Table 1. Clinical Characteristics of Polysubstance Use in Inflammatory Bowel Disease

Variable	Total (n=315)	Polysubstance Use (n=66)	No Polysubstance Use (n=249)	Odds Ratio	95% Confidence Limits		P Value
Gender [female (%)]	166 (52.7%)	34 (51.5%)	132 (53.0%)	0.942	0.547	1.621	0.890
IBD subtype (CD/UC)	214 / 101	46 / 20	168 / 81	0.902	0.501	1.624	0.769
Moderate or Severe Inflammation (%) (on endoscopic evaluation)	118 (37.5%)	27 (40.9%)	91 (36.5%)	1.2	0.691	2.092	0.568
Extra-Intestinal Manifestations (%)	108 (34.3%)	31 (47.0%)	77 (30.9%)	**1.97**	**1.138**	**3.440**	**0.0193**
Anxiety or Depression (%)	131 (41.6%)	24 (36.4%)	107 (43.0%)	0.759	0.432	1.329	0.400
Antidepressant or Anxiolytic Use (%)	112 (35.6%)	35 (53.0%)	77 (30.9%)	**2.51**	**1.451**	**4.385**	**0.00130**
Steroid Use (%)	167 (53.0%)	37 (56.1%)	130 (52.2%)	1.17	0.677	2.016	0.678
Mesalamine Use (%)	71 (22.5%)	13 (19.7%)	58 (23.3%)	0.808	0.412	1.585	0.621
Immunomodulatory Use (%)	75 (23.8%)	13 (19.7%)	62 (24.9%)	0.74	0.378	1.447	0.420
Biologic Use (%)	150 (47.6%)	31 (47.0%)	119 (47.8%)	0.968	0.562	1.666	1.00
Fatigue (%)	270 (85.7%)	55 (83.3%)	215 (86.3%)	0.791	0.377	1.660	0.554
Abdominal Pain (%)	206 (65.4%)	46 (69.7%)	160 (64.3%)	1.28	0.712	2.298	0.468
Diarrhea (%)	117 (37.1%)	29 (43.9%)	88 (35.3%)	1.43	0.826	2.488	0.201
Fecal Urgency (%)	218 (69.2%)	52 (78.8%)	166 (66.7%)	1.85	0.973	3.544	0.0715
Rectal Bleeding (%)	125 (39.7%)	27 (40.9%)	98 (39.4%)	1.07	0.614	1.854	0.888
Healthcare Resource Utilization (%)	220 (69.8%)	50 (75.8%)	170 (68.3%)	1.45	0.779	2.708	0.291

Note: CD = Crohn's disease, UC = ulcerative colitis.

Table 2. Multivariable Logistic Regression Model, Polysubstance Use in Inflammatory Bowel Disease.

Variable	Odds Ratio	95% Confidence Limits		P Value
Gender [female (%)]	0.8192	0.4501	1.491	0.514
Age	1.005	0.9859	1.025	0.607
IBD Subtype (Ulcerative Colitis)	0.7017	0.3508	1.404	0.317
Moderate or Severe Inflammation (on endoscopic evaluation)	1.346	0.7155	2.532	0.357
Extra-Intestinal Manifestations	**1.973**	**1.075**	**3.622**	**0.0284**
Anxiety or Depression	0.5937	0.3049	1.156	0.125
Steroid Use	0.863	0.4514	1.65	0.656
Antidepressant or Anxiolytic Use	**2.628**	**1.452**	**4.757**	**0.00142**
Mesalamine Use	0.8762	0.3991	1.924	0.742
Immunomodulatory Use	0.574	0.2743	1.201	0.1407
Biologic Use	0.8554	0.4656	1.571	0.615
Fatigue	0.5329	0.2147	1.323	0.175
Abdominal Pain	1.445	0.7015	2.977	0.318
Diarrhea	1.41	0.7288	2.727	0.308
Fecal Urgency	2.052	0.9461	4.452	0.0688
Rectal Bleeding	0.9243	0.4849	1.762	0.811
Healthcare Resource Utilization	1.303	0.6277	2.704	0.478

SELF-COMPASSION IN ADOLESCENTS AND YOUNG ADULTS WITH INFLAMMATORY BOWEL DISEASE: RELATIONSHIP OF SELF-COMPASSION TO PSYCHOLOGICAL AND PHYSICAL OUTCOMES

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Background: Adolescents and young adults (AYA) with Inflammatory Bowel Disease (IBD) are at increased risk for poor psychological and physical well-being. Self-compassion (i.e., understanding and acceptance towards oneself) has been associated with better psychological and physical outcomes in AYA with chronic health conditions. There is limited research exploring self-compassion in AYA with IBD.

Aims: To examine: 1) the reliability of a Self-Compassion Scale (SCS-SF), and 2) how self-compassion relates to physical (i.e., pain interference, fatigue) and psychological (i.e., stress, anxiety, depression) outcomes in a sample of AYA with IBD.

Methods: This study was a collaboration with ImproveCareNow, and all procedures were approved by Stanford's Institutional Review Board. Study participants included 85 AYA (mean=18 yrs) with IBD (52% Crohn's; 55% female; 61% White). Participants completed a one-time online survey. The internal reliability of SCS-SF was a = 0.88, indicating high internal consistency. Hierarchical linear regression (HLR) analyses examined the unique contribution of self-compassion to pain interference, fatigue, physical stress, psychological stress, anxiety, and depression after controlling for significant demographic and medical variables (sex, IBD diagnosis, mental health diagnosis).

Results: The overall HLR models were significant for all dependent variables. For physical outcomes, the overall model examining pain interference was significant ($F(3, 72) = 4.517$; $P = 0.003$), with sex, IBD diagnosis, and mental health diagnosis accounting for 13% of the variance in pain interference. Self-compassion accounted for an additional 20% of the variance in pain interference over and above demographic/medical variables. For psychological outcomes, the overall model examining anxiety was significant ($F(3, 73) = 15.54$; $P < 0.001$), with sex, IBD diagnosis, and mental health diagnosis accounting for 33% of the variance in anxiety. Self-compassion accounted for an additional 46% of the variance in anxiety over and above demographic/medical variables. HLR also demonstrated that self-compassion was a significant independent predictor of pain interference (b = -0.30, $P = 0.015$), fatigue (b = -0.38, $P = 0.001$), psychological stress (b = -0.51, $P = < 0.001$), anxiety (b = -0.41, $P = < 0.001$), and depression (b = -0.59, $P = < 0.001$). Participants reporting higher levels of self-compassion had less pain interference, fatigue, stress, anxiety, and depression.

Conclusion: Preliminary results suggest self-compassion may be an important factor in explaining the variability of key physical and psychological outcomes among AYA with IBD. Research should investigate self-compassion in diverse IBD populations, and explore if feelings of kindness and acceptance towards oneself can be a protective factor for AYA by supporting positive coping and adjustment to IBD.

THE EVALUATION OF SERUM SEROTONIN LEVEL AMONG PATIENTS WITH CROHN'S DISEASE AND ITS IMPACT ON QUALITY OF LIFE

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Background and aims: Serotonin affects intestinal physiology, mood, as well as circadian rhythm. Moreover, serotonin has proinflammatory function. Therefore, the aim of this study was to investigate the role of serotonin in clinical severity of Crohn's Disease (CD) and its effect on pain and sleep quality.

Methods: Fifty-nine CD patients (34 in exacerbation and 25 in remission according to the Harvey-Bradshaw Index-HBI) and 25 health control individuals(HC) were recruited. Sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI) and subjective severity of pain by the Visual Analog Scale (VAS). Seventeen patients were treated with anti-TNF-α induction therapy for 14 weeks.

Results: Serotonin level was higher in CD (145.12ng/mL, IQR:98.14–179.25) compared to HC (87.52ng/mL, IQR:70.04–129.39; p=0.002) and in exacerbation of CD (157.66ng/mL, IQR:111.94–197.64) compared to remission (122.33ng/mL, IQR:83.28–163.67; p=0.029). Serotonin level with cut-off point of 92.45 ng/mL is useful for distinguishing participants with CD from HC (sensitivity: 78%, specificity: 60%, positive predictive value: 82%). Positive correlation between serotonin and HBI (r=0.279, p=0.032) and severity of diarrhoea (r=0.260, p=0.047) were found. Serotonin does not correlate with PSQI (r=0.152, p=0.168), but correlates with presence of sleep fragmentation for example by getting up to use the bathroom (joined 5b-5j PSQI questions; r=0.270, p=0.039). Correlations between serotonin and VAS were also obtained (r=0.220, p=0.045). Moreover, serotonin level significantly decreased after anti-TNF-α therapy (192.35ng/mL, IQR:150.36–225.56 vs. 121.11ng/mL, IQR:91.28–188.87; p=0.006). The study was funded by National Science Centre, Poland (#2018/31/N/NZ5/03715).

Conclusions: Serotonin level correlates with the severity of CD and decreases after anti-TNF-α therapy. It is associated with sleep fragmentation, which may be caused by diarrhea.

Therapeutic Drug Monitoring

ANTI-TNF PHARMACOKINETICS AND RESPONSE TO THERAPY IN PEDIATRIC ACUTE SEVERE ULCERATIVE COLITIS (THE ARCH STUDY)

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Background and Aims: 25% of children hospitalized with acute severe ulcerative colitis (ASUC) rescued with infliximab (IFX) at labeled dosing undergo a colectomy prior to discharge. Our aim was to determine whether IFX pharmacokinetics (PK) are associated with treatment response in pediatric ASUC.

Methods: We prospectively enrolled hospitalized pediatric patients initiating IFX for ASUC or IBD-U (PUCAI ≥65) at 7 North American centers and followed for 26 weeks in this pilot and feasibility cohort study. Serial IFX levels (Prometheus Biosciences, Inc.) were obtained and individual PK parameter estimates, such as volume of distribution, clearance (CL), elimination half-life ($T_{1/2}$) and IFX exposure (area under the concentration-time curve) were estimated using Bayesian methodology. The primary outcome was Day 7 clinical response (CR-D7, PUCAI <35). Key secondary outcomes were Week 8 clinical remission (CR-W8, PUCAI <10) and Week 26 corticosteroid-free clinical remission (CFR-W26).

Results: 38 participants (mean age 14.5 years, 50% female, 95% UC, 87% extensive/pancolitis) were treated with IFX at a mean higher than labeled dosing of 9.9 [9.3,10.3] mg/kg, and 16% received an early second dose 4–6 days after the first infusion. CR-D7, CR-W8, and CFR-W26 were achieved in 71%, 55%, and 41%, respectively. Only one participant (2.7%) underwent colectomy by week 26. Using 304 IFX level measurements, we developed a novel pediatric population PK model for IFX in ASUC that incorporated albumin, antibodies to IFX, CRP, and height to characterize the PK profile for participants. The median IFX $T_{1/2}$ was 5.8 [4.2,7.0] days at Day 7 and lengthened to 7.4 [5.4,8.4] days by Week 26 (P=0.014), but notably remained below the median 10.8 [8.6, 15.4] days reported in a randomized controlled trial of IFX for moderate to severe pediatric UC (Fig. 1). IFX exposure was not associated with CR-D7, CR-W8, or CSR-W26. More rapid IFX CL at Week 26 was significantly associated with inability to achieve CFR-W26 (P=.013). This finding was in line with a higher, but not statistically significant, median trough IFX level nearest Week 26 in those with (19.5 [13.6, 30.3]) versus without (14.2 [6.0, 21.3] µg/ml) CFR-W26 (P=.13) (Fig. 2).

Conclusion: At the higher than standard IFX dosing used to treated children with ASUC in this observational study, we observed a lower colectomy rate compared to prior studies but did not observe a positive association between IFX exposure and clinical outcomes. Albumin, CRP, height, and ATI were associated with IFX PK and incorporated into a new pediatric ASUC PK model. Initial 10 mg/kg IFX dosing may be sufficient to optimize early outcomes in pediatric ASUC. Additional studies are needed to determine if sustained intensification of maintenance IFX regimens

can overcome persistent rapid clearance and improve later outcomes in pediatric ASUC.

Figure 1. Infliximab elimination half-life in pediatric ASUC at Day 7, Week 8, and Week 26 from start of treatment. The elimination half-life reported in the pediatric randomized control trial for moderate to severe UC is provided as a reference comparison.

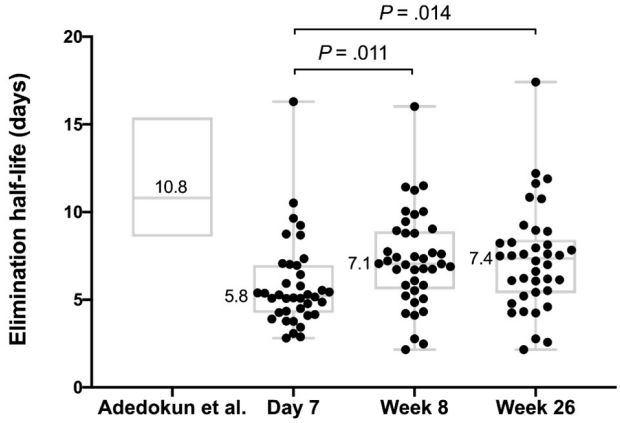
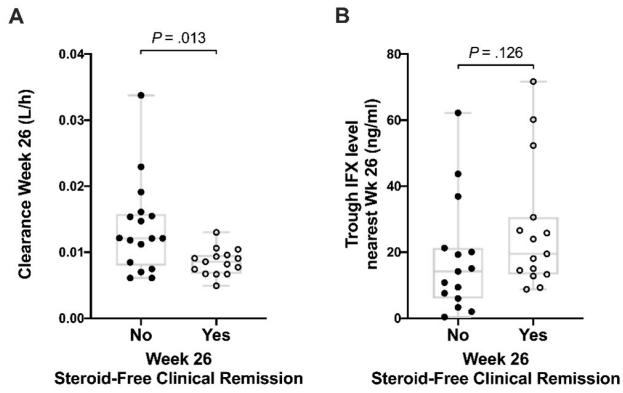


Figure 2: Infliximab clearance (A) and trough levels (B) at Week 26 compared between participants achieving and not achieving Week 26 steroid-free clinical remission.



CHARACTERIZATION OF IMMUNE PHENOTYPES AS PREDICTIVE BIOMARKERS FOR RESPONSE TO THE α4β7 INTEGRIN BLOCKER, VEDOLIZUMAB

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The etiology of inflammatory bowel disease (IBD) is unknown. However, chronic inflammation from T cell activation and its subsequent tissue damage is implicated in the pathogenesis of IBD. Vedolizumab (VDZ), a monoclonal antibody against α4β7 integrin that prevents T cell homing to intestinal mucosae, has shown efficacy in treating both ulcerative colitis (UC) and Crohn's disease (CD), with greater efficacy in UC. We aimed at identifying immunophenotypic and gene regulatory characteristics that could predict which IBD patients will benefit from VDZ therapy. Peripheral blood mononuclear cells and lamina propria mononuclear cells (PBMC and LPMC) were isolated before treatment with VDZ and after treatment (PBMC; between weeks 14 and 22). PBMCs/LPMCs were stained for T cell markers, gut homing receptors, and other immune cell markers. Sorted $CD4^+$ memory (Tmem) and regulatory (Treg) T cells underwent RNA sequencing (RNA-seq). Clinical response was defined as at least a two-point drop in partial Mayo scores (UC) and Harvey-Bradshaw (CD) indices following VDZ therapy. Using an agnostic approach to the flow cytometry data, we examined cell clustering by CytofKit and related immunophenotypic markers to disease type and responsiveness. We performed differential gene analysis (DEseq2) of RNA-seq data on T cell populations from the periphery and lamina propria. In total, 71 patients were enrolled and 37 received VDZ. Of 37 patients, 14 responded (37.8%); 21% of UC patients, 16% of CD patients. A cohort of patients responsive with long term VDZ therapy, despite initial refractoriness, was identified. Unsupervised clustering revealed the largest immunophenotypic differences between ileal and colonic biopsies, regardless of IBD subtype or inflammation state. Likewise, T cells, both Tmems and Tregs, showed the greatest number of DEGs between tissue types. In patients who received VDZ, we examined immunophenotypic biomarkers able to predict response. Specific clusters found to predict response were either specific to disease state or independent of disease state. Tissue-related immunophenotypes isolated by flow and RNA signatures in T cell subsets, especially Tregs, offered the best predictors of response, compared to blood. We examined changes in PBMC and T cell gene expression after VDZ in blood. After VDZ treatment, especially in UC, we saw an increase in α4β7+ T cells that were also positive for the gut specific CCR9 marker. In the peripheral blood following VDZ treatment, we saw a decrease in inflammatory pathway activation in Tregs.

The results show that intestinal profiling better represents CD and UC than peripheral blood. Using a combination of clinical data, immunophenotyping, and gene expression allows for a more comprehensive view of the mucosal immune response in IBD. These biomarkers may allow rational use of VDZ given its safety profile.

PERFORMANCE CHARACTERISTICS OF A FRET-BASED IMMUNOASSAY FOR QUANTITATION OF ADALIMUMAB ON A POINT-OF-CARE INSTRUMENT SYSTEM

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Introduction: A fast (<5 min), time-resolved fluorescence resonance energy transfer (FRET)-based immunoassay was developed for the quantitative detection of adalimumab (ADL) and biosimilars for use in therapeutic drug monitoring using only 20 µL of fingerstick whole blood or serum at the point-of-care. The Procise ADL assay and the ProciseDx analyzer are CE-marked. Studies were performed to characterize analytical performance of the Procise ADL assay on the ProciseDx analyzer.

Methods: Analytical testing was performed by spiking known amounts of ADL into negative serum and whole blood specimens. Analytical sensitivity was determined using limiting concentrations of ADL. Linearity was determined by testing ADL across the assay range. Hook effect was assessed at ADL concentrations beyond levels expected to be found within a patient. Testing of assay precision, cross-reactivity and potential interfering substances, and biosimilars was performed. The Procise ADL assay was also compared head-to-head with another CE-marked assay: LISA-TRACKER adalimumab ELISA test (Theradiag, France). The accuracy of the Procise ADL assay is established through calibrators and controls traceable to the WHO 1st International Standard for Adalimumab (NIBSC code: 17/236).

Results: The Procise ADL assay shows a Limit of Blank, Limit of Detection, and Lower Limit of Quantitation (LLoQ) of 0.1, 0.2, and 0.6 µg/mL in serum and 0.5, 0.9, and 1.3 µg/mL in whole blood, respectively. The linear assay range was determined to be 1.3 to 51.5 µg/mL in serum and whole blood. No hook effect was observed at an ADL concentration of 200 µg/mL as the value reported as ">ULoQ". Assay precision testing across 10 days with multiple runs and reagent lots showed an intra-assay coefficient of variation (CV) of 2.8%, an inter-assay CV of ≤1.5%, and a total CV of 3.5%. The presence of potentially interfering/cross-reacting substances showed minimal impact on assay specificity with %bias within ±7.4% of control. Testing of biosimilars (adalimumab-atto and adalimumab-xxxx) showed good recovery. A good correlation to the Theradiag adalimumab ELISA was obtained for both serum (slope=0.94; r=0.99) and whole blood (slope=1.13; r=0.98) samples (Figure 1).

Conclusion: Results indicate that the Procise ADL assay is sensitive, specific, and precise yielding results within 5 minutes from both whole blood and serum without the operator needing to specify sample type. Additionally, it shows good correlation to a comparator assay that takes several hours and sample manipulation to yield results. This makes the Procise ADL assay ideal for obtaining fast and accurate ADL quantitation, thus allowing for immediate drug level dosing decisions to be made by the physician during patient treatment.

Figure 1. Assay correlation between Procise ADL and Theradiag tests in serum specimens (left) and in whole blood (Procise) vs. recovered plasma (Theradiag) specimens (right).