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The effect of compliance during exclusive enteral nutrition on faecal calprotectin levels in children with Crohn's disease

S. Mckirdy*[1], R. Russell[2], R. Hansen[3], V. Svolos[1], K. Gkikas[1], M. Logan[1], K. Gerasimidis[1]

[1]*University of Glasgow, Human Nutrition, Glasgow, United Kingdom,* [2]*Royal Hospital for Children and Young People, Department of Paediatric Gastroenterology, Edinburgh, United Kingdom,* [3]*Royal Hospital for Children, Department of Paediatric Gastroenterology, Glasgow, United Kingdom*

Background: It is yet unclear whether suboptimal response to exclusive enteral nutrition (EEN), in some children with Crohn's disease (CD), is explained by poor compliance. All proprietary feeds used for EEN are gluten-free; hence patients' compliance to EEN could be determined by detecting gluten immunogenic peptide (GIP), a biomarker of gluten intake, in faeces.

Methods: The concentration of GIP was measured in the faeces of, 45 children (3–17 years) with CD prior to and during (33 &, 54 days) treatment with EEN. Associations with GIP and faecal calprotectin (FCAL) levels were explored at, 33 and, 54 days of EEN.

Results: GIP was present in, 37 of the, 40 (93%) patients who provided stool samples prior to starting EEN, indicating typical gluten consumption in CD patients. In patients with undetectable GIP at both, 33 and, 54 days of EEN, FCAL significantly decreased from baseline (mean decrease, 33 days: -743mg/kg, 54 days: -1043mg/kg, p<0.001), but not in patients who had detectable GIP. At EEN completion, patients with undetectable GIP had a lower FCAL by, 763mg/kg than patients with a positive GIP result (p=0.041) and demonstrated a greater decline from baseline FCAL (-69% vs +5.%, p=0.021).

Conclusion: Poor response to EEN might be explained at least in part by diminished compliance and dietary transgressions. Faecal GIP might be useful as a proxy biomarker of EEN compliance.

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Comparison of adalimumab drug levels and drug survival in proactive vs reactive therapeutic drug monitoring

S. Shields*[1], A. Dunlop[2], S. Barry[3], P. Galloway[2], J.P. Seenan[1], J. Macdonald[1]

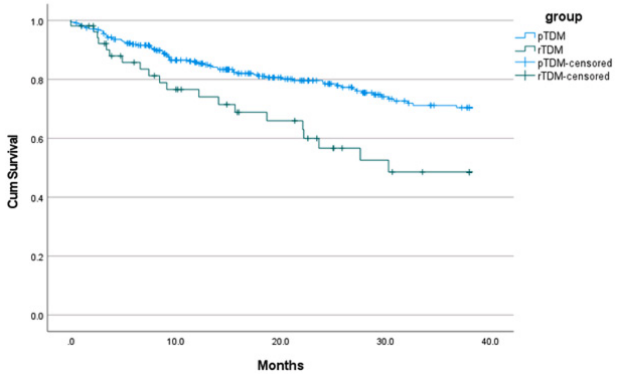
[1]*Queen Elizabeth University Hospital, Gastroenterology, Glasgow, United Kingdom,* [2]*Queen Elizabeth University Hospital, Biochemistry, Glasgow, United Kingdom,* [3]*University of Strathclyde, Department of Mathematics and Statistics, Glasgow, United Kingdom*

Background: The therapeutic landscape for inflammatory bowel disease (IBD) has expanded in recent years. The anti-TNF drug adalimumab remains one of the most commonly prescribed treatments. However, rates of loss of response to adalimumab are significant. Therapeutic Drug Monitoring (TDM) has emerged as a tool to prevent loss of response to treatment but there is no consensus on the optimum TDM testing strategy., 2 testing strategies are commonly used - proactive TDM (pTDM), performed during sustained clinical response and reactive TDM (rTDM), performed following loss of response. The aim of this work was to compare adalimumab drug levels (DL) and drug survival (DS) for patients exposed to pTDM compared to rTDM testing strategies.

Methods: Data for patients with IBD, treated with adalimumab, and exposed to TDM, was extracted from the Scottish Biologic TDM database. Patients were assigned to pTDM or rTDM groups based on the indication of their first TDM test. Prescribing information was extracted from the NHS Scotland Safe Haven homecare prescribing database. Homecare delivery dates were used to infer start and end dates of adalimumab treatment. Where adalimumab start date was before, 2017, a start date of, 1/1/2017 was used to coincide with the introduction of the Scottish TDM service. The study period was, 1/1/2017 to, 1/3/2020 giving a maximum duration of drug exposure of, 38 months. The most recent drug level was used for each patient to reflect the impact of the TDM strategy employed. SPSS was used to perform statistical analysis.

Results:, 367 patients were included for analysis, 190 males and, 177 females, 262 with Crohn's disease and, 105 with Ulcerative Colitis., 314 patients were assigned to the pTDM group, and, 53 to the rTDM group. The mean DL across both groups was, 9.5 mcg/ml, with no significant difference seen between pTDM and rTDM groups (p=0.642). Median DS in the pTDM group was, 21 months versus, 15.6 months in the rTDM group. 277 patients (75.5%) remained on treatment at the end of the study, 244 (77.7%) in the pTDM group, versus, 33 (62.3%) in the rTDM group. DS was significantly higher in the pTDM group compared to the rTDM (p=0.004) group (Fig., 1), with divergence of the survival curve seen after, 6 months.

Fig.1
DS for adalimumab treated IBD patients exposed to pTDM vs rTDM



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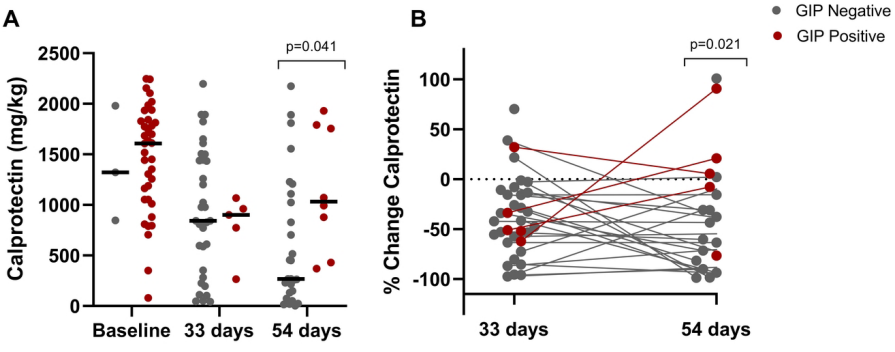

Conclusion: pTDM has been clearly favoured by clinicians from the outset of the TDM service. Whilst our data shows that DLs do not vary significantly between TDM groups, importantly, the DS with adalimumab is longer with pTDM as part of routine clinical care, when compared to rTDM. Further evaluation of clinical outcomes including steroid prescription, hospital admissions and surgery rates in the context of pTDM and rTDM strategies is therefore warranted, and in progress.

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In silico evaluation and pre-clinical efficacy of anti-TNF and anti-IL-23 combination therapy in Inflammatory Bowel Disease

J. Perrigoue[1], L. Muniz-Bongers[1], L. Ong[1], Y. Chen[2], L. Chang*[2], K. Ngo[2], A. Stojmirovic[1], C. O'Brien[1], M. Germinaro[1], R. Rao[1], M. Vetter[1], J. Towne[2]; VEGA

[1]Janssen Research & Development- LLC, Immunology, Spring House, United States, [2]Janssen Research & Development- LLC, Immunology, San Diego, United States

Background: Despite advances in the treatment of inflammatory bowel diseases (IBD), fewer than, 40% of patients reach clinical remission, suggesting that improved response rates may require targeting of multiple pathogenic pathways through combination therapy. However, the rational selection of combination therapies based on patient and pre-clinical data remains a significant challenge.

Methods: Here, we used Crohn's disease (CD) patient-derived molecular networks as a platform for bridging pre-clinical animal models of combination therapy to human disease. Intestinal transcriptional signatures of anti-TNF, anti-IL-23 or combination treatments were generated from the anti-CD40 agonistic antibody murine colitis model and the murine genes mapped to their human orthologues. Humanized gene signatures were intersected with human disease networks to generate treatment subnetworks and enrichment analyses performed.

Results: The anti-TNF subnetwork was enriched in genes expressed in myeloid cells, chemokine signaling and NFkB signaling, while the anti-IL-23 subnetwork was enriched in genes expressed in the intestinal epithelium, IL-17 signaling, and cell adhesion. The intersection of these two therapeutic gene signature subnetworks was significantly enriched in IBD GWAS loci genes and human CD inflammatory gene signatures, suggesting that the molecular mechanisms reflected in the pre-clinical model faithfully captures aspects of the human disease. Simultaneous inhibition of these two pathways could result in enhanced efficacy through targeting shared inflammatory pathways and complementary biology in myeloid and epithelial cells to reduce colitis. To test this hypothesis, mice were treated with varying doses of anti-IL-23, anti-TNF, or the combination of both. A synergistic response to combination therapy was observed both in reduction of systemic weight loss and inhibition of local colonic tissue inflammation by histopathology. A set of genes uniquely significantly modulated by the combination therapy compared to either monotherapy was mapped to our human IBD network. Upregulated gene networks in the combination therapy enriched in stromal cells, epithelial mesenchymal transition and extracellular matrix pathways, and adhesion pathways while downregulated gene networks were enriched in IBD disease signatures, M1 macrophages, neutrophils and IFN-γ signaling.

Conclusion: These results provide a novel, data-driven approach to predict effective combination therapies for inflammatory diseases and suggest that anti-TNF and anti-IL-23 combination therapy may drive more patients into deep remission through impacts on both shared and unique molecular pathways involved in IBD pathogenesis.

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Which should come first? Surgery or biologic therapy for ileocaecal Crohn's disease in biologic naïve patients

C. Witjes[1,2], A. Patel*[1,3], D. Zocche[1], C. van 't Hullenaar-[1], S. Cripps[4], S. Travis[5], B. George[1]

[1]Oxford University Hospital- NHS Foundation Trust- Oxford, Department of Colorectal surgery, Oxford, United Kingdom, [2]Ijsselland Hospital, Department of General Surgery and Colorectal Surgery-, Capelle aan den IJssel, The Netherlands, [3]University hospital of Coventry and Warwickshire NHS Trust, Department of Colorectal surgery, Coventry, United Kingdom, [4]Oxford University Hospital-NHS Foundation Trust, Pharmacy Department – Gastroenterology/Hepatology, Oxford, United Kingdom, [5]Oxford University Hospital-NHS Foundation Trust, Translational Gastroenterology Unit, Oxford, United Kingdom

Background: The L!RIC trial confirmed that surgical treatment of limited ileocaecal Crohn's disease (ICCD) has comparable outcomes to antiTNF therapy. However, strict exclusion criteria for a randomised controlled trial make it difficult to determine if results can be generalised to a wider population. We therefore compared clinical outcomes between surgical resection or antiTNF or other biologic therapy amongst biologic-naïve patients with ileocaecal Crohn's disease to provide real world experience.

Methods: All patients with ICCD who were naïve both to biologic therapy and surgery, treated at our institution between January, 2011 and December, 2018 were identified from surgical and pharmacy databases. Electronic case records were used to obtain data on patient characteristics retrospectively and treatment-specific outcomes. The, 5-year cumulative recurrence rate was calculated after composite consideration of endoscopic recurrence, recurrence on imaging, switch to different therapy, or surgical re-intervention.

Results: Overall, 222 patients were identified.149 (67%) underwent surgical resection first, of whom, 54 patients (36%) subsequently required antiTNF or other biologic therapy., 73 patients were treated with antiTNF or other biologic therapy first, of whom, 29(40%) subsequently required surgical resection (p=0.60). There were, 95/149 patients (64%) who were successfully treated by a surgical resection first approach alone.

There was no difference in, 1- and, 5-year cumulative recurrence rates between the two treatment approaches (17%, 55% for surgery vs, 14%, 54% for biologics (p=0.53)), median follow-up was, 74 months (0–406) and, 71 months (13–235), respectively.

There was no significant difference in time to switch from surgery to biologic or vice versa (p=0.10). Patients who underwent surgery more likely need post-operative biologic therapy if female (p=0.010), obstructive symptoms (p=0.028), or smoker (p=0.030). Patients on biologic therapy more likely undergo surgery if the disease was limited to terminal ileum (p=0.001), was stricturing or penetrating rather than inflammatory and if the patient had obstructive symptoms (p=0.003). Only, 3/149 patients required endoscopic dilatation because of an anastomotic stricture. None of the patients needed a second surgical resection.In comparison, 26 patients (20%) reported side effects from biologic therapy and as result of these side-effects or due to loss of response (n=9), biologic agents was changed in, 28 patients (22%).