patients, and after a similar median time (slightly longer than 1 year).
More than half of patients treated with adalimumab and infliximab discontinued treatment during the follow-up, and this occurred after a comparable median time (slightly longer than 2 years).
Although a significant proportion of patients required concomitant use of corticosteroids and/or immunosuppressants, the average number of required cycles was low.
Despite the common use of anti-TNFs as the first biologic in CD, we have not found any major difference between adalimumab and infliximab that could lead to a preferred treatment option.

Disclosure:

P1801 - A PROPENSITY SCORE-WEIGHTED COMPARISON OF VEDOLIZUMAB, ADALIMUMAB, AND GOLIMUMAB IN PATIENTS WITH ULCERATIVE COLITIS: REAL-LIFE DATA FROM THE SICILIAN NETWORK FOR INFLAMMATORY BOWEL DISEASE (SN-IBD)

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Introduction:

The recent VARSITY trial showed that Vedolizumab (VDZ) was superior to Adalimumab (ADA) in achieving clinical remission and mucosal healing in patients with ulcerative colitis (UC). Conversely, no real-life data on the comparative effectiveness of VDZ, ADA, and Golimumab (GOL) in UC have been published yet.

Aims and Methods:

Data of consecutive patients with UC treated with VDZ, ADA, and GOL from June 2015 to December 2018 were extracted from the cohort of the Sicilian Network for Inflammatory Bowel Disease (SN-IBD). A three-arms propensity score-adjusted analysis was performed to reduce bias caused by imbalanced covariates at baseline, including the proportion of TNF-α inhibitor naïve and non-naïve patients, using the Inverse Probability of Treatment Weighting (IPTW) approach. The effectiveness was evaluated at 8 weeks, 52 weeks, and as treatment persistence at the end of follow up. The clinical endpoints were steroid-free clinical remission (partial Mayo score < 2 without steroid use) and clinical response (reduction of the partial Mayo Score ≥2 points with a concomitant decrease of steroid dosage compared with baseline). The sum of the two outcomes was defined as clinical benefit. The achievement of mucosal healing (endoscopic Mayo score 0-1) was assessed after at least 6 months of biological treatment.

Results:

A total of 463 treatments (187 VDZ; 168 ADA; 108 GOL) were included, with a median follow-up of 47.6 weeks (IQR 20.0-85.9). At 8 weeks, a clinical benefit was achieved in 70.6% patients treated with VDZ, in 68.5% patients treated with ADA, and in 67.6% patients treated with GOL (p = n.s. for all comparisons); at 52 weeks, VDZ showed better rates of clinical benefit compared with both ADA (71.6% vs. 47.5; OR: 2.79, 95% CI 1.63-4.79, p< 0.001) and GOL (71.6% vs. 40.2%; OR: 3.77, 95% CI 2.08-6.80, p< 0.001), while the difference between ADA and GOL was not significant. Cox survival analysis demonstrated that patients treated with VDZ had a reduced probability of treatment discontinuation compared to those treated with ADA (HR: 0.42, 95% CI 0.28-0.64, p< 0.001) and GOL (HR: 0.30, 95% CI 0.19-0.46, p< 0.001), while patients treated with ADA had a significantly reduced risk of treatment discontinuation compared to those treated with GOL (HR: 0.71, 95% CI 0.50-1.00, p=0.048). Post-treatment mucosal healing rates showed a numerical but non-significant difference in favour of VDZ (48.1%) compared with ADA and GOL (38.0% and 34.6%, respectively).

Conclusion:

In the first study comparing at the same time the clinical effectiveness of VDZ, ADA, and GOL in UC patients via propensity score-adjusted analysis, VDZ was superior to both subcutaneous agents at 52 weeks and as treatment persistence, while ADA showed a superior treatment persistence compared to GOL.

Disclosure:

P1806 - IMPACT OF THE SWITCH FROM ORIGINAL ADALIMUMAB TO BIOSIMILAR ADALIMUMAB SB5 ON SERUM DRUG TROUGH LEVELS, CLINICAL AND BIOLOGICAL DISEASE ACTIVITY IN PATIENTS WITH IBD

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Introduction:

Biosimilar adalimumab SB5 is a biosimilar monoclonal antibody for the treatment of patients with autoimmune diseases such as inflammatory bowel disease (IBD). Generally, biosimilars are biological products showing high resemblance to the reference biological products, and they exhibit no clinically meaningful differences in terms of safety and effectiveness. Since monitoring of adalimumab serum trough levels hold an important significance in treatment modalities, insufficient data about monitoring of drug serum trough levels in IBD patients treated with SB5 are present to date.

Aims and Methods:

In this study, we applied original adalimumab-validated ELISA based on TNFa as a target antigen to determine drug serum levels of SB5. The primary objective of current study was to compare serum trough levels of original adalimumab and SB5 before and after switching from the original to the biosimilar drug. Secondary aims were to assess clinical effectiveness of biological treatment after the switching from original adalimumab to SB5 by symptom activity indexes (Harvey-Bradshaw index (HBI) in Crohn's disease, and partial Mayo score (pMayo) in ulcerative colitis and response as assessed by systemic and local inflammatory markers (C-reactive protein, CRP; and fecal calprotectin, FC).
Eighty-seven IBD patients, responders in maintenance adalimumab treatment period, after the switching from original adalimumab to SB5, with known previous three measurements of the original adalimumab trough levels, were included. Sera form IBD Blood Bank established according to the Ethics Committee of *ISCARE* (Nr 2015/Ia) were used, and patient data were anonymously processed according to the latest version of the Helsinki Declaration of Human Research Ethics.
Biosimilar adalimumab trough levels at W10 after the switching were measured by enzyme immunoassay (ADALIMUMAB ELISA ImmunoGuide, REF: IG-AA103). CRP serum concentrations

measured by immunonephelometry and fecal calprotectin levels measured by fluoroimmmunoassay on switching day were compared with W10 values after the switching.

Results:

Of 87 patients, 47 were women and 40 were men; 77 with Crohn's disease and 10 with ulcerative colitis; median age 39.5 (23 to 70) years. No differences in CRP and FC values before and after the switching were observed (Spearman's rank correlation coefficients r = 0.320 (p = 0.0048) and r = 0.833 (p < 0.0001), respectively). Similarly, no significant differences were found in HBI and pMayo values: Kruskal-Wallis H-test have shown p = 0.824 for HBI and p = 0.855 for pMayo indexes. Moreover, excellent quantitative agreement was observed between mean adalimumab trough levels before and after the switching from the original drug to SB5: Spearman's rank coefficient values were r = 0.756 and p < 0.0001.

Conclusion:

TNFa-based ELISA kit for measuring adalimumab trough levels showed similar overall performance in the detection of original and biosimilar adalimumab-containing sera. Clinical effectiveness of adalimumab treatment after the switching from the original to the biosimilar adalimumab SB5 assessed by symptom activity indexes and by systemic and local inflammatory markers remained identical after the switching.

Disclosure:

OP005 - REAL-WORLD SAFETY OF VEDOLIZUMAB AND ANTI-TNF THERAPIES IN BIOLOGIC-NAïVE ULCERATIVE COLITIS AND CROHN'S DISEASE PATIENTS: RESULTS FROM THE EVOLVE STUDY

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Introduction:

The GEMINI phase III clinical trials showed a favourable safety profile for vedolizumab (VDZ) in treating patients (pts) with moderate-to-severely active ulcerative colitis (UC) and Crohn's disease (CD), however real-world studies are needed comparing the safety of VDZ to anti-tumour necrosis factors (anti-TNF) agents.

Aims and Methods:

The objective was to compare the safety of VDZ and anti-TNF agents in a real-world cohort of biologic (bio)-naïve pts with UC or CD. This was a multi-country (Canada, Greece and the United States), retrospective chart review study of bio-naïve pts (≥18 years old) with ≥ 6 months follow-up, initiating treatment (Tx) with VDZ or an anti-TNF [adalimumab, infliximab, golimumab, certolizumab pegol] between May 2014 and March 2018. Data were collected from Tx initiation to earliest of death, chart abstraction date or 6 months post-Tx discontinuation (Canada only). Serious adverse events (SAEs) and serious infections (SIs) (defined as either life threatening, requiring hospital admission, resulting in significant disability/incapacity, or recorded in the chart as an important medical event) occurring from Tx initiation up to five half-

lives post-Tx discontinuation were assessed. Incidence rates (per 100 person-years [PYs]) of SAEs and SIs were estimated. A Cox proportional hazards model adjusted for baseline characteristics was used to compare incidence rates between Tx cohorts. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) are reported.

Results:

This study included 1,095 pts (VDZ: 598 [UC: 380; CD: 218]; anti-TNF: 497 [UC: 224; CD: 273]) from 42 sites. Compared to anti-TNF pts, the VDZ cohort were older (mean [SD] age [years]: VDZ, 47.9 [17.4]; anti-TNF, 39.6 [15.2] [p< 0.01]), were proportionately more male (male: VDZ, 56.9%; anti-TNF, 49.9% [p=0.02]) and had a longer disease duration (median [range: min-max] disease duration [years]: VDZ, 5.0 [0.04- 54.0]; anti-TNF, 2.0 [< 0.1 - 49.0] [p< 0.01]). Median (range: min-max) follow-up (months) was: VDZ, 15.3 (3.0-47.0); anti-TNF, 16.3 (3.5-51.0). Incidence rates of first occurrence (per 100 PY [95% CI]) of SAEs (VDZ: 4.6 [3.5-6.8]; anti-TNF: 10.3 [9.5-14.9]) and SIs (VDZ: 2.6 [1.9-4.4]; anti-TNF: 7.0 [5.9-10.2]) were significantly lower in VDZ versus anti-TNF pts (adjusted HR: SAE, 0.42 [0.27-0.66]; SI, 0.33 [0.18-0.58]). Similar trends were shown when data were stratified by UC and CD, separately (Table 1). Lastly, the proportion of pts who experienced gastrointestinal (GI) infections was significantly higher among anti-TNF versus VDZ pts (4.4% versus 1.5%, respectively, p< 0.01).

Outcome	Ulcerative Colitis			Crohn's Disease		
	Vedolizumab IR (95% CI) N=380	Anti-TNF IR (95% CI) N=224	Adjusted Hazard Ratio (95% CI)	Vedolizumab IR (95% CI) N=218	Anti-TNF IR (95% CI) N=273	Adjusted Hazard Ratio (95% CI)
Serious Adverse Events	3.8 (2.6-6.2)	11.3 (8.9-17.5)	0.34 (0.19-0.63)*	3.0 (1.8-5.0)	5.7 (3.5-9.4)	0.47 (0.22-1.02)
Serious infections	6.1 (4.1-10.5)	9.5 (7.7-14.5)	0.45 (0.23-0.89)*	1.9 (0.8-4.5)	7.9 (5.5-11.3)	0.18 (0.06-0.50)*

Data are incidence rates (95% CI) and hazard ratios (95% CI). Incidence rates are unadjusted and are per 100 person-years; hazard ratios are from adjusted Cox proportional hazards models (adjusted for baseline confounders: age, sex, disease duration, albumin, C-reactive protein, UC/CD-related hospitalisations [prior 12 months] and disease severity). Indication (UC/CD) was a covariate for the overall analysis and was not included for disease specific models. CD: Crohn's Disease; UC: Ulcerative colitis, IR: Incidence rate.

Half-lives for treatments: VDZ: 125days (18 weeks), Infliximab: 47.5 days (6.8 weeks), Infliximab-dyyb: 47.5 days (6.8 weeks), Infliximab-abda: 47.5 days (6.8 weeks), Adalimumab: 70 days (10 weeks), Adalimumab-atto: 70 days (10 weeks), Golimumab: 70 days (10 weeks), Certolizumab pegol: 70 days (10 weeks). *Significant difference between VDZ and Anti-TNF cohorts based on adjusted HRs.

Conclusion:

Bio-naïve pts treated with VDZ had a significantly lower likelihood of experiencing SAEs and SIs, including GI infections, than those treated with anti-TNF therapies. These data support a favourable safety profile of VDZ versus anti-TNF in bio-naïve inflammatory bowel disease pts in real-world clinical practice

Disclosure:

P0434 - REAL LIFE EFFECTIVENESS OF VEDOLIZUMAB IN PATIENTS WITH IBD: A SINGLE CENTER EXPERIENCE

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Introduction:

Vedolizumab is a fully humanized monoclonal antibody that selective binds the α4β7 integrin, recently approved for the treatment of patients with Inflammatory Bowel Diseases (IBD). It acts blocking the migration of circulating T-lymphocytes into inflamed gastro-intestinal tissue

Aims and Methods:

Here we present a real-life experience with patients affected with IBD treated with Vedolizumab. All consecutive patients observed at a single Center (Gastroenterology Department of "Casa Sollievo della Sofferenza" Hospital) treated with Vedolizumab from September 2016 were included. Demographic and clinical data (age at disease diagnosis, disease location and duration, behavior, and previous therapies) were collected. We also collect clinical activity before and during therapy with Vedolizumab and concomitant medications. The clinical response to induction (valued by means of Harvey Bradshaw index and partial Mayo score for Crohn's disease and Ulcerative Colitis patients respectively) was assessed after 3 months of therapy. Persistence of therapy with Vedolizumab was also evaluated.

Results:

A total of 68 patients (30 Crohn's Disease (CD) and 38 Ulcerative Colitis (UC)) were included. Thirty-eight patients were male (55.8%), and the mean disease duration was 10.2±7.3 years and 11.8±6.8 years for CD and UC respectively. The majority of patients had moderate activity when started Vedolizumab (90% and 86.8% of those with CD and UC, respectively). Fifty-two patients (76.5%) had been treated with Anti TNF alpha before Vedolizumab. Clinical response after three months of therapy was achieved in 22 CD patients (73%) and 33 UC patients (87%). Fifteen patients (11 CD and 4 UC) definitively discontinued Vedolizumab (9 for primary non response, 1 for intolerance, and five for loss of response after a mean of 25±2.9 months of therapy - range 21-30). Fifty-two patients (76.4%) are ongoing in treatment with a mean persistence of therapy of 12.2±7,3 months (range 1 - 33). No significant differences for clinical response rate were found between patients naïve vs previous treated with anti TNF alpha (87% vs 83%, p=1.0), short (≤ 2 years) vs long disease duration (75% vs 83%, p=0.6), older (≥ 65 years) vs younger patients (70% vs 85%, p=0.1), and disease behavior for Crohn's disease (66.6% of patients with B1 responded to Vedolizumab vs 80% both for B2 and B3, p=0.3).

Conclusion:

Vedolizumab was effective in patients with IBD (both CD and UC), irrespective of previous anti TNF alpha therapy, age of patients, disease duration and disease behavior in Crohn's disease.

Disclosure:

Nothing to disclose

P1091 - CLINICAL EFFECTIVENESS OF FIRST-LINE ANTI-TNF THERAPIES AND SECOND-LINE ANTI-TNF THERAPY POST-VEDOLIZUMAB DISCONTINUATION IN PATIENTS WITH ULCERATIVE COLITIS OR CROHN'S DISEASE

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Introduction:

Real-world data is needed to understand outcomes in patients with ulcerative colitis (UC) or Crohn's disease (CD) who discontinue first-line (1L; biologic-naive) vedolizumab (VDZ) treatment (Tx) and go on to receive subsequent anti-tumour necrosis factors (anti-TNF) Tx.

Aims and Methods:

The objective was to compare the clinical effectiveness of second-line (2L) anti-TNF Tx post 1L VDZ and 1L anti-TNF use in patients with UC or CD. This was a real-world, multi-country, retrospective chart review study in adult (≥18 years old) UC and CD patients treated with 1L anti-TNF or 2L anti-TNF after discontinuation of 1L VDZ for any reason (received May 2014 to March 2018). Patients were included from sites across Canada, Greece and the United States. Anti-TNF therapies included: adalimumab, infliximab, golimumab and certolizumab pegol. The index date was defined as date of 1L Tx initiation. Clinical effectiveness data were collected from 1L or 2L Tx initiation to earliest of death, chart abstraction date or 6 months post-1L Tx discontinuation (Canada only). Cumulative rates of Tx persistence, clinical response, and clinical remission were estimated using the Kaplan-Meier method for UC and CD (separately and combined) over 6 months. Cumulative rates of clinical response and clinical remission were assessed using pre-defined hierarchical algorithms of standard disease measures as reported in the medical records. P-values were generated using the log-rank test.

Results:

This analysis included 579 anti-TNF patients (1L: 497 [UC: 224; CD: 273]; 2L: 82 [UC: 58; CD: 24]) from 36 sites. The proportion of patients in each cohort were: adalimumab (1L: 41.4%; 2L:19.5%), infliximab (1L: 52.7%; 2L: 79.3%), golimumab (1L: 4.8%; 2L: 1.2%) and certolizumab pegol (1L: 0.8%; 2L: 0.0%). Mean (SD) age at index date: 1L, 39.6 (15.2); 2L, 49.4 (18.6) years, male: 1L, 49.9%; 2L, 61.0%, median (range: min-max) disease duration: 1L, 2.0 (< 0.1 - 49.0); 2L, 3.7 (0.1 - 54.0) years. At 6 months, cumulative rates of Tx persistence (1L: 83.9%; 2L: 83.6%), clinical response (1L: 49.5%; 2L: 65.6%) and clinical remission (1L: 29.5%; 2L: 31.4%), were similar between 1L and 2L patients (Table 1). Results were similar when data were stratified by UC and CD, albeit sample sizes were small (Table 1).

Outcomes	Overall		Ulcerative Colitis		Crohn´s Disease	
	First-Line N=497	Second-Line N=82	First-Line N=224	Second-Line N=58	First-Line N=273	Second-Line N=24
Treatment Persistence: 3 months, % [N at risk]	91.7 [451]	95.1 [64] P=0.45	87.4 [195]	94.3 [47] P=0.18	95.2 [256]	96.4 [17] P=0.81
Treatment Persistence: 6 months, % [N at risk]	83.9 [411]	83.6 [36] P=0.87	76.6 [170]	79.5 [26] P=0.50	90.0 [241]	92.2 [10] P=0.82
Clinical Response: 3 months, % [N at risk]	33.9 [269]	43.6 [23] P=0.25	38.4 [109]	44.8 [16] P=0.54	30.1 [160]	41.3 [7] P=0.52
Clinical Response: 6 months, % [N at risk]	49.5 [186]	65.6 [9] P=0.09	57.1 [61]	61.1 [6] P=0.58	43.5 [125]	74.8 [3] P=0.13
Clinical Remission: 3 months, % [N at risk]	17.5 [310]	22.6 [30] P=0.44	9.7 [136]	11.0 [24] P=0.92	22.9 [174]	49.2 [6]* P=0.02
Clinical Remission: 6 months, % [N at risk]	29.5 [240]	31.4 [13] P=0.56	19.6 [104]	14.7 [12] P=0.69	36.2 [136]	74.6 [1]* P<0.01

Cumulative data were generated from Kaplan-Meier analyses and p-values are from the log-rank test. *Significant difference (P<0.05) between first and second-line. N at risk: Number of patients still on treatment at timepoint and clinical outcome can still be assessed. Rates of clinical response and clinical remission were assessed using pre-defined hierarchical algorithms of: CD: Crohn's disease activity index → Harvey Bradshaw index→ medical record documentation of complete or partial response → Physician global assessment. UC: Mayo Overall Score → Mayo Partial score → medical record documentation of complete or partial response → Physician global assessment.

[Clinical Effectiveness of First-Line Anti-TNF and Second-Line Anti-TNF (Post-Vedolizumab) Therapies in Ulcerative Colitis and Crohn's Disease Patients]

Conclusion:

Cumulative rates of Tx persistence, clinical response and clinical remission observed in the first 6 months of Tx were comparable between 1L anti-TNF patients and those who switched to a 2L anti-TNF following the discontinuation of 1L VDZ. This suggests that 1L VDZ may not impact the effectiveness of subsequent anti-TNF Tx in real-world clinical practice. As 2L sample size was limited, these hypothesis-generating data warrant further study.

Disclosure:

P1105 - VEDOLIZUMAB INDUCES DEEP REMISSION AND IMPROVES QUALITY OF LIFE IN PATIENTS WITH INFLAMMATORY BOWEL DISEASES: THE ANCONA EXPERIENCE

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Introduction:

Vedolizumab (VDZ) is an α4β7 integrin antagonist approved for the treatment of adult patients (pts) with moderate to severe ulcerative colitis (UC) and Crohn´s disease (CD).

Aims and Methods:

The primary outcome of the study was to evaluate the effect of VDZ on clinical response in pts with UC and CD at the 14th week. Secondary outcomes were to evaluate clinical remission, mucosal healing, deep remission, steroid-free remission and quality of life at different time points (14th week, 6, 12 and 24 months).
We retrospectively evaluated 39 pts who referred to our Inflammatory Bowel Disease Unit and received VDZ for moderate-severe UC (26 pts) and moderate-severe CD (13 pts). As concerns the UC and CD outcomes, clinical response was defined by a reduction in Mayo score ≥3 points and in Harvey-Bradsaw index (HBI) ≥3 points, clinical remission by a Mayo score ≤2 and by a HBI < 5 and endoscopic remission by endoscopic Mayo subscore ≤1 and by endoscopic SES-CD score ≤2, respectively. Steroid free-remission was evaluated in UC pts only. Deep remission was defined, in both diseases, as clinical, endoscopic and biochemical remission. Serum C-reactive protein (CRP) and faecal calprotectin (FC) were evaluated in pts at all time points. Quality of life (QoL) was evaluated by the 32-item version of Inflammatory Bowel Disease Questionnaire (IBDQ-32).

Results:

UC pts: 12 out of 26 UC pts had previously failed anti-TNF therapy; clinical response at the 14th week was observed in 77% of the pts and no significant differences were found between naive and anti-TNF treated pts. Non-responder pts showed a more severe Mayo endoscopic subscore (2.8 vs 2.2; P< 0.02). Clinical remission occurred in 60%, 64%, 67% and 75% of pts at the 14th week, 6, 12 and 24 months, respectively. Steroid-free remission was 85% (17/20) at the 14th week and 75% at 24 months. Mucosal healing was above 70% at all time points. In pts who had a clinical response, FC levels decreased from 529.15 mg/kg at baseline to 103.7 mg/kg at the 14th week and was always less than 50 mg/kg after 6, 12 and 24 months. Similarly, CRP levels decreased from 1.85 mg/dl at baseline to 0.9 mg/dl at the 14th week, and were within the normal range (< 0.50 mg/dl) after 12 and 24 months. Deep remission was 35% at the 14th week and 75% at 24 months. QoL in responder pts was 131±34 at baseline, significantly increased after 14 weeks (171,9±29; P< 0.001) and remained stable over time.
CD pts: 12 out of 13 pts had previously failed anti-TNF therapy; clinical response at the 14th week was observed in 46% of the pts, whereas clinical remission rates were 100%, 80%, 100% and 100% at the 14th week, 6, 12 and 24 months, respectively. Mucosal healing was observed in 25% of pts at 12 months and in 100% of pts at 24 months, whereas deep-remission was achieved in 25% and 50% of pts at the same time points. In responder pts, FC, CRP and QoL showed a significant improvement starting from the 6th month.
Advers events were observed in 5/39 pts: psoriasis (2 pts), joint symptoms (1 pt), arterial hypertension (1 pt) and mild urticaria (1 pt); however only 1 pt with psoriasis had to discontinue the treatment.

Conclusion:

VDZ was effective and safe for induction and maintenance of deep remission and of steroid-free remission in pts with UC, and significantly improved their QoL; serum CRP and FC levels correlated with clinical response. Even if data in CD pts are limited, VDZ appeared effective for induction and maintenance of clinical and endoscopic remission also in these pts, although the improvement in biochemical indices and in the QoL required at least 6 months.

Disclosure:
Nothing to disclose

P1109 - COMBINED ENDOSCOPIC AND HISTOLOGICAL HEALING WITH VEDOLIZUMAB IN THERAPY-REFRACTORY CROHN'S DISEASE, DATA FROM THE LOVE-CD TRIAL

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Introduction:

Efficacy of vedolizumab (VDZ) has been confirmed in Crohn's disease (CD), but there is limited data on mucosal healing, a combination of endoscopic and histological remission. In the LOVE-CD (LOw countries VEdolizumab in CD) trial we explored this novel endpoint in patients with active CD receiving VDZ for 52 weeks

Aims and Methods:

The aim of this exploratory analysis was to assess mucosal healing, the combination of endoscopic and histological healing, through week 26 in CD patients treated with VDZ. We included patients who had centrally read endoscopy at week 0 and 26 and paired biopsies at the same time points. Only patients with active histological inflammation at baseline (Robarts Histopathology Index (RHI) score > 7) were studied. All patients had active CD (Crohn's Disease Activity Index (CDAI) > 220 and presence of mucosal ulcerations at baseline endoscopy) and were treated with VDZ 300 mg infusions at week 0, 2, 6 and every 8 weeks thereafter to week 52, with an additional infusion at week 10 in the absence of clinical response. Mucosal biopsies were collected from the edge of the most prominent ulcer in the terminal ileum and 4 colonic segments (ascending, transverse, descending colon and sigmoid and rectum), or from the most severely affected area if no ulcers were present. If a segment was completely normal, two biopsies were taken at random per segment. Histopathology was assessed blindly using the RHI, which represents a reproducible and responsive index that incorporates four histologic descriptors (i.e. severity of chronic inflammatory infiltrate, the number of neutrophils in the lamina propria, the number of neutrophils in the epithelium and the severity of erosions or ulceration), each of which is graded from 0 to 3 (Mosli M et al. Gut. 2017;66(1):50-58). In case more than one biopsy was available per segment, the biopsy sample with the maximum RHI score was used for further analysis.

Results:

Paired biopsies from the same segment were available in 65 patients, 40 of which (62%) had active histological inflammation (RHI score > 7) at baseline. Out of these patients, 35/40 (88%) failed on prior anti-TNF therapy and median disease duration was 8 (4-18) years. Fourteen out of these 40 patients (35%; 95% CI (0.21, 0.52)) achieved mucosal healing at week 26 (SES-CD < 4 and RHI ≤ 6). Endoscopic remission at week 26 was observed in 17/40 (43%) and histologic remission in 23/40 (58%).

Conclusion:

Mucosal healing was achieved in 35% of CD patients with active histological inflammation at baseline after 26 weeks treatment with VDZ. These outcomes show that VDZ is able to induce both endoscopic and histological healing in therapy-refractory CD.

References:

Mosli M et al. Gut. 2017;66(1):50-58

Disclosure:

Nothing to disclose

P1127 - TREATMENT OUTCOMES FOLLOWING ADMINISTRATION OF VEDOLIZUMAB IN PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS

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Introduction:

The anti-integrin monoclonal antibody vedolizumab (VDZ) has been approved for the treatment of moderate to severe ulcerative colitis (UC). There is a need for evaluating the clinical efficacy of VDZ in real-world clinical settings. In addition, the effect of VDZ on the endoscopic activity of UC and its ability to induce mucosal healing are still being explored.

Aims and Methods

We aimed to report the clinical and endoscopic response to VDZ in a large cohort of Greek patients with UC who were refractory to previous therapies. Patients were recruited from 11 tertiary Greek IBD centers. VDZ was administered according to standard induction and maintenance protocols. Short-term response was evaluated at week 12 and defined according to the Gemini 1 criteria (reduction in the Mayo Clinic score of at least 3 points and a decrease of at least 30% from baseline, with a decrease of at least 1 point on the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1). Long-term efficacy was evaluated at week 54. Persistence of treatment at week 54 was considered as an indicator of clinical efficacy. The Gemini 1 Criteria for remission at 54 weeks (full Mayo score of 2 or lower and no subscore higher than 1) were also independently applied. Mucosal healing was defined as endoscopy Mayo score of 0.

Results:

In total, 97 patients with UC [males=57, mean age: 45, (range: 17-79 years)] have been included in the study. Three patients had proctitis (E1), 37 left-sided colitis (E2), and 57 extensive disease (E3). Twenty-three patients (23.7%) had at least one active extraintestinal manifestation at VDZ commencement. There were 53 anti-TNF naive patients. We present herein data from the 78 patients who have completed at least one-year from initiation of VDZ treatment.

Short-term response data: At wks 12-14, 17/78 patients (21.8%) exhibited no response, while 61/78 (78.2%) fulfilled criteria for clinical response. Twenty-two patients (28.2%) were on concomitant treatment with corticosteroids and 13 (16.7%) with azathioprine/6-mercaptopurine. A colonoscopy at 12-14 wks was performed in 48 patients; 27% had complete mucosal healing (endo Mayo score=0), whereas an additional 48% had partial endoscopic response (decrease in endoscopic Mayo Score). We observed statistically significant improvement in patient-reported outcomes (PRO) from week 0 to week 12 of treatment with VDZ. In particular, PRO-UC1/rectal bleeding decreased from 1.22 ± 0.98 to 0.32 ± 0.65, ($P< 0.0001$) and PRO-UC2/number of bowel movements from 2.69 ± 1.12 to 1.51 ± 0.78, ($P< 0.0001$), whereas SIBDQ score increased from 43 ± 13 to 55 ± 10, ($P< 0.0001$).

Long-term response data: At week 54, 52/78 patients were still on VDZ therapy (drug persistence: 68%). Less than 10% of patients were receiving concomitant steroids and 15% azathioprine/6-mercaptopurine. Of the patients who had a colonoscopy at week 52 (n=30), 30% demonstrated complete mucosal healing and another 43% had a partial endoscopic response. At wk 54, PRO-UC1/rectal bleeding decreased from 1.34 ± 1.03 to 0.31 ± 0.6, ($P< 0.0001$) and PRO-UC2/number of bowel movements from 1.82 ± 1.12 to 0.67 ± 0.88, ($P< 0.0001$), whereas SIBDQ score increased from 41 ± 16 to 50 ± 13, p=056).

Conclusion:

In this national multicenter study, VDZ demonstrated high response rates both in the short- and long-term evaluations. Satisfactory outcomes were obtained at the clinical and endoscopic measurements combined with improved quality of life. Our study adds to other published data on real-world evidence and supports the notion that VDZ is a reliable therapeutic option for patients with UC

Disclosure:

P1132 - UTILITY OF VEDOLIZUMAB DRUG LEVEL MONITORING IN IBD PATIENTS - REAL LIFE EXPERIENCE: PILOT STUDY

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Introduction:

Therapeutic drug monitoring has become an accepted tool in the therapy management in Inflammatory Bowel Disease (IBD). The assessment of trough levels and neutralising anti-drug antibodies are widely used to optimise the therapeutic management, and its usefulness has been more studied in anti-TNF therapies especially in situations of treatment failure. However, there is not enough data published on the usefulness of the measurement of vedolizumab (VDZ) levels in IBD patients, with no established cut-off points. The objective of our study was to evaluate the correlation between VDZ level at induction and maintenance treatment with the clinical response in patients with IBD.

Aims and Methods:

This is a retrospective observational, single center study. We included adult patients with UC and EC treated with VDZ between January and December 2018, VDZ serum levels were prospectively collected before induction at 6, 14 and 24 weeks. Clinical and biochemical response was collected at 14 and 24 weeks. Data was analyzed by classification tree model to establish variables related with remission.

Results:

12 patients were included, 58.3% with UC and 41.7% with CD. 69.2% were women with a mean age of 41 ± 12 and a mean disease duration of 11.5 ± 8.15 years. 91.7% were treated with anti-TNF therapy previously. The median VDZ level was 33.4 mg/ml (26,7 -39,1), 10,3 mg/ml (7,26-12,8), 11,2ug/ml (8,47-14,45) at baseline, week 14 and week 24 respectively. Clinical remission was achieved in 33.3% (4/12) at week 14, and 41.6% (5/12) at week 24. 33.3% (4/12) in patients who had VDZ level at week 6 between 35 - 47,4 ug/ml. The only variable that was correlated with the remission at weeks 14 and 24 in the tree model CRT was the VDZ level at week 6 (induction therapy) (Table 1).

Clinical remission Week 14 and 24	VDZ level week 6 (ug/ml)	Prediction certainty (%)
Yes	35 - 47.4	100
No	<35 // >47,4	100

Conclusion: In our cohort, the only variable that was correlated with the remission at weeks 14 and 24 was the VDZ level at week 6. VDZ level at week 14 and 24 were not correlated with clinical remission.

Disclosure: Nothing to disclose

P1136 - CORRELATION OF VEDOLIZUMAB TROUGH LEVELS WITH CLINICAL AND BIOCHEMICAL MARKERS IN INFLAMMATORY BOWEL DISEASE

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Introduction:

The clinical utility of vedolizumab (VDZ) trough levels (VTLs) is not well established.

Aims and Methods:

The aim of this study was to determine if there is a correlation between VTLs and clinical and biochemical outcomes. We performed a prospective, cross-sectional study to examine the association between VTLs and clinical and biochemical outcomes. VTLs immediately prior to VDZ infusion were collected simultaneously with CRP and Harvey Bradshaw index (HBI)/Simple Clinical Colitis Activity index (SCCAI) (for Crohn's disease, CD, and ulcerative colitis, UC, respectively). Biochemical remission was defined as CRP ≤ 5 mg/L and clinical remission was defined as HBI ≤ 4 or SCCAI ≤ 2. Combined remission was defined as those meeting criteria for both clinical and biochemical remission. Fishers exact and Mann-Whitney U tests were used to compare groups and ROC analysis to identify a therapeutic threshold.

Results:

 45 samples with matched clinical and biochemical data were collected for 43 patients (24 UC, 15 CD and 4 inflammatory bowel disease- unclassified). Approximately equal numbers of patients had 4-weekly VDZ infusions (n=21) compared to 8-weekly (n=22). 25 out of 43 patients (58%) were on concomitant immunomodulation. The median trough level was 18.3 µg/mL (range < 2 - 44.7 µg/mL) and anti-VDZ antibodies were not detected in any patient. No significant difference could be detected between median VTLs for active disease vs combined remission (24.1 µg/mL vs 16.4 µg/mL, p=0.84). In the UC subgroup, there was a difference in median VTLs between those in biochemical remission compared to those with active disease (24.5 µg/mL vs 7.3 µg/mL, p=0.088). ROC analysis did not identify an optimal therapeutic threshold to achieve combined remission [AUC (95% CI) 0.52 (0.32-0.72)]. However, in the UC cohort a potential therapeutic threshold was identified [AUC (95% CI) 0.76 (0.41-1.0)]. A VTL of 10.7 µg/mL differentiated those with a normal CRP from those with a raised CRP. A comparison (using Fisher's exact test) of the highest vs lowest VTL quartiles did not show a significant difference in the proportion of patients who were in remission vs active disease.

Conclusion:

A correlation between VTLs and clinical and biochemical markers of disease activity was not shown. However, in the UC cohort a level of 10.7 µg/mL differentiated those in biochemical remission from those with active disease. This is a preliminary, small sample size study and analysis of VTLs for our entire VDZ cohort is being conducted.

Disclosure:

Nothing to disclose

OP167 - COMPARISON OF VEDOLIZUMAB AND INFLIXIMAB EFFICACY IN ULCERATIVE COLITIS AFTER FAILURE OF A FIRST SUBCUTANEOUS ANTI-TNF AGENT: A MULTICENTRE COHORT STUDY

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Introduction:

Few data are available so far to select the best therapeutic option after failure of a first subcutaneous anti-TNF agent in ulcerative colitis (UC). The objective of the present study was to compare the efficacy of infliximab (IFX) and vedolizumab (VDZ) in UC patients who stopped a first subcutaneous anti-TNF agent.

Aims and Methods:

Consecutive UC patients who started IFX or VDZ from February 2009 to November 2018 in 12 French referral centres after receiving at least one injection of adalimumab or golimumab have been included in a retrospective study. Inclusion corresponded to the first administration of IFX or VDZ. Outcomes were rate of clinical remission (defined as a partial Mayo score - PMS - ≤ 1) at week 14, survival without treatment discontinuation, and survival without any UC-related event (treatment discontinuation, colectomy, acute severe UC or hospitalization). Predictors of clinical remission at week 14 were determined by multivariate analysis logistic regression.

Results:

 Among the 225 patients included [133 (59%) male; median age: 41; InterQuartileRange: 27-55) years; median PMS was 6/9 (5-8)], 154 (68%) received IFX and 71 (32%) VDZ after failure of a first subcutaneous anti-TNF agent. At inclusion, patients treated with IFX were significantly more often men, having more recent UC and more primary non-response to the first anti-TNF (116 (77%) in the IFX group, 44 (62%) in the VDZ group), were more often admitted for the current flare, received more combotherapy and had a higher median PMS [6 (5-8)] as compared to those treated with VDZ [5.5 (3-7)]. At week 14, 40 (26%) patients treated with IFX were in clinical remission as compared to 35 (49%) patients treated with VDZ (p< 0.01; odds ratio (OR): 2.77; 95%-confidence interval (95%CI): 1.54; 4.99). After adjustment on baseline characteristics, the difference between both drugs was nearly significant (OR 2.12; 95%CI: 0.95-4.80; p=0.07). With a median follow-up duration of 115 (55-165) months, survival rates without treatment discontinuation at 1 year and 3 years were 86% and 69% for patients receiving IFX, and 97% and 91% for those receiving VDZ (p< 0.01). Survival rates without UC-related event at 1 year and 3 years were 85% and 67% with IFX and 93% and 87% with VDZ (p< 0.01).

Conclusion:

After failure of a first subcutaneous anti-TNF agent, patients treated with VDZ achieved more clinical remission at week 14 and less UC-related events - including treatment discontinuation,

colectomy, acute severe UC and hospitalization - than those treated with IFX. Such results have to be confirmed by head-to-head trials.

Disclosure:

Nothing to disclose

P1109 - COMBINED ENDOSCOPIC AND HISTOLOGICAL HEALING WITH VEDOLIZUMAB IN THERAPY-REFRACTORY CROHN'S DISEASE, DATA FROM THE LOVE-CD TRIAL

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Introduction:

 Efficacy of vedolizumab (VDZ) has been confirmed in Crohn's disease (CD), but there is limited data on mucosal healing, a combination of endoscopic and histological remission. In the LOVE-CD (LOw countries VEdolizumab in CD) trial we explored this novel endpoint in patients with active CD receiving VDZ for 52 weeks.

Aims and Methods:

 The aim of this exploratory analysis was to assess mucosal healing, the combination of endoscopic and histological healing, through week 26 in CD patients treated with VDZ. We included patients who had centrally read endoscopy at week 0 and 26 and paired biopsies at the same time points. Only patients with active histological inflammation at baseline (Robarts Histopathology Index (RHI) score > 7) were studied. All patients had active CD (Crohn's Disease Activity Index (CDAI) > 220 and presence of mucosal ulcerations at baseline endoscopy) and were treated with VDZ 300 mg infusions at week 0, 2, 6 and every 8 weeks thereafter to week 52, with an additional infusion at week 10 in the absence of clinical response. Mucosal biopsies were collected from the edge of the most prominent ulcer in the terminal ileum and 4 colonic segments (ascending, transverse, descending colon and sigmoid and rectum), or from the most severely affected area if no ulcers were present. If a segment was completely normal, two biopsies were taken at random per segment. Histopathology was assessed blindly using the RHI, which represents a reproducible and responsive index that incorporates four histologic descriptors (i.e. severity of chronic inflammatory infiltrate, the number of neutrophils in the lamina propria, the number of neutrophils in the epithelium and the severity of erosions or ulceration), each of which is graded from 0 to 3 (Mosli M et al. Gut. 2017;66(1):50-58). In case more than one biopsy was available per segment, the biopsy sample with the maximum RHI score was used for further analysis.

Results:

Paired biopsies from the same segment were available in 65 patients, 40 of which (62%) had active histological inflammation (RHI score > 7) at baseline. Out of these patients, 35/40 (88%) failed on prior anti-TNF therapy and median disease duration was 8 (4-18) years. Fourteen out of these 40 patients (35%; 95% CI (0.21, 0.52)) achieved mucosal healing at week 26 (SES-CD < 4 and RHI ≤ 6). Endoscopic remission at week 26 was observed in 17/40 (43%) and histologic remission in 23/40 (58%).

Conclusion:

Mucosal healing was achieved in 35% of CD patients with active histological inflammation at baseline after 26 weeks treatment with VDZ. These outcomes show that VDZ is able to induce both endoscopic and histological healing in therapy-refractory CD.

Disclosure:

Nothing to disclose

OP215 - MAINTENANCE OF REMISSION AMONG PATIENTS WITH INFLAMMATORY BOWEL DISEASE AFTER VEDOLIZUMAB IS STOPPED: A MULTICENTER COHORT STUDY FROM THE GETAID

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Introduction:

It is unclear whether vedolizumab therapy can be discontinued in patients with inflammatory bowel disease (IBD) after achieving clinical remission. The aim of this study was to assess the risk of relapse after vedolizumab therapy was discontinued in patients with IBD.

Aims and Methods:

We performed a retrospective observational study, collecting data from 21 tertiary centers in France affiliated to the GETAID from January 2017 to April 2019, on consecutive patients with IBD treated with vedolizumab in clinical remission for at least 3 months who discontinued vedolizumab therapy. Disease activity was assessed using the Harvey-Bradshaw Index for Crohn's disease (CD) and the partial Mayo Clinic score for ulcerative coliits (UC). Relapse was defined as partial Mayo Clinic score ≥ 3 and/or a stool frequency or rectal bleeding subscores of >1 for UC and Harvey-Bradshaw index >4 for CD and the initiation of second line therapy. Relapse-free survival was studied with Kaplan-Meier method, log-rank test and Cox regression model. Patients were censured when vedolizumab was reintroduced despite persistence of clinical remission.

Results:

95 patients (24 male; median age: 32.5 [IQR 27.3-42.4] years; 58 with CD) were included in the present study. Before discontinuation, the median duration of vedolizumab therapy was 17.5 [10.6-25.4] months. Patients discontinued vedolizumab therapy for pregnancy in 37 cases (38.9%), adverse events in 26 (27.4%), by their own choice in 24 (25.3%) and reimbursement issue in 8 (8.4%). At baseline, Harvey-Bradshaw index and partial Mayo Clinic score was 1.7 ±

1.4 and 0.9 ± 1.1, respectively. Only 6 (6%) were still treated with immunomodulator when they discontinued vedolizumab therapy. After a median follow-up period of 11.2 (5.8-17.7) months, 61 of the 95 patients experienced a relapse. Four patients were retreated with vedolizumab after pregnancy in three cases and ovarian cyst work up in one, with a mean delay of 0.7 ± 0.5 years. The probabilities of relapse-free survival were 83%, 59% and 36% at 6, 12 and 18 months, respectively. The multivariate analysis demonstrated that patients with CRP level < 5 at the time of vedolizumab discontinuation (OR = 0.56, CI95%[0.33-0.95], p = 0.03) and patients who discontinued vedolizumab by their own choice (OR = 0.41, CI95%[0.21-0.80], p = 0.009) were less likely to experience relapse. Among the 61 relapsers, vedolizumab was re-introduced in 24 cases permitting to re-induce steroid-free clinical remission after 14 weeks in 71%. After a median follow-up of 11.0 [5.4-13.3] months, 15 (62.5%) patients were still in clinical remission on vedolizumab therapy.

Conclusion:

Almost two thirds of patients with IBD who discontinued vedolizumab therapy while achieving clinical remission experienced a relapse within 1 year after discontinuation of vedolizumab. Normal CRP level (< 5 mg/L) and patients' choice rather than pregnancy, adverse events and reimbursement issues was associated with a lower probability of relapse. After re-introduction of vedolizumab therapy, more than two thirds of patients achieved steroid-free clinical remission after 14 weeks.

Disclosure: Nothing to disclose

OP217 - VEDOLIZUMAB EFFICACY, SAFETY AND PHARMACOKINETICS WITH REDUCED FREQUENCY OF DOSING FROM EVERY 4 TO EVERY 8 WEEKS IN PATIENTS WITH ULCERATIVE COLITIS AND CROHN'S DISEASE

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Introduction:

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic diseases generally requiring long-term maintenance therapy. Vedolizumab (VDZ) is a humanised monoclonal antibody targeting $\alpha_4\beta_7$ integrin to reduce lymphocyte migration to the gut. VDZ was effective and well tolerated with 8-wk (Q8W) and 4-wk dosing (Q4W) in CD and UC in the GEMINI Phase 3 studies and with Q4W dosing in the GEMINI long-term safety (LTS) study. After GEMINI LTS, an extended access program (XAP) with Q8W dosing was initiated. Data from patients (pts) who reduced VDZ dosing from Q4W to Q8W are limited. From the XAP pharmacokinetics (PK) substudy, we report clinical efficacy, PK, and safety for pts who reduced VDZ frequency from Q4W to Q8W.

Aims and Methods:

VDZ XAP (NCT02743806) is a prospective, open-label, multinational, interventional study to provide pts access to VDZ and monitor safety. Eligible pts were on VDZ 300mg IV Q4W during GEMINI LTS with continued clinical benefit. In XAP, VDZ frequency was reduced to 300mg IV Q8W and pts were followed for 56 wk; return to Q4W dosing was allowed based on physician's assessment of pt clinical status and Medical Monitor approval. Blood samples for PK analyses were obtained at enrolment (last Q4W dosing visit) and wks 8, 16, and 56; serum VDZ was measured using a validated ELISA. Clinical remission was defined as Harvey-Bradshaw Index (HBI) ≤4 for pts with CD and partial Mayo score ≤2 with no subscore >1 for pts with UC. Clinical response after restarting Q4W dosing was defined as decreased HBI of ≥3 from XAP baseline, or

decreased partial Mayo score of ≥2 and ≥25% from baseline with a decrease of ≥1 point in rectal bleeding subscore (RBS) from baseline or an RBS of ≤1 point.

Results:

A total of 167 pts (88 CD, 79 UC) enrolled in the XAP-PK substudy. Overall, pts had a median of 6.5 y (range, 4.4-10.0) of prior VDZ use; 69% of pts were anti-TNF naïve at VDZ initiation in prior studies. Of pts with CD and UC, 91% and 92%, respectively, completed the 56-wk substudy, with 86% and 90% remaining on Q8W dosing. Rates of clinical remission and corticosteroid (CS)-free clinical remission in pts remaining on Q8W were stable through wk 56 (Table). Four pts with CD and 2 pts with UC returned to Q4W dosing; 3 of 4 CD pts regained clinical response. Pts remaining on Q8W VDZ through wk 56 had low CRP levels that were stable over time; 2.2 mg/L and 1.7 mg/L at baseline and wk 56 for CD pts and 2.2 mg/L and 1.2 mg/L for UC pts. Median trough VDZ was 43.6 μg/mL at baseline and 10.4 μg/mL at wk 56 in pts with CD and 42.4 μg/mL and 13.3 μg/mL in pts with UC. Adverse events (AEs) related to VDZ were infrequent; no new or serious AEs related to VDZ were reported.

	Baseline		Week 8		Week 16		Week 56	
	CD	UC	CD	UC	CD	UC	CD	UC
Clinical remission, %	84.0	95.8	84.2	91.5	83.8	91.2	82.7	94.4
CS-free remission, %	78.7	91.5	78.9	87.3	78.4	86.8	76.0	91.5
CRP, median, mg/L	2.4	1.8	1.9	1.6	2.2	1.2	2.6	1.2
Trough VDZ, median, μg/mL	43.6	42.4	16.2	18.6	12.6	14.2	10.4	13.3

CD, Crohn's disease; CRP, c-reactive protein; CS, corticosteroid; Q8W, every 8 weeks; UC, ulcerative colitis; VDZ, vedolizumab.

[Table. Efficacy, Safety and PK in CD (N=76) and UC (N=71) Patients Who Remained on Q8W Dosing for 56 Weeks]
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Conclusion:

In a clinically stable cohort, high pt persistence was observed after reducing dose frequency from VDZ Q4W to Q8W. High clinical and CS-free remission rates were maintained for 56 wk. Return to Q4W dosing was necessary in only a few pts and half of them regained clinical response afterwards. VDZ trough concentrations decreased from baseline as expected. AEs were consistent with previous reports.

Disclosure:

OP274 - INTEGRIN EXPRESSION CHANGES ON THE T CELL SUBSETS INFLUENCE THE RESPONSE TO VEDOLIZUMAB IN INFLAMMATORY BOWEL DISEASE PATIENTS

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Introduction:

Vedolizumab is a gut-selective alpha4beta7 integrin inhibitor approved for the treatment of Ulcerative Colitis (UC) and Crohn's disease (CD). The exact mechanism of action remains to be unraveled and there is no consensus whether the response to vedolizumab is associated with integrin expression profiles of the innate, adaptive immunity or both. Response prediction to vedolizumab is particularly relevant since it is a rather slow-acting molecule

Aims and Methods:

We investigated whether baseline levels and/or early changes in the integrin-expressing T cell subsets during the induction phase can predict the response to vedolizumab in inflammatory bowel disease (IBD) patients.

In this prospective multi-centric study, 71 patients with CD (n=28) or UC (n=43) with moderate-to-severe disease were included at the start of vedolizumab treatment. The response to vedolizumab was determined on a clinical, biochemical and endoscopic level at the end of the induction phase (week (W)14). The clinical response was defined as a drop in the Harvey Bradshaw index (HBI) of at least 3 points for CD and a reduction in Mayo score of at least 3 points with no rectal bleeding for UC. The biochemical response was defined as a 50% reduction of CRP or when the CRP normalized (< 10 mg/l) for CD and a 50% reduction or normalization (< 250mg/g) of calprotectin for UC. The endoscopic response was evaluated positive when there was a drop of at least 1 point in the SES-CD score for CD or the endoscopic Mayo score for UC. During the induction phase, peripheral blood mononuclear cells (PBMCs) were collected at W0, W2, W6, W10 (only CD) and W14, before vedolizumab administration. Variation between the different centers was reduced by isolating the cells 6h after blood collection. The PBMCs were analyzed by flow cytometry to evaluate the CD4+/CD8+ Alpha4Beta7+, Alpha4Beta1+, AlphaEBeta7+ and AlphaEBeta1+ T cell populations. Based on the distribution of the data, statistics were performed by an independent sample t-test or a Mann-Whitney U test.

Results:

The flow cytometry analyses revealed that only the CD4+ Alpha4Beta7+ T cell subset at baseline was significantly increased in UC patients with a favorable clinical (P= 0.042), biochemical (P=0.025) and endoscopic response (P= 0.054). This was not the case in CD. In CD, the baseline number of CD4+ Alpha4Beta1+ T cells was lower in clinical (P= 0.094) and biochemical responders (P= 0.004). In addition, lower baseline CD4+ AlphaEBeta1+ T cells and the CD8+ AlphaEBeta1+ T cells were also associated with a biochemical response in CD (P= 0.032 and P= 0.025), respectively. No other significant baseline or delta change differences were identified between the responders and non-responders in the other investigated T cell subsets in both UC and CD.

Conclusion:

This prospective cohort study showed that in UC patients, clinical, biochemical and endoscopic response to vedolizumab treatment is associated with a high number of CD4+ Alpha4Beta7+ T cells in circulation at baseline. In CD patients, the relationship is less clear and the response is rather linked to a low number of Beta1+ T cells. A second cohort is being recruited to confirm our findings. The final aim is to build a predictive model that is feasible for use in clinical practice.

Disclosure: Support provided by Takeda.

P1783 - FECAL CONCENTRATION OF VEDOLIZUMAB CORRELATES WITH TISSUE DRUG LEVELS AND ENDOSCOPIC ACTIVITY IN INFLAMMATORY BOWEL DISEASE PATIENTS

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Introduction:

Therapeutic drug monitoring is being incorporated into everyday clinical management with anti-TNF therapy; however, measurement of serum drug and antibody levels of vedolizumab (VDZ) is less clear to guide drug dosing in the clinical practice. According to all available data, serum trough levels alone seem to be inadequate to predict clinical response with VDZ therapy. At present, no data is available on the potential correlation between mucosal or fecal VDZ concentration and therapeutic response to VDZ.

Aims and Methods:

The aim of this study is to assess the correlation between serum, mucosal and fecal VDZ concentrations to get a better view on the pharmacokinetic-pharmacodynamic relationships of the drug in inflammatory bowel disease (IBD-Crohn's disease [CD], ulcerative colitis [UC]) patients receiving maintenance therapy. Patients with luminal CD and UC receiving maintenance VDZ therapy were enrolled in the study. Clinical disease activity was assessed, blood samples and fecal specimens were collected and colonoscopy with biopsy samples was performed in every patient. Biopsy samples were obtained from inflamed and uninflamed tissue from the colon. Serum, mucosal and fecal VDZ levels were determined by ELISA assay.

Results:

Data of 26 patients (8 CD, 18 UC) have been available so far. The mean duration of VDZ therapy was 5.8 months. Seven patients were naive to biological therapy at induction. Twenty patients had endoscopic activity during colonoscopy. Mucosal drug level did not show difference between either samples obtained from the inactive vs. active part of the bowel (0.54 vs. 0.39 µg/g, p=0,28), or between samples obtained from patients with endoscopic activity vs. mucosal healing (0.44 vs. 0.86 µg/g, p=0.11). Similarly, median serum trough level did not differ significantly between patients with endoscopic activity and remission (31.96 µg/ml vs. 28.99 µg/ml, p=0.3). However, median fecal concentration of VDZ was significantly lower in patients with endoscopic activity compared to those showing mucosal healing (0.22 µg/ml vs. 0.55 µg/ml, p< 0.001). Fecal drug level showed significant correlation with tissue drug levels obtained from both inflamed and uninflamed region of the colon (r=0.80, p=0.001 and r=0.78,

p=0.0003), however no correlation was shown between serum and fecal and between serum and tissue drug levels.

Conclusion:

Our study would be the first that simultaneously examine serum, mucosal and fecal concentrations of VDZ comparing with endoscopic activities. Our data suggest that determination of fecal drug concentration may be promising in the evaluation of endoscopic response to VDZ therapy and may help to identify a useful surrogate marker of tissue drug concentration.

Disclosure:
Nothing to disclose

P1789 - CIRCULATING CD8 α4β7+ MEMORY T CELLS AS EARLY BIOMARKERS OF REMISSION TO VEDOLIZUMAB IN ULCERATIVE COLITIS

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Introduction:

Vedolizumab (VDZ) is a humanized monoclonal antibody targeting the $\alpha_4\beta_7$ integrin us in ulcerative colitis (UC). So far, no VDZ response biomarker has been identified.

Aims and Methods:

To assess whether baseline circulating CD4+ and CD8+ memory T lymphocytes subpopulations could be biomarkers of response to VDZ treatment in patients with UC.Prospective study, n=15 patients with active UC defined as Ulcerative Colitis Disease Activity Index (UCDAI) >3, Mayo endoscopic subscore > 1 and fecal calprotectin >250 mcg/g. Treatment with VDZ (300mg iv) was scheduled as standard induction regime. Peripheral blood samples were obtained before the first dose of VDZ. Purification of circulating memory T cells (CD45RO+) and simultaneous analysis of CD4+ and CD8+ lymphocytic subpopulations ($\alpha_4\beta_7$+/-, HLA-DR+/-, IL23R+/-, CCR9+/-, IL17A+/-, IL-23R+/-, IL-9+/-, β_7 +/-) by flow citometry were performed. Clinical response and remission, faecal calprotectin levels and Mayo endoscopic subscore were evaluated at week 14.

Results:

 8 females, median of age was 45 (IQR=32) years, disease extent (Montreal - E1: 2 patients, E2: 8 patients, E3: 5 patients), 7 severe colitis (UCDAI > 9). Most patients (14) had prior failure to antiTNF-α: primary non-response in 8 patients and loss of response in 6.
Washout period were: 1 month for infliximab, 2 weeks for adalimumab. Vedolizumab treatment combined with steroids (prednisone 1 mg/kg/day PO) was started in 13 patients.
At week 14: 10 patients achieved steroid-free clinical remission, 9 patients had fecal calprotectin levels < 250mcg/g and 9 patients achieved biochemical and/or endoscopic remission (calprotectin levels < 250 mcg/g and/or Mayo endoscopic subscore ≤ 1).
Patients with steroid-free clinical remission presented baseline absolute account of CD8 α4β7+ memory T cells significantly higher when compared with patients with no VDZ response (table 1). Patients with biochemical and/or endoscopic remission at week 14 presented baseline absolute account of CD8 α4β7+ T cells significantly higher and CD8 CCR9+ T cells significantly

lower than non-responders.
No differences were identified according to flare severity, the extent of disease or the type of antiTNF-α failure. No statistically differences were found in the other lymphocyte subpopulations included in the study

Baseline lymphocytes (absolute account/ml)	CLINICAL REMISSION 14Wk	NON CLINICAL REMISSION 14Wk	p value
CD4	394,47	327,66	0,026
CD8 α4β7+	19,265	11,4	0,026
Baseline lymphocytes (absolute account/ml)	BIOCHEMICAL AND/OR ENDOSCOPIC REMISSION 14W	NON BIOCHEMICAL AND/OR ENDOSCOPIC REMISSION 14W	p value
CD8CCR9+	0,33	1,12	0,041
CD8 α4β7+	24,1	10,57	0,007

Conclusion:

The absolute account of CD8 α4β7+ memory T cells before starting VDZ therapy could be an early biomarker of remission and therefore help us to select a subset of responders.

Disclosure:

P1792 - EOTAXIN-1 AND MUCOSAL EOSINOPHIL ABUNDANCE PREDICT TREATMENT RESPONSE TO VEDOLIZUMAB IN INFLAMMATORY BOWEL DISEASE

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Introduction:

Vedolizumab, an antibody against α4β7-integrin capable of blocking immune cell migration across intestinal endothelia expressing MADCAM-1, is a second-line biological treatment for moderate-to-severe inflammatory bowel disease (IBD). Because of moderate response rates to this drug, there is an urgent need for predictive markers to identify patients who are likely to benefit from vedolizumab. Our aim was to explore the predictive value of selected serum inflammatory biomarkers regarding response to vedolizumab induction therapy.

Aims and Methods:

76 IBD patients (Crohn's disease (CD), n=33, ulcerative colitis (UC), n=43) completed vedolizumab induction therapy and 10 serum inflammatory biomarkers were quantified prior to vedolizumab treatment (CRP, SAA, TNF-α, IFN-γ, IL-6, IL-8, IL-10, IL-17A, eotaxin-1 and eotaxin-3).
Eosinophils were quantified in serum and in non-inflamed colon tissue (numbers per High Power Field (HPF 0.24 mm^2)) prior to treatment. Eosinophil numbers were quantified up to 60/HPF and when ≥60 were set at 60. Clinical response was defined as a decrease of at least 3 points in the Harvey Bradshaw Index (HBI) for CD or Simple Clinical Colitis Activity Index (SCCAI) for UC.

Results:

Baseline serum eotaxin-1 levels were significantly higher in vedolizumab responders, compared to primary non-responders (0.31 [0.22-0.46] vs. 0.20 [0.16-0.29] ng/mL, P< 0.05). Doubling of baseline serum eotaxin-1 levels was significantly associated with increased odds of attaining clinical response or remission at week 14 (adjusted OR: 3.28, P< 0.05). The final prediction model based on serum eotaxin-1 levels showed an adjusted area under the receiver operating characteristics curve (AuROC) of 0.81, with an optimally balanced cut-off value for serum eotaxin-1 >0.49 ng/mL with a sensitivity of 75.0% and specificity of 76.7% (Youden's index 0.52). A significant inverse correlation was observed between serum eotaxin-1 levels and serum eosinophil count (P< 0.01). As eotaxin-1 regulates the migration of eosinophilic granulocytes into the intestinal mucosa, we also analyzed mucosal eosinophilic granulocyte abundance in a subset of 24 IBD patients (10 CD and 14 UC) prior to treatment. Baseline median eosinophil numbers in non-inflamed tissue were significantly higher in responders compared to non-responders (60 ± 12 vs. 25 ± 7.5 eosinophils/HPF, P< 0.001). Patients with >30 eosinophils/HPF achieved clinical response in 83.3% of cases (n=12), whereas only 8.3% of patients with < 30 eosinophils showed therapy response (n=12). Preliminary analyses (in 15 patients) revealed a positive correlation between serum eotaxin-1 and mucosal eosinophil abundance, though this was not significant yet in this small sub cohort. None of the other tested serum biomarkers showed significant predictive value for response or non-response to vedolizumab in this patient cohort.

Conclusion:

Serum eotaxin-1 and mucosal eosinophil abundance in non-inflamed colon tissue are reliable predictors for vedolizumab response in IBD patients. Our findings await further validation in an independent patient cohort.

Disclosure:
Nothing to disclose

P1801 - A PROPENSITY SCORE-WEIGHTED COMPARISON OF VEDOLIZUMAB, ADALIMUMAB, AND GOLIMUMAB IN PATIENTS WITH ULCERATIVE COLITIS: REAL-LIFE DATA FROM THE SICILIAN NETWORK FOR INFLAMMATORY BOWEL DISEASE (SN-IBD)

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Introduction:

The recent VARSITY trial showed that Vedolizumab (VDZ) was superior to Adalimumab (ADA) in achieving clinical remission and mucosal healing in patients with ulcerative colitis (UC). Conversely, no real-life data on the comparative effectiveness of VDZ, ADA, and Golimumab (GOL) in UC have been published yet.

Aims and Methods:

Data of consecutive patients with UC treated with VDZ, ADA, and GOL from June 2015 to December 2018 were extracted from the cohort of the Sicilian Network for Inflammatory Bowel Disease (SN-IBD). A three-arms propensity score-adjusted analysis was performed to reduce bias caused by imbalanced covariates at baseline, including the proportion of TNF-α inhibitor naïve and non-naïve patients, using the Inverse Probability of Treatment Weighting (IPTW) approach. The effectiveness was evaluated at 8 weeks, 52 weeks, and as treatment persistence at the end of follow up. The clinical endpoints were steroid-free clinical remission (partial Mayo score < 2 without steroid use) and clinical response (reduction of the partial Mayo Score ≥2 points with a concomitant decrease of steroid dosage compared with baseline). The sum of the two outcomes was defined as clinical benefit. The achievement of mucosal healing (endoscopic Mayo score 0-1) was assessed after at least 6 months of biological treatment.

Results:

A total of 463 treatments (187 VDZ; 168 ADA; 108 GOL) were included, with a median follow-up of 47.6 weeks (IQR 20.0-85.9). At 8 weeks, a clinical benefit was achieved in 70.6% patients treated with VDZ, in 68.5% patients treated with ADA, and in 67.6% patients treated with GOL (p = n.s. for all comparisons); at 52 weeks, VDZ showed better rates of clinical benefit compared with both ADA (71.6% vs. 47.5; OR: 2.79, 95% CI 1.63-4.79, p< 0.001) and GOL (71.6% vs. 40.2%; OR: 3.77, 95% CI 2.08-6.80, p< 0.001), while the difference between ADA and GOL was not significant. Cox survival analysis demonstrated that patients treated with VDZ had a reduced probability of treatment discontinuation compared to those treated with ADA (HR: 0.42, 95% CI 0.28-0.64, p< 0.001) and GOL (HR: 0.30, 95% CI 0.19-0.46, p< 0.001), while patients treated with ADA had a significantly reduced risk of treatment discontinuation compared to those treated with GOL (HR: 0.71, 95% CI 0.50-1.00, p=0.048). Post-treatment mucosal healing rates showed a numerical but non-significant difference in favour of VDZ (48.1%) compared with ADA and GOL (38.0% and 34.6%, respectively).

Conclusion:

In the first study comparing at the same time the clinical effectiveness of VDZ, ADA, and GOL in UC patients via propensity score-adjusted analysis, VDZ was superior to both subcutaneous agents at 52 weeks and as treatment persistence, while ADA showed a superior treatment persistence compared to GOL.

Disclosure:

P1805 - EARLY VEDOLIZUMAB TROUGH LEVELS PREDICT TREATMENT PERSISTENCE OVER THE FIRST YEAR IN INFLAMMATORY BOWEL DISEASE

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Introduction:

The role of Therapeutic Drug Monitoring widely validated for anti TNF-α drugs, especially in case of loss of response, remains debated with Vedolizumab.

Aims and Methods:

We investigated the utility of early serum Vedolizumab trough levels for predicting the first-year Vedolizumab therapy outcome and identifying patients at higher risk of therapy failure. We included consecutive patients affected by Crohn's disease and Ulcerative Colitis, who started Vedolizumab therapy at two hospitals in Italy. Vedolizumab trough levels and anti-Vedolizumab antibodies were assayed by ELISA at week 6 and 14. Clinical remission (according to Harvey Bradshaw Index and Partial Mayo Score, as appropriate) was assessed at week 6, 14, 22 and 54. The primary endpoint was to explore the correlation between early Vedolizumab trough levels and Vedolizumab persistence over the first year of treatment, defined as the maintenance of therapy because of sustained clinical benefit.

Results:

101 patients (82% exposed to anti TNF-α drugs) were included. Median VTL were 28.3 μg/mL (IQR 16.9-39.8) at week 6 and 18.4 μg/mL (IQR 11.8-25) at week 14 after the first infusion of vedolizumab. A cut-off TL of 16.55 μg/ml at week 14 predicted Vedolizumab persistence within the first year of therapy with a sensitivity of 73.3 % and a specificity of 59.4% (p =0.0009, AUROC 0.686, 95% CI 0.581-0.779). Week 14 Vedolizumab trough levels were significantly higher in patients with clinical remission at week 14, 22, 54, as well as in those patients achieving mucosal healing within 54 weeks. Early Vedolizumab trough levels were significantly correlated with serum albumin levels (Spearman's rho=0.204, p=0.0107).

Conclusion:

High VTL at week 14 were associated with a higher probability of maintaining Vedolizumab therapy over the first year because of a sustained clinical benefit.

Disclosure:

Nothing to disclose

P1810 - SHORT- AND LONG-TERM EFFICACY OF VEDOLIZUMAB THERAPY ON CLINICAL AND ENDOSCOPIC ACTIVITY IN PATIENTS WITH ANTI-TUMOR NECROSIS FACTOR ALPHA RESISTANT INFLAMMATORY BOWEL DISEASE

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Introduction:

Vedolizumab (VDZ) therapy as alternative option in the management of moderate and severe IBD has been registered since 2016 in Hungary, however all newly initiated VDZ therapy was individualized, it should be approved by the steering committee of five Hungarian IBD-specialist up to 2019. This situation resulted that only those patients could be received VDZ treatment whose longstanding disease showed inadequate response to the conventional anti-TNF-alpha and/or immunosuppressant therapy. The aim of our observational study was to assess the efficacy of short- and long-term VDZ therapy on clinical and endoscopic activity in moderate and severe active IBD in real-life setting.

Aims and Methods:

Our non-interventional multicenter cohort study enrolled all adult IBD patients with moderate and severe activity who received VDZ therapy between July 2016 and December 2018 in our entire country. The therapeutic response was assessed based on the changes of clinical (Crohn's Disease Activity Index [CDAI], Mayo score) and endoscopic (Simple Endoscopic Score for Crohn Disease [SES-CD], endoscopic Mayo score) scores. Clinical response was defined as >3 points decrease in the total Mayo score or >100 decrease in CDAI score from baseline. Remission was defined as Mayo score ≤2, with no individual subscores >1, or as CDAI score ≤150. Mucosal healing was defined as Mayo endoscopic subscore ≤1 or as SES CD score ≤4.

Results:

83 Crohn's disease (CD) and 121 ulcerative colitis (UC) patients completed VDZ induction therapy. The mean age was 39.9 years (range 18-78; median 36) and the average disease duration was 9.6 years (range 1-36; median 8). Extraintestinal manifestations occurred in 57 patients (27.9%), and in 11 cases (5.4%) IBD was associated with primary sclerosing cholangitis (PSC). The mean value of activity scores significantly decreased by the end of short-term treatment period both in CD (SES-CD: 20.93 vs. 13.55; p< 0.00001; CDAI: 303.58 vs. 167.66; p< 0.00001) and UC (Mayo: 9.74 vs. 4.33; p< 0.00001; eMayo: 2.80 vs. 1.41;su p< 0.00001) subgroups. The rate of clinical response during the short-term VDZ therapy was substantially higher in the UC group compared with CD group (84.3% vs. 61.5%; p< 0.0001). No significant difference in terms of the proportion of clinical remission and steroid-free remission was observed between the UC and CD subgroups (49.6% vs. 51.8%, p=0.777; and 27.3% vs. 37.4%, p=0.169). In 124 cases (72 UC and 52 CD) the first-year VDZ treatment could have been completed during the study period, however in 32 cases (25.8%) primary non-response for induction therapy was observed. 92 patients (60 UC and 32 CD) received maintenance VDZ

therapy. The rate of response, clinical remission and steroid-free remission were substantially higher in UC (65.3%, 47.2% and 44.4%) compared with CD (42.3%, 32.7% and 30.8%) by the end of first-year therapy (p< 0.001). Significant difference was observed between UC and CD subgroups in terms of mucosal healing both by the end of induction and by the end of first-year therapy (52.9% and 21.7%, p< 0.0001vs. 51.4%and 21.2%, p=0.015).

Conclusion:

Our results suggest that both the short-term and the one-year long maintenance VDZ therapy is effective and safe therapeutic option in anti-TNF-alpha failure or intolerant IBD patients with moderate or severe disease activity, however significant difference was observed between the UC and CD subgroups. Mucosal healing was achievable in every second UC and in only every fifth CD patients both by the end of the induction and by the end of first-year treatment in this difficult-to-treat population

Disclosure:

Nothing to disclose

P1818 - THE EFFICACY AND THE SAFETY OF VEDOLIZUMAB IN A GROUP OF ANTI-TNF EXPERIENCED PATIENTS WITH IBD ; A REAL-LIFE DATA FROM TURKEY

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Introduction:

Vedolizumab is a new agent acting as an anti-Integrin which has been started to be use in treatment of Crohn's disease (CD) and Ulcerative Colitis (UC). In this retrospective study we aimed to examine the safety and effectiveness of vedolizumab treatment in anti-TNF experienced patients with CD and UC. In addition we aimed to show whether there is a role for thiopurines in vedolizumab treatment.

Aims and Methods:

Chart review was performed retrospectively in patients with UC and CD in Cerrahpasa University, Ankara University and Acıbadem University IBD outpatient clinics. Clinical response and clinical remission rates were calculated by using Harvey-Bradshaw Index and Partial Mayo score.

Results:

Total of 101 patients [mean age 39,4±12,7 yr, 51 Male, 57 CD (56%)] were enrolled into the study. The clinical response rates were 66%, 62% and 44% in 3, 6 and 12 months of vedolizumab treatment in CD patients. The Clinical remission rates were 22%,34% and 36% in the same intervals in CD patients. The clinical response rates were 59%, 62% and 36% in 3, 6 and 12 months of vedolizumab treatment in UC patients. The Clinical remission rates were 25%,39% and 33% in the same intervals in UC patients. There was no correlation found between thiopurin use, disease duration, clinical response and clinical remission rates in either

diseases.
No serious side effects were recorded during vedolizumab treatment.

Conclusion:

Vedolizumab treatment is effective and safe in patients who were previously treated with anti-TNF agents. Thiopurins did not show any beneficiary effect over Vedolizumab treatment.

Disclosure:

Nothing to disclose

P1047 - EARLY MONITORING OF RESPONSE (MORE) TO GOLIMUMAB THERAPY BASED ON FECAL CALPROTECTIN AND TROUGH SERUM LEVELS IN PATIENTS WITH ULCERATIVE COLITIS: A MULTICENTER PROSPECTIVE OBSERVATIONAL STUDY

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Introduction:

Study objective: In order to evaluate early prediction markers for the therapy response of golimumab (GLM) in ulcerative colitis, we aimed to assess the association of an detectable GLM trough serum level together with a reduction in fecal calprotectin level in week 6 (W6) with a clinical response in week 26 (W26) in patients with moderate-severe ulcerative colitis.

Aims and Methods:

The study was designed as a prospective, single-arm, multicenter, observational study with no interim analyses in Germany between October 2014 and December 2017. Patients aged ≥ 18 years, with diagnosed moderate-severe active ulcerative colitis and starting GLMtreatment were offered participation in this ethics approved study at ten registered IBD centers. These sites were recruited by the IBD study platform "German Inflammatory Bowel Disease Study Group" (GISG). After screening, for each eligible patient enrolled, the study duration was 26 weeks with six visits at weeks 0 (baseline), 2, 6, 14, 22 and 26.
The primary outcome was clinical response measured by Partial Mayo Scoring Index (PMS). Clinical response was defined by a Partial Mayo Score ≤ 1 or a reduction in the PMS by two points. Calprotectin level for response in was defined as reduction of ≥50 % in comparison to baseline. Detectable GLM trough level was defined as ≥2.5 µg/ml.
The sample size was calculated for 61 patients (including 3 % drop-outs). Analysis of the primary outcome was done according to the Intention-To-Treat (ITT) method. Missing (outcome) data were imputed as follows: between W0 - W6 classified as therapy failure; between W6 - W26 as Last Observation Carry Forward (LOCF) Effect estimates were reported as relative risks with corresponding 95 % confidence intervals (CI).

Results:

61 patients were enrolled, two patients were excluded due to screening failures. During the course of the study 28 patients discontinued their participation (47,5%) due to 1. withdrawal of GLM therapy (n = 21; 35,6%), 2. withdrawal of consent (n=7; 11,9%).

In the ITT cohort, gender distribution was almost equal (female 52.5%; male 47.5%), the median age was 40.1 (Interquartile Range: 22.1), the mean duration of ulcerative colitis was 8.7 years (95% CI, 6.5 - 10.9). Patients had moderate disease according to PMS with a mean scoring point of 5.6 (95% CI, 5.2 - 6.1). 54.2 % of the enrolled patients were anti-TNF naïve, 8.5 % had experienced a primary and 37.3 % a secondary loss of TNF-alpha therapy prior to the start of GLM therapy.

We showed that patients with an early detectable positive GLM trough level in W6 and a change in calprotectin at the same time had a 1.54 fold increase chance (RR: 0.65, 95% Cl: 0.44-0.95; n=45) to achieve a clinical remission at w26 in comparison to patients who had no early detectable positive GLM trough level and no change in calprotectin in w6. On the other hand we analyzed that patients without early detectable GLM trough level and no change in calprotectin in w6 had a 3.46 fold higher risk (RR 3.46; 95%: Cl 0.56-22.45; p=0.1; n=45) for not achieving response in w26.

Conclusion:

In this prospective multicenter study we were able to show the impact of fecal calprotectin and serum golimumab level at week 6 to predict the therapeutic response at week 26. Further studies are needed to confirm the statistical significance our primary result.

Disclosure:

P1815 - THE DUBLIN INFLAMMATORY BURDEN SCORE PREDICTS EARLY CLINICAL AND BIOCHEMICAL RESPONSE TO GOLIMUMAB TREATMENT IN UC; EARLY RESULTS OF THE GOAL-ARC STUDY

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Introduction:

Golimumab (GLM) is an anti-TNF monoclonal antibody licensed for the treatment of Ulcerative Colitis. Higher trough levels are associated with enhanced response to therapy. (GOAL-ARC) is a randomized multi-centered trial of the impact of personalized dosing of Golimumab based on inflammatory burden (assessed by FCP - faecal calprotectin) and therapeutic drug monitoring versus standard of care (with dosing according to label). We aimed to evaluate the impact of inflammatory burden in UC on drug levels and early response to GLM treatment.

Aims and Methods:

All study participants had a diagnosis of UC, with moderate to severe disease activity (Mayo 6-12), with an endoscopic sub-score of ≥2. Clinical response was defined as a decrease in baseline modified partial mayo score of 2 points or a decrease of ≥30% from baseline. GLM was administered at 200mg at week 0, 100mg at week 2 in all patients in advance of week 6 assessment.

Induction data was analyzed to week 6 including baseline inflammatory burden (DUBLIN Score - Rowan et al, JCC 2019), FCP and modified partial mayo scores and week 6 trough GLM levels.

Results:

70 patients have been recruited to GOAL-ARC. 90% have completed the induction phase to week 6. Moderate disease activity was present in 79% with a Mayo endoscopic sub-score of 2 at screening. 56% had a weight < 80Kg.

Pre and post induction data was available on 51 patients,. Clinical response was achieved in 57% at week 6. The median modified partial mayo score decreased from 4(IQR 3-5) at baseline to 2(IQR 1-3) at week 6 (p< 0.001). Median FCP reduced from 1380 (IQR 685-3000) at baseline to 180 (IQR 15-1122) at week 6 (p=0.001). A lower baseline DUBLIN score was associated with clinical response at week 6 (p=0.048).

Median GLM level at week 6 was 3.97 (IQR 2.3-5.8). Higher week 6 drug levels were associated with clinical response. (p=0.012). Week 6 GLM level was inversely proportional to week 6 FCP(p=0.001). Baseline DUBLIN score was inversely proportional to week 6 drug levels (p=0.021).

	Baseline	Week 6	p value
Faecal Calprotectin µg/g Median (IQR)	1380 (685-3000)	179.5 (15-1122)	0.001
Modified Partial Mayo score median (IQR)	4 (3-5)	2 (1-3)	<0.001

[Table 1.Comparison of baseline and week 6 median faecal calprotectin and modified partial mayo scores following induction with Golimumab]

Conclusion:

Early results of GOAL-ARC demonstrate the majority (57%) of UC patients treated with GLM show early clinical response (by week 6). Significant improvements are observed in modified partial Mayo scores and FCP by week 6, with higher drug levels being significantly associated with achieving clinical response and reductions in faecal calprotectin. Lower baseline DUBLIN (inflammatory burden) scores are associated with higher trough drug levels and clinical response at week 6 indicating that a higher inflammatory burden is associated with poorer outcomes.

References:

1. Rowan CR, Cullen G, Mulcahy HE, Sheridan J, Moss AC, Ryan EJ, et al. DUBLIN (Degree of Ulcerative colitis Burden of Luminal INflammation) score, a simple method to quantify inflammatory burden in Ulcerative Colitis. J Crohns Colitis 2019 Mar.

Disclosure:

P0331 - MOLECULAR RESPONSE TO USTEKINUMAB IN MODERATE-TO-SEVERE ULCERATIVE COLITIS BY SERUM PROTEIN AND COLON TRANSCRIPTOMIC ANALYSIS: RESULTS FROM THE UNIFI PHASE 3 MAINTENANCE STUDY

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Introduction:

The cytokines IL-12 and IL-23 are elevated in ulcerative colitis (UC), and genetic association suggests that they play causative roles in the disease. Ustekinumab (UST), an anti-IL-12p40 monoclonal antibody that binds both cytokines, is an effective therapy for moderate-to-severe UC. We previously observed a partial normalization of UC disease signatures in colonic biopsy gene expression and serum protein levels following UST induction therapy.[1] However, the molecular effects of maintenance UST therapy in UC patients are unknown.

Aims and Methods:

We evaluated the molecular effects of UST in the UNIFI Phase 3 maintenance study of UST in moderate-to-severe UC (n=961). Subjects in response to UST 8 weeks after intravenous induction were randomized to receive maintenance treatment with subcutaneous placebo, UST 90 mg every 8 (q8w) weeks, or UST 90 mg every 12 weeks (q12w). Colonic biopsy mRNA and serum samples from the first ~60% of patients treated in the UNIFI phase 3 induction study[2] were analyzed, with equal representation of patients with or without a history of biologic therapy failure (Table 1). Biopsy and serum samples from healthy subjects were analyzed as controls.

Results:

At Week 44 after the start of maintenance therapy, the expression of colonic genes dysregulated in UC was altered towards normal levels in all treatment groups, with the greatest improvements among those receiving UST and those in clinical remission (p< 0.05 for maintenance Week 44 versus start of maintenance). No dose effect was observed between q8w and q12w UST treatment arms, and no significant improvements in disease signature occurred in non-responders to placebo or UST. Ustekinumab maintenance therapy magnified the normalization of serum proteins following UST induction; among subjects receiving q8w UST who were in remission at Week 44, the proteins IFNγ, IL-17A, MMP3, and SAA reached concentrations comparable to those seen in healthy controls. Similar trends occurred in subjects in remission following q12w UST and to a lesser degree among UST-treated subjects not in remission at Week 44. Among subjects receiving placebo maintenance therapy who were in remission at Week 44, the disease-associated serum proteins that decreased following UST induction were not further reduced during maintenance. As previously observed in the induction studies, UST maintenance did not reduce serum TNF levels.

	Biopsy mRNA (550 UC and 18 healthy cntl)	Serum Protein (574 UC and 50 healthy cntl)
Analytes	Affymetrix HG U133 PM arrays	12 serum markers: • Matrix metalloproteinases: MMP-1,3,9 • Cytokines and cytokine receptors: IFNy, IL-17A, IL-22, IL-10, IL-2R, TNFa, TNFR1 • Acute Phase Reactant: SAA Inflammatory marker: NGAL
Methods	Generalized linear model (GLM) & Gene Set Variation Analysis	GLM
Time points	Screening, induction Week 8 (maintenance Week 0), and maintenance Week 44	-
Significance cutoffs	|fold change| > 1.5x and p < 0.05	-

[Table 1. Biopsy mRNA and serum protein assessments in UNIFI]

Conclusion:

UST maintenance therapy suppressed IL-12 and IL-23-related serum proteins and promoted normalization of the UC disease transcriptomic profile. These results provide insight into the molecular mechanisms associated with the efficacy of UST maintenance therapy.

References:

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Disclosure:

Drs.Li, Yang, Hayden, Strawn, Wadman, Bhagat, Marano, and Friedman are all employees of Janssen Research & Development, LLC

P1003 - PHARMACOKINETICS AND EXPOSURE-RESPONSE RELATIONSHIPS OF USTEKINUMAB IN PATIENTS WITH ULCERATIVE COLITIS: RESULTS FROM THE UNIFI INDUCTION AND MAINTENANCE STUDIES

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Introduction:

Serum concentrations of monoclonal antibody-based biologics have been shown to correlate with their efficacy. PK, exposure-response (ER), and immunogenicity of ustekinumab (UST) were evaluated in UNIFI induction and maintenance studies in UC. Induction results were presented previously[1].

Aims and Methods:

PK, immunogenicity, efficacy & safety data were obtained from two Phase 3, double-blind, PBO-controlled trials in adult patients (pts) with moderate-severe UC. These included 1 induction study which enrolled 961 pts (UNIFI). Patients enrolled in the induction study received a single IV infusion at Week 0 of PBO, UST 130 mg, or weight-range-based doses approximating 6 mg/kg UST (~ 6 mg/kg: 260 mg for pts ≤55 kg, 390 mg for pts >55 kg & ≤85 kg, & 520 mg for pts >85 kg). Responders to a single IV infusion of UST comprised the primary study population for the maintenance study (n=523) & were randomly assigned to receive SC UST 90 mg q12w, UST 90 mg q8w, or PBO. Blood samples were collected to measure serum UST concentration and antibodies to ustekinumab. Key efficacy outcomes were based on the Mayo score and inflammatory biomarkers (C-reactive protein [CRP] and fecal calprotectin [fCal]). Relationships between serum UST concentrations & efficacy, and the incidence of selected safety events of infections, serious infection & serious adverse events (SAE) were evaluated.

Results:

Serum UST concentrations over time were dose proportional, unaffected by concomitant immunosuppressants, & similar between pts who were biologic failures & non-failures. Median peak serum UST concentrations in the induction study were 43.2 μg/mL & 127.0 μg/mL for the 130 mg & ~6 mg/kg dose groups, respectively. At induction week 8, median UST concentrations were 2.51 μg/mL & 8.59 μg/mL, respectively. Steady-state was reached by the start of the second SC maintenance dose (16 or 20 weeks from the IV induction dose for the q8w and q12w regimen respectively). Median steady-state trough serum UST concentrations over time in the UST q8w group (2.69 to 3.09 μg/mL) were 3-fold higher than in the q12w group (0.92 to 1.19 μg/mL). During induction & maintenance, serum UST concentrations were positively associated with the proportions of pts achieving response & remission, respectively (Table), and there was an inverse association between serum UST concentrations and CRP and fCal levels. No relationship was observed between serum UST concentrations & the incidence of infections, serious infections or SAEs during induction or maintenance treatment with UST. The incidence of antibodies to UST through 1 year using a drug-tolerant assay was 3.4% among those receiving UST maintenance vs. 9.1% in the PBO group; no impact of antibodies on efficacy was observed.

	Serum Ustekinumab Concentration (μg/mL)*/Proportion of Patients (%)			
Efficacy Outcome	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile
Clinical Response at Induction Week 8	<2.2/41.2	2.2 to <3.9/47.7	3.9 to <8.8/61.1	≥8.8/74.2
Clinical Remission at Maintenance Week 44	<0.9/29.9	0.9 to <1.9/46.2	1.9 to <3.2/46.8	≥3.2/61.5

*Serum concentration quartiles based on ustekinumab concentration at Week 8 for the induction analysis, and average steady-state trough concentration for the maintenance analysis

[Table. Proportions of Patients Achieving Efficacy Endpoints by Serum Ustekinumab Concentration]

Conclusion:

Serum UST concentrations were approximately dose-proportional. A positive E-R of serum UST with clinical efficacy measures and an inverse relationship with inflammatory markers was observed during UST IV induction & SC maintenance treatment. Adverse events including infections did not increase with increased serum UST concentrations at the doses evaluated in induction and maintenance. These findings are consistent with those in UST for Crohn's disease.

References:

1.Adedokun OJ, Xu Z, Marano C, O'Brien C, Szapary P, Zhang H, Johanns J, Leong R, Hisamatsu T, van Assche G, Danese S, Abreu MT, Sands BE, Sandborn WJ. Pharmacokinetics and Exposure-response Relationships of Intravenously Administered Ustekinumab during Induction Treatment in Patients with Ulcerative Colitis: Results from the UNIFI Induction Study. Poster presentation at: ECCO 2019; Copenhagen, Denmark.

Disclosure:

P1008 - EFFECTS OF USTEKINUMAB MAINTENANCE THERAPY ON ENDOSCOPIC IMPROVEMENT AND HISTOLOGIC IMPROVEMENT IN THE UNIFI PHASE 3 STUDY IN ULCERATIVE COLITIS

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Introduction:

Ustekinumab is an effective therapy for moderate-to-severe ulcerative colitis (UC),[1,2] but its effects on mucosal healing (endoscopic improvement + histologic improvement) during maintenance treatment are unknown.

Aims and Methods:

We evaluated the effects of maintenance ustekinumab on histologic and endoscopic activity in the UNIFI Phase 3 study of ustekinumab in moderate-to-severe UC (n=961). Subjects in response 8 weeks after receiving intravenous ustekinumab were randomized to receive maintenance treatment with subcutaneous (SC) placebo or ustekinumab 90 mg every 8 (q8w) or 12 weeks (q12w). Two colonic biopsies were collected from the distal colon at screening and Weeks 0 and 44 of maintenance. Endoscopic improvement (EI) was defined as a Mayo endoscopy subscore $\leq$ 1; histologic improvement (HI) comprised the following Geboes score-based criteria: absence of erosions or ulcerations, absence of crypt destruction, and < 5% of crypts with neutrophil infiltration. To encompass both macro- and microscopic scales, histo-endoscopic mucosal healing (MH) was defined as achieving both EI and HI.

Results:

At maintenance Week 44, EI was achieved in 28.6%, 43.6%, and 51.1% of subjects treated with placebo, ustekinumab q12w (p=0.002 vs placebo), and ustekinumab q8w (p< 0.001), respectively. HI was achieved at Week 44 in 32.9%, 54.0%, and 59.3% of subjects treated with placebo, ustekinumab q12w, and ustekinumab q8w, respectively (p< 0.001 for both q12w and q8w). MH was achieved at Week 44 in 24.1%, 38.8%, and 45.9% of subjects treated with placebo, ustekinumab q12w (p=0.002), and ustekinumab q8w (p,0.001), respectively. HI at Week 44 (irrespective of maintenance treatment) was significantly associated with EI and MH (p< 0.001) and with both lower absolute levels and larger post-treatment changes in total Mayo score, partial Mayo score, and Mayo symptom sub-scores for stool frequency and rectal bleeding at Week 44. Both EI and HI following 8 weeks of ustekinumab treatment were associated with

clinical remission and steroid-free clinical remission at Week 44 (p< 0.05), as well as remission through Week 44 (i.e. at both Week 8 and Week 44). For example, 26% of subjects with induction HI were in clinical remission through Week 44, versus 4% of subjects without induction HI. Induction MH was similarly associated with positive outcomes at maintenance Week 44.

P1112 - PEAK USTEKINUMAB CONCENTRATION AFTER INTRAVENOUS LOADING DOSE PREDICTS FAECAL CALPROTECTIN NORMALISATION IN CROHN'S DISEASE: POTENTIAL ROLE FOR THERAPEUTIC DRUG MONITORING?

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Introduction:

Up to one third of patients with Crohn´s disease do not respond or respond partially to the intravenous loading dose of ustekinumab. This was partially explained by low ustekinumab concentrations during maintenance phase (1). However, exposure-response relationship during induction, particularly during the first 4 weeks following intravenous loading, has not been sufficiently studied in the real-life setting yet.

Aims and Methods:

We prospectively investigated the association of ustekinumab induction drug levels to calprotectin normalisation (defined as levels < 100 mg/kg) after intravenous induction in Crohn's disease in a real-life setting.
Ustekinumab drug levels (ELISA assay) at 4 prespecified time points during induction (one hour post-infusion (peak level), week 2, week 4 and week 8) were correlated to faecal calprotectin (Calprest assay) levels at weeks 8, 16 and 24 of starting ustekinumab. We recruited 52 consecutive patients who started ustekinumab due to active Crohn's disease at a tertiary referral university centre. All patients received an intravenous loading dose of ustekinumab (approximately 6 mg/kg as per label, infused over 60 min) followed by 90 mg q 8 weeks maintenance. Median disease duration at start of treatment was 15 years (IQR: 8-23), most patients (35/52 (67%)) had failed previous biological treatment (25 anti-TNF, 9 vedolizumab, 1 both). At inclusion 8/52 (15%) were on systemic steroids. Mann-Whitney U-test and ROC analysis were used to test for differences and identify optimal cut-offs of ustekinumab drug levels to predict calprotectin normalisation.

Results:

Median calprotectin decreased from 134 (IQR:72-235) to 80 (IQR: 26-173) by week 8, to 65 (IQR:32-188) by week 16 and 66 (IQR: 35-203) by week 24 of start of ustekinumab. Faecal calprotectin was normal in 27/47 (57%), 23/42 (55%), 26/41 (63%) of patients at week 8, 16 and 24, respectively. Median ustekinumab drug levels were higher at all assessed time points in patients with normal calprotectin at weeks 8, 16 and 24 compared to those with increased calprotectin levels (Table 1). Ustekinumab levels of >94 (sensitivity 85%, specificity 65%, PPV 74%) 1-hour post-infusion, >25 (sensitivity 90%, specificity 56%, PPV 69%) at week 2, >20 (sensitivity 60%, specificity 100%, PPV 100%) at week 4, and >7 (sensitivity 60%, specificity 95%, PPV 94%) at week 8 were identified as optimum cut-offs for calprotectin normalisation at week 8, with similar values for weeks 16 and 24. Importantly, these cut-offs had a high negative

predictive values (at 1h post-infusion: 71% and at week 2: 70%) for calprotectin normalisation at 6 months.

Ustekinumab concentration [μg/mL], median (IQR)	Faecal calprotectin at week 8		P value	Area under the ROC curve (95% confidence interval)
	<100 mg/kg	≥100 mg/kg		
Peak (1 h after infusion)	111 (98-124)	92 (83-116)	0.033	0.73 (0.56-0.91)
Week 2	32 (28-36)	25 (21-30)	0.005	0.77 (0.61-0.92)
Week 4	20 (16-24)	12 (7-17)	<0.0001	0.82 (0.68-0.96)
Week 8	7 (4-11)	3 (2-5)	<0.0001	0.84 (0.71-0.97)

[Table 1]

Conclusion:

Our data indicate that induction concentrations of ustekinumab after an intravenous loading dose, as early as 1 hour after infusion, predict faecal calprotectin normalization during the first 6 months in Crohn's disease. These data indicate that therapeutic drug monitoring of ustekinumab during induction could potentially improve outcomes by identifying patients in need of early proactive dose optimisation.

References:

1. Verstockt B, Dreesen E, Noman M, Outtier A, van den Berghe N, Aerden I, et al. Ustekinumab exposure-outcome analysis in Crohn's disease only partly explains limited endoscopic remission rates. J Crohns Colitis 2019: 10.1093/ecco-jcc/jjz008. [published ahead of print]

Disclosure:

P1134 - EFFICACY OF USTEKINUMAB INTENSIFICATION AND RE-INDUCTION IN CROHN'S DISEASE PATIENTS WITH INSUFFICIENT OR LOSS OF RESPONSE

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Introduction:

Ustekinumab (UST) has proven to be an efficient maintenance therapy for moderate to severe Crohn's disease (CD). However, a significant percentage of patients treated with subcutaneous maintenance UST experience a secondary loss of response (LOR) or partial response. We evaluated the clinical, biological and endoscopic response to UST optimization including IV re-induction (intravenous UST at a dose of 6 mg/kg) and/or shortening of the dosage interval (mainly every 4 weeks) in this context.

Aims and Methods:

A retrospective, single-center study was performed including patients with CD who were treated with maintenance UST and received either IV re-induction and/or shortening of the dosage interval for a partial response or LOR. The clinical and endoscopic response was based on the physician's assessment. A biological response was defined as a decrease of ≥50% in C-reactive protein (CRP) and/or fecal calprotectin (FC); remission as a normalization of these parameters.

Results:

Eighteen out of the 51 (35.3%) UST-treated CD patients needed optimization of UST: 2 patients only received IV re-induction, 9 patients only shortening of the dosage interval and 7 patients received both IV re-induction and intensification.
The median time to optimization was 34.5 weeks (IQR 20.3-42.3). Response to dose optimization was assessed at a median of 15.5 weeks (IQR 6.8-19.3).
One of the 2 patients who underwent re-induction alone experienced a good clinical and endoscopic response; the other patient had no clinical, biological nor endoscopic response and UST was discontinued.
A combined re-induction and shortening of the dosage interval was performed in 7 patients. Of these, 6 experienced a clinical response and 1 patient had no response. Biological remission was confirmed in 3/6 patients, whereas the other 3/6 had no biological response. Endoscopic response was observed in 1/3 patients. Despite optimization, UST was ended in one patient due to a persistent LOR.
Nine patients underwent intensification alone, which was successful in inducing a clinical response in 3/9 (33.3%) and a clinical remission in 4/9 (44.4%). Two patients (22.2%) had no clinical response. Biological remission was observed in 4/7 patients (57.1%) and 3/7 patients had no biological response (42.9%). Endoscopic evaluation in 4 patients showed a response in 2/4 and no response in the other 2. In 2/9 patients (22.2%) UST was stopped; one due to LOR and the other patient due to an adverse event (flare of underlying spondyloarthropathy). Other adverse events (AEs) were seen in 2 patients: 1 patient had arthralgia and 1 patient developed a rash, both AEs were mild and UST could be continued.

Conclusion:

About a third of patients treated with maintenance UST underwent optimization. Of these 18 patients, 10 (55.6%) regained a good clinical response and 4 (22.2%) were in clinical remission. UST could be continued in the majority of patients.

Disclosure:

Nothing to disclose.

OP169 - IMPACT OF RESPONSE AND INFLAMMATORY BURDEN AT START OF MAINTENANCE THERAPY ON CLINICAL EFFICACY OF USTEKINUMAB DOSING REGIMEN IN UC: WEEK 44 RESULTS FROM UNIFI

Panaccione R.[1], Peyrin-Biroulet L.[2], Danese S.[3], Marano C.[4], O'Brien C.D.[4], Szapary P.[4], Zhang H.[4], Johanns J.[4], Leong R.[5], Arasaradnam R.P.[6], Rowbotham D.[7], Abreu M.T.[8], Sands B.E.[9] [1]University of Calgary, Medicine, Calgary, Canada, [2]Nancy University Hospital Inserm U 954, Dept. of Hepato-Gastroenterology, Vandoeuvre les Nancy, France, [3]Humanitas Research Hospital, Gastrointestinal immunopathology, Rozzano, Italy, [4]Janssen Research & Development, LLC, Spring House, United States, [5]Concord and Macquarie University Hospitals, Sydney, Australia, [6]University Hospital Coventry and Warwickshire, Dept. of Gastroenterology, Surrey, United Kingdom, [7]Auckland City Hospital, Gastroenterology & Hepatology, Auckland, New Zealand, [8]University of Miami, Miller School of Medicine, Crohn's and Colitis Center, Miami, United States, [9]Icahn School of Medicine at Mount Sinai, Division Of Gastroenterology, New York, United States

Introduction:

The UNIFI maintenance study was a Phase 3, double-blind, placebo-controlled, randomized-withdrawal study in pts with moderate to severely active ulcerative colitis (UC) who failed conventional or biologic therapy and were in clinical response 8 weeks after receiving a single ustekinumab (UST) IV induction dose. In this study, patients were randomized to placebo, UST 90 mg SC q8w or q12w.

Aims and Methods:

To examine the relative efficacy of the UST 90 mg SC q8w or q12w maintenance regimens, subgroup analyses were performed for clinical outcomes of clinical remission, symptomatic remission, and endoscopic improvement at Week 44 for patients who did and did not achieve these endpoints at the start of maintenance. Additionally, analyses of clinical remission and endoscopic improvement at Week 44 based on pre-specified cut-points of the concentrations of inflammatory biomarkers (CRP [≤3 mg/L, >3 mg/L] and fecal calprotectin [≤250 mg/kg, >250 mg/kg]) at maintenance baseline were conducted.

Results:

For patients who had achieved clinical remission, symptomatic remission, or endoscopic improvement at maintenance baseline, efficacy of UST q8w and UST q12w regimens for the respective endpoint at Week 44 was similar (Table 1). By contrast, for patients who did not achieve clinical or symptomatic remission or endoscopic improvement at maintenance baseline, UST q8w demonstrated greater efficacy than UST q12w for that endpoint at Week 44. Patients with low inflammatory burden marked by CRP ≤3 mg/L at maintenance baseline achieved similar efficacy at Week 44 with UST q8w and q12w dosing regimens as measured by

clinical remission and endoscopic improvement (Table 1). By contrast, patients with high inflammatory burden, marked by CRP>3 mg/L at maintenance baseline, achieved greater efficacy at Week 44 with UST q8w versus q12w dosing over the endpoints. Generally similar trends were seen in patients with fecal calprotectin measurements for low (≤ 250 mg/kg) and high (>250 mg/kg) inflammatory burden at maintenance baseline.

Endpoint	Patients attaining outcome at maintenance baseline			Patients not attaining outcome at maintenance baseline		
	Placebo SC[a]	UST 90 mg q12w	UST 90 mg q8w	Placebo SC[a]	UST 90 mg q12w	UST 90 mg q8w
Clinical remission[b]	37.8% (17/45)	70.0% (28/40) *	65.8% (25/38) *	19.2% (25/130)	28.8% (38/132)	37.7% (52/138) *
Symptomatic remission[c]	51.6% (63/122)	73.0% (89/122) *	73.1% (87/119) *	30.2% (16/53)	36.0% (18/50)	56.1% (32/57) *
Endoscopic improvement[d]	35.2% (25/71)	60.3% (41/68) *	64.9% (37/57) *	24.0% (25/104)	32.7% (34/104)	44.5% (53/119) *

Endpoint	Subjects with CRP ≤3 mg/L at maintenance baseline			Subjects with CRP >3 mg/L at maintenance baseline		
	Placebo SC[a]	UST 90 mg q12w	UST 90 mg q8w	Placebo SC[a]	UST 90 mg q12w	UST 90 mg q8w
Primary efficacy analysis set	111	121	111	60	49	65
Clinical remission at Week 44[b]	29 (25.4%)	53 (43.8%)*	50 (45.0%)*	13 (21.7%)	12 (24.5%)	27 (41.5%)*
Endoscopic improvement at Week 44[d]	33 (28.9%)	57 (47.1%)*	59 (53.2%)*	17 (28.3%)	16 (32.7%)	31 (47.7%)*

a: Patients who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study
b: A Mayo score ≤2 points, with no individual subscore >1.
c: Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.
d: A Mayo endoscopy subscore of 0 or 1.
* Nominal p-value < 0.05.

Conclusion:

Among patients with a clinically meaningful response to a single IV induction dose of UST, maintenance treatment with UST q8w or q12w demonstrated similar efficacy at Week 44. By contrast, the efficacy of UST q8w at Week 44 was greater than the q12w regimen for patients with higher inflammatory burden or who did not achieve clinical or symptomatic remission or endoscopic improvement at week 8. These data suggest that multiple clinical measures can help inform the decision on the most appropriate maintenance dosing regimen for UST in the treatment of patients with UC.

Disclosure:

OP191 - IMMUNOGENICITY OF USTEKINUMAB IN PATIENTS WITH CROHN'S DISEASE: RESULTS FROM THE IM-UNITI STUDY

Sandborn W.J.[1], **Sands B.E.**[2], **Nussbaum J.**[3], **Oortwijn A.**[4], **Gasink C.**[5], **Jacobstein D.**[6], **Gao L.-L.**[7], **Adekokun O.J.**[7], **de Villiers W.**[8], **Ghosh S.**[9] [1]University of California, San Diego, United States, [2]Icahn School of Medicine at Mount Sinai, Division of Gastroenterology, New York, United States, [3]Janssen Scientific Affairs, LLC, Immunology-GI, Horsham, United States, [4]Janssen Biologics BV, Leiden, Netherlands, [5]Janssen Scientific Affairs, LLC, Horsham, United States, [6]Janssen Research & Development, Immunology Development GI, Spring House, United States, [7]Janssen Research & Development, LLC, Spring House, United States, [8]Stellenbosch University, Stellenbosch, South Africa, [9]Institute of Translational Medicine, Birmingham, United Kingdom

Introduction:

Patients (pts) with moderately to severely active Crohn's disease (CD) who completed induction treatment with IV ustekinumab(UST) were eligible for a study of maintenance treatment with SC UST or placebo (PBO). Previous analyses of randomized pts who did not undergo dose adjustment in the maintenance study showed that rates of antibody formation were higher for

those who received a single IV UST induction dose and SC PBO maintenance (4.9%) than those who received IV UST induction and SC UST maintenance (2.9% and 2.0% for q12w and q8w groups, respectively). The aim of this analysis was to further characterize pts who had antibodies to UST in the maintenance study, including randomized and nonrandomized pts.

Aims and Methods:

In the induction trials (UNITI-1, n=741; UNITI-2, n=628), pts were randomly assigned to a single dose of IV PBO or UST (130 mg or ~6 mg/kg). Pts who responded to UST induction were randomly assigned to SC PBO or UST 90mg (q12w or q8w) at Wk 0 of the maintenance study (IM-UNITI) (n=397). Randomized pts who lost response between Wks 8 and 32 were eligible for dose adjustment to UST 90mg q8w. Nonrandomized pts (n=884) received SC UST q12w or UST q8w. Blood samples drawn at baseline and Wk 6 in the induction trial and Wks 12, 24, 36, and 44 in the maintenance trial were evaluated for antibodies to UST using a validated, drug-tolerant electrochemiluminescence immunoassay. Analysis set included all pts who were treated in the maintenance study, received ≥1 dose of UST induction or maintenance, and had ≥1 sample evaluable for antibodies from induction Wk 6 through maintenance Wk 44.

Results:

Of the 914 pts who received UST in the induction trials, 2(0.2%) were positive for antibodies through Wk 8. Of the 1,154 pts who were treated in the maintenance study, received UST in the induction or maintenance study, and had samples that were appropriate for antibody testing, 27(2.3%) had antibodies detected through Wk 44. Among the 27 pts who were positive for antibodies, 7 had at least one sample with high titers (>1:800), 7 had positive samples at ≥3 visits including Wk 44, and 7 were receiving immunomodulators at baseline (Table). No pts had infusion or injection-site reactions at the visit they were positive for antibodies. Among pts who were receiving UST maintenance, median trough UST serum concentrations at the visits of the positive antibody results were 0.18 and 0.72 µg/mL for pts whose highest antibody titers were >1:800 and ≤1:800, respectively

Conclusion:

Antibodies to UST were uncommon in pts with CD who received induction and maintenance treatment with UST. When antibodies did occur, they were usually transient and low titer.

Disclosure:

Hanauer S.B.[1], Sands B.E.[2], Feagan B.G.[3], Oortwijn A.[4], van Kruchten R.[4], Laliman V.[5], Izanec J.[6], Adedokun O.J.[7], Gao L.-L.[8], Sloan S.[9], Gasink C.[6], Targan S.[10], de Villiers W.[11], Rutgeerts P.[12], Colombel J.-F.[13], Ghosh S.[14] [1]Feinberg School of Medicine, Northwestern University, Chicago, United States, [2]Icahn School of Medicine at Mount Sinai, Division of Gastroenterology, New York City, United States, [3]Robarts Clinical Trials Inc., Gastroenterology, London, Canada, [4]Janssen Biologics BV, Leiden, Netherlands, [5]AMARIS, Toronto, Canada, [6]Janssen Scientific Affairs, LLC, Horsham, United States, [7]Janssen Research & Development, LLC, Spring House, United States, [8]Janssen Research & Development, LLC, Horsham, United States, [9]Janssen, Global Medical Affairs, Horsham, United States, [10]Cedars-Sinai Med Ctr, Los Angeles, United States, [11]Stellenbosch University, Stellenbosch, South Africa, [12]University Hospitals, Leuven, Leuven, Belgium, [13]Icahn School of Medicine at Mount Sinai, Gastroenterology, New York City, United States, [14]Institute of Translational Medicine, Birmingham, United Kingdom

Introduction:

Ustekinumab (UST) therapy induced and maintained response and remission in patients with moderate-to-severe Crohn's disease (CD) in induction, maintenance, and 2-year extension trials in the IM-UNITI program. Secondary loss of response (LoR) was observed in some patients during follow-up. This post-hoc analysis aims to characterize and identify potential predictors of LoR through 2 years of UST (Wk 96).

Aims and Methods:

The analysis included initial responders (IR) to UST IV at Wk 8 who were randomized to 90 mg SC UST q8w or q12w maintenance therapy and delayed responders (DR: responders at Wk 16 after not achieving clinical response at Wk 8; subsequently received UST q8w). LoR was defined as CDAI score ≥220 and a ≥100-point increase in CDAI score from Wk 8 or 16. Discontinuation due to lack of efficacy was also considered LoR, while patients who discontinued for other reasons were excluded from the analysis. Baseline (BL), Wk 8, and Wk 16 variables were described for LoR and no LoR patients. Univariate and multivariate logistic regression modeling was conducted on BL and Wk 8/16 variables.

Results:

This analysis included 473 patients, of whom 191 (40.4%) met criteria for LoR through Wk 96: 36.6% among IR randomized to UST q8w, 37.6% among IR randomized to UST q12w, and 43.8% among DR on q8w dosing. Patients with LoR versus patients without LoR during follow-up had higher mean CDAI scores at BL and at Wk 8 (321.6 [SD 60.6]and 227.8 [SD 108.3] vs 305.7 [61.6] and 184.5 [90.75] and higher FeCal at Wk 8 (622.5 [SD 1065.5] vs 446.7 [SD 671.2]). In addition, LoR was more frequent among patients with previous anti-TNF exposure (72.2%) and no use of 5-ASA (71.2%). Univariate analysis identified higher CDAI at induction and maintenance BL, lower delta CDAI after induction, Wk 8 FeCal levels, previous anti-TNF exposure and previous TNF failure as factors associated with increased risk for LoR (Table 1). Serum UST levels and concomitant IMM use were not identified as potential predictors of LoR. At multivariate analysis, only CDAI at maintenance baseline (OR: 1.42; 1.14-1.77), and previous TNF failure (OR: 2.05; 1.15-3.65) remained significant predictors of LOR.

Predictors of LoR (vs no LoR) by Univariate Logistic Regression Model

	OR	95% CI	p-value
Induction baseline CDAI (per 100-points)	1.52	1.13, 2.05	0.0063
Maintenance baseline CDAI (per 100-points)	1.56	1.28, 1.88	<0.0001
Delta CDAI induction/ Maintenance (per 100-points)	1.40	1.13, 1.72	0.0016
FeCal levels at Week 8 (per 100 mg/kg)	1.03	1.00, 1.05	0.040
Previous TNF exposure	2.13	1.44, 3.16	0.0002
Previous TNF failure	2.46	1.69, 3.58	<0.0001

Predictors of LoR (vs no LoR) by Multivariate Logistic Regression Model

	OR	95% CI	p-value
Maintenance baseline CDAI score (per 100-points)	1.42	1.14, 1.77	0.0021
Previous TNF exposure	1.06	0.58, 1.94	n.s.
Previous TNF failure	2.46	1.15, 3.65	0.015

[Table 1: Predictors of LoR (vs no LoR): univariate and multivariate logistic regression models]

Conclusion:

Throughout 2 years of follow up, secondary LoR occurred in ~40% of initial or delayed responders to UST. Patients with higher CDAI at maintenance BL, and history of previous anti-TNF failure were found to be at increased risk for LoR. UST levels were not helpful as potential predictors of LoR and concomitant use of IMM did not reduce the risk of LoR during UST therapy.

Disclosure:

Drs. Hanauer, Sands, Feagan, Targan, de Villiers, Rutgeerts, Colombel, and Ghosh are all investigators for Janssen Research & Development, LLC Dr. Laliman is a consultant to Janssen Research & Development, LLC Drs. Oortwijn and van Kruchten are employees with Janssen Biologics BV Drs. Izanec and Gasink are employees of Janssen Scientific Affairs, LLC Drs Adedokun and Gao are employees of Janssen Research & Development, LLC Dr. Sloan is an employee of Janssen Global Services, LLC

P1803 - ASSOCIATION OF USTEKINUMAB SERUM CONCENTRATIONS AND PERIANAL FISTULA RESOLUTION IN THE CROHN'S DISEASE UNITI PROGRAM

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Introduction:

Previous studies have demonstrated the efficacy and safety of ustekinumab (UST) IV induction and SC maintenance in Crohn´s disease. Analysis from the Phase 2 and 3 UST trials also demonstrated possible benefit in fistula resolution at week 8 [14.1% (10/71) PBO vs 24.7% (37/150) all UST doses combined] despite a small proportion (10.8 to 15.5% across the studies) of patients with active perianal fistulas at baseline (Sands et al DDW 2017). Here we examine the

relationship between perianal fistula resolution at induction week 8 (maintenance week 0) and maintenance week 44 based on serum UST levels at maintenance weeks 0 and 24 in patients receiving IV UST induction and SC UST maintenance.

Aims and Methods:

Patients in UNITI-1 and 2 induction studies were randomized to IV PBO or UST (130mg or ~6mg/kg). Patients with open, draining perianal fistulas at baseline had their fistulas assessed by physical exam (including gentle compression). Patients were analyzed for complete fistula resolution (100% reduction) at subsequent study visits. Fistula resolution at induction week 8 was also analyzed based on week 8 UST serum concentration quartiles, while fistula resolution at maintenance week 44 was analyzed based on maintenance week 24 UST serum concentration quartiles (incorporating non-randomized and randomized groups). Patients who started a prohibited medication (e.g. another biologic) were considered not to be in fistula resolution

Results:

In observed data, among randomized patients with open, draining perianal fistulas at baseline of UNITI-1/2 27.5% (11/40) receiving 130mg, 23.7% (9/38) receiving ~6mg/kg UST and 25.6% (20/78) combined UST had fistula resolution induction week 8 compared to 9.3% (4/43) in the PBO group (p=0.03, 0.08, and 0.03, respectively). At week 44, 85.7% (6/7) and 71.4% (5/7) patients randomized to UST maintenance (90mg Q8W or Q12W) had perianal fistula resolution, compared to 44.4% (4/9) of patients randomized to PBO (p=0.15 and 0.36, respectively). Incorporating all patients (randomized and non-randomized) treated with UST maintenance, perianal fistula resolution occurred in 42% (21/50) of patients. In the induction week 8 quartile analysis, perianal fistula resolution was 38.9% (7/18) in Q1, 11.8% (2/17) in Q2, 27.8% (5/18) in Q3, and 29.4% (5/17) in Q4 for all UST treated patients (Table 1). Fistula resolution at maintenance week 44 based on week 24 concentration quartiles also did not show any exposure response relationship

Fistula Resolution at Week 8 Post Induction (Week 0 Maintenance) by Serum Concentrations at Week 8 Post Induction (Week 0 Maintenance)

UST Concentration Quartiles WK 0[a]	130mg UST[b]	~6mg/kg[c]	Combined
Q1	33.3% (3/9)	44.4% (4/9)	38.9% (7/18)
Q2	11.1% (1/9)	12.5% (1/8)	11.8% (2/17)
Q3	44.4% (4/9)	11.1% (1/9)	27.8% (5/18)
Q4	33.3% (3/9)	25.0% (2/8)	29.4% (5/17)

Fistula Resolution at Week 44 Post Maintenance by UST Serum concentrations at Week 24 Post Maintenance

UST Concentration Quartiles WK 24[a]	90 mg Q8W[d]	90mg Q8W or Q12W[e]	-
Q1	85.7% (6/7)	75% (9/12)	-
Q2	57.1% (4/7)	50% (6/12)	-
Q3	28.6 (2/7)	25% (3/12)	-
Q4	14.3% (1/7)	27.3% (3/11)	-

a Patients in fistula resolution with missing PK data were excluded from this analysis
b Q1: <1.18 µg/ml; Q2 1.18 µg/ml <1.62 µg/ml; Q3: >1.62 µg/ml <2.84 µg/ml; Q4 >2.84 µg/ml
c Q1 <3.40 µg/ml; Q2 >3.40 µg/ml <5.04 µg/ml; Q3 >5.04 µg/ml <9.30 µg/ml; Q4 >9.30 µg/ml
d Q1: <1.34 µg/ml; Q2: >1.34 µg <1.99 µg/ml; Q3: >1.99 µg/ml< 3.01 µg/ml; Q4 > 3.01 µg/mL
e Q1: <1.25 µg/ml; Q2: >1.25 µg <2.31 µg/ml; Q3: >2.31 µg/ml< 3.47 µg/ml; Q4 > 3.47 µg/mL

Conclusion:

Some evidence of efficacy in perianal fistula resolution is present with UST in both induction and maintenance, despite a relatively small number of patients with perianal fistulas. However, perianal fistula resolution did not appear to be associated with higher UST serum concentrations.

Disclosure:

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Aims and Methods:

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patients randomized to UST maintenance (90mg Q8W or Q12W) had perianal fistula resolution, compared to 44.4% (4/9) of patients randomized to PBO (p=0.15 and 0.36, respectively). Incorporating all patients (randomized and non-randomized) treated with UST maintenance, perianal fistula resolution occurred in 42% (21/50) of patients. In the induction week 8 quartile analysis, perianal fistula resolution was 38.9% (7/18) in Q1, 11.8% (2/17) in Q2, 27.8% (5/18) in Q3, and 29.4% (5/17) in Q4 for all UST treated patients (Table 1). Fistula resolution at maintenance week 44 based on week 24 concentration quartiles also did not show any exposure response relationship

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Fistula Resolution at Week 44 Post Maintenance by UST Serum concentrations at Week 24 Post Maintenance

UST Concentration Quartiles WK 24[a]	90 mg Q8W[d]	90mg Q8W or Q12W[e]	-
Q1	85.7% (6/7)	75% (9/12)	-
Q2	57.1% (4/7)	50% (6/12)	-
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d Q1: <1.34 µg/ml; Q2: >1.34 µg <1.99 µg/ml; Q3: >1.99 µg/ml< 3.01 µg/ml; Q4 > 3.01 µg/mL
e Q1: <1.25 µg/ml; Q2: >1.25 µg <2.31 µg/ml; Q3: >2.31 µg/ml< 3.47 µg/ml; Q4 > 3.47 µg/mL

Conclusion:

Some evidence of efficacy in perianal fistula resolution is present with UST in both induction and maintenance, despite a relatively small number of patients with perianal fistulas. However, perianal fistula resolution did not appear to be associated with higher UST serum concentrations.

Disclosure:

P0385 - PRELIMINARY ANALYSIS OF UTILISATION AND CLINICAL RESULTS FROM THE NHS SCOTLAND THERAPEUTIC DRUG MONITORING SERVICE FOR BIOLOGIC MEDICINES

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Introduction:

Anti-tumour necrosis factor α (anti-TNFα) drugs infliximab (IFX) and adalimumab (ADL) are effective treatments for inflammatory bowel disease (IBD) and have greatly improved outcomes for many individuals. However, treatment effects are not universally favourable with primary non-response (PNR) to treatment occurring in up to 30% and secondary loss of response (SLR) in up to 46% of IFX and ADL treated IBD cohorts (1,2).Therapeutic drug level and anti-drug antibody monitoring (TDM) has emerged as a useful tool for optimising the effectiveness of these drugs, identifying individuals who may benefit from dose or treatment frequency adjustments to regain control of disease after relapse, or even to prevent PNR or SLR.

Aims and Methods:

Ensuring safe and effective use of biologic medicines has been identified as a key priority for NHS Scotland. Inequity and inconsistency of access to TDM across the nation was recognised as a barrier to delivering best practice and so a nationally commissioned TDM service was established in January 2018 to support clinical practice, providing universal access to TDM for IBD services across Scotland. A service webpage was developed to provide guidance on testing strategies and interpretation of TDM results (3). Preliminary data and initial clinical observations from the first year of the service have now been collated. Data collection and analysis of results regarding usage and clinical impact of the service were identified as key outcome measures to assess service success and sustainability.
An automated search of clinical data and test results recorded within the clinical biochemistry electronic results management system was conducted to identify all TDM tests performed between 01/01/2018 and 31/12/2018. Outcomes for descriptive analysis included the number of samples received and processed, overall testing population, service utilisation by Health Board, and the number and results of TDM tests performed per patient. TDM results were interpreted according to published guidance on the service webpage and comparison was made with previously published data (4).

Results:

3609 specimens were received for testing, from 13 of the 14 Scottish Health Boards. 3561 drug level (DL) tests were performed; 1786 IFX, 1775 ADL. 2717 total antidrug anti-body (TABT) tests and 681 free antidrug anti-body tests (FABT) were performed according to service protocol. 2791 individuals had one or more TDM tests during the 12-month period, of whom 541 were tested twice or more (range 2-5).

		INFLIXIMAB	ADALIMUMAB	
Drug level by category	Supratherapeutic DL > 8mcg/ml	546 (30.6%)	708 (39.9%)	Supratherapeutic DL > 10 mcg/ml
	Therapeutic DL ≥3<8.1mcg/ml	738 (41.3%)	636 (35.8%)	Therapeutic DL ≥5<10.1 mcg/ml
	Sub-therapeutic DL < 3mcg/ml	502 (28.1%)	431 (24.3%)	Sub-therapeutic DL < 5 mcg/ml
TABT by category	Negative (<10 AU/ml)	791 (54.2%)	905 (71.9%)	Negative (<10 AU/ml)
	Positive (>10 AU/ml)	668 (45.8%)	353 (28.1%)	Positive (>10 AU/ml)
FABT by category	Negative (< 5AU/ml)	376 (82.8%)	176 (77.6%)	Negative (<10 AU/ml)
	Positive (> 5 AU/ml)	78 (17.2%)	51 (22.4%)	Positive (>10 AU/ml)

[Table 1 – IFX & ADL DL, TABT and FABT results by category as defined in service guidance (AU/ml = Arbitrary Units/ml)]

Conclusion:

TDM has been enthusiastically embraced with rapid uptake of testing in IBD. It is estimated that > 50% of individuals treated with IFX or ADL have been tested at least once in the first year. DL results were found to be similar to previously published data, as were rates of antibody positivity. The large volume of data generated by the service may provide additional evidence regarding the utility of TDM in predicting clinical response. Next steps are to conduct a comparative effectiveness analysis where proactive vs reactive TDM testing strategies will be compared, with the primary outcome measure being the proportions of patients with SLR.

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Disclosure: