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Combined clinical and biological response (concomitant CRP and faecal calprotectin reductions) in induction and maintenance from the phase 3 ustekinumab Crohn’s disease studies

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Background: Ustekinumab (UST) has been shown to induce and maintain clinical response and remission in Crohn’s disease (CD) in two induction [(UNITI-1 (anti-TNF failures) and UNITI-2 (conventional therapy failures)] and 1 maintenance (IM-UNITI) randomised, PBO-controlled Phase 3 trials. The use of a more stringent composite outcome of clinical response and ≥50% reduction from baseline (BL) in either fecal calprotectin (FeCa) or CRP concentration has been shown to decrease PBO rate and facilitate assessment of meaningful treatment effect.1 This post-hoc analysis describes the rates of achievement of this composite outcome with UST/PBO IV induction and SC maintenance.

Methods: In the UNITI trials, patients received PBO, UST 130 mg or ~6 mg/kg IV and were evaluated after 6 weeks. UST IV responders at week 8 were re-randomised to PBO, UST 90 mg q8w or 90 mg q12w during maintenance. Patients with elevated CRP or FeCa at BL and evaluable measurement to assess a ≥50% change at week 6 were included in this analysis (n = 613 UNITI 1; n = 539 UNITI 2; n = 351 IM-UNITI). Rates of clinical response (CDAI decrease from BL ≥100 points or CDAI<150) and clinical remission (CDAI<150) associated with ≥50% reduction from BL in CRP or FeCa at wk6 and wk44 were determined per treatment arm.

Results: Clinical and biological response (CBR) at wk6 was achieved in a significant higher proportion of patients on UST 130 or 6mg/kg vs. PBO respectively 21.3% and 20.8% vs. 8.4% in UNITI 1; p < 0.0001 and 32.2% and 37.6% vs. 12.8% in UNITI 2; p < 0.0001. A similar pattern was observed for clinical remission and biological response (Table). Among all randomised patients in IM-UNITI with an elevated FeCa or CRP at induction BL, a significantly higher proportion of UST patients achieved CBR outcomes vs. PBO (Table). Among patients in clinical response to PBO, UST q12w and UST q8w respectively 21/49 (42.9%), 44/63 (69.8%), and 45/62 (72.6%) also had biologic response. The use of the composite endpoint reduced PBO rates and heightened differences between UST arms and PBO (Figure).

Conclusions: Clinical and biological response rate was significantly greater for patients receiving UST vs. PBO/IV induction and SC maintenance in both anti-TNF and conventional therapy failure CD populations. Biologic response was observed in approximately 70% of responders to SC UST maintenance therapy. The use of a composite endpoint reduced PBO rates and heightened differences between UST and PBO arms in the maintenance trial.

Reference
(M = 20) diagnosed to have CRC in this cohort, 20 adenocarcinomas were diagnosed on histology of biopsies at colonoscopy. Of 28 CRC, 26 were associated with UC, 2 with Crohn’s disease, and 5 had primary sclerosing cholangitis. 70% of the CRC were in left colon and rectum. Only 32% of patients had surveillance within 5 years of cancer detection and majority had white light endoscopy (WLE) with random biopsies; 4 CRC patients had previous surveillance within 1 year. 29% had active disease on endoscopy. Over the 10-year period there was no change in the detection rate of dysplasia or CRC.

Conclusions: In our cohort of patients, male gender and UC were associated with higher risk of CRC. Our data show high interval cancer risk highlighting that WLE with random biopsies are likely to miss early dysplastic lesions. There was no change in detection rate of CRC in IBD patients over 10-year period. Unless surveillance techniques and protocols are rigorously optimised, the risk of interval CRC should be kept in mind when implementing guidelines regarding surveillance frequency.

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Predicting outcomes in paediatric Crohn’s disease: A systematic review

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Background: Crohn’s disease (CD) developing during childhood and adolescence encompasses a spectrum of phenotypes and disease severity. Risk stratification to facilitate early, more individualised therapy is key to optimizing outcomes. We aimed to systematically review the evidence pertaining to prediction of chronically active inflammatory disease and disease complications in paediatric CD.

Methods: We searched Pubmed and EMBASE from 1992 to 2017 for observational or controlled, English language studies reporting longitudinal associations between patient/disease characteristics and chronically active inflammatory disease or the following CD complications: B2/B3/perianal disease, linear growth impairment, bone disease, surgery, response to therapy and disease extension. Study selection was performed by two reviewers. Risk of bias was assessed with the Newcastle-Ottawa tool.

Results: The search identified 97 eligible studies (all observational). The majority focused on associations with surgery (n = 46), internal stricturing (B2) (n = 32) or penetrating (B3) (n = 30) complications; fewer on growth impairment (n = 20) or perianal fistulising disease (n = 19); and very few on chronically active inflammatory disease (n = 9) or bone disease (n = 10). In a large (n = 913) prospective study, older age and non-Caucasian ethnicity were associated with adjusted hazard ratios (aHRs) of 1.4 (95% confidence interval (CI) 1.2–1.8) and 3.2 (1.4–7.3), respectively, for B3 complications. Across several studies, ASCA IgG was associated with aHRs of 2.7 to 2.8 for B3 disease and CBir1 with aHRs of 2.3 to 3.0 for B2 and/or B3 disease. In a single large study, the aHR of OmpC for B2 and/or B3 disease was 2.4 (1.2–4.9). Across several studies, male sex was associated with HRs of 3.6 to 3.9 for linear growth impairment. Lower weight and BMI, and more active disease were associated with lower bone mineral density over time. Table 1 lists factors for which at least one study reported an association with an outcome of interest. The number of studies demonstrating a positive association, amongst all studies examining the predictor, is shown in brackets. No clear risk factors were identified for chronically active inflammatory disease.

Conclusions: The majority of identified predictors are observed demographic or phenotypic associations. To date, only antimicrobial serology provides additional guidance for individualising treatment based on risk prediction. Molecular predictors of chronically active inflammatory disease and biologic treatment responsiveness are badly needed.

P284
Risk of colorectal neoplasia, colectomy and responsiveness to biologic therapy in patients with inflammatory bowel disease and concomitant primary sclerosing cholangitis: A systematic review

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Background: Primary sclerosing cholangitis (PSC) is a chronic immune-mediated liver disease commonly associated with inflammatory bowel disease (IBD) with the majority being diagnosed with ulcerative colitis (UC). Concomitant PSC with IBD can modify the

Abstract P283 – Factors with at least 1 study demonstrating an association with an outcome of interest (numbers in brackets indicate the number of studies showing an association amongst all studies examining that factor).

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<td>L1 ± L4b disease (1/3 +)</td>
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<td>Older age (2/4 +); non-Caucasian ethnicity (2/4 +)</td>
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<td>Development of B2 and/or B3 disease</td>
<td>Non-Caucasian ethnicity (1/1 +)</td>
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<tr>
<td>Intestinal resection</td>
<td>Older age (5/13 +); growth impairment at diagnosis (3/5 +)</td>
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<td></td>
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<tr>
<td>Perianal fistulising disease</td>
<td>Older age (2/3 +); non-Caucasian ethnicity (2/2 +)</td>
<td>Male sex (4/9 +); younger age (4/8 +); diagnosis (1/7 +); growth delay (2/4 +)</td>
<td>Antimicrobial serologies (1/2 +)</td>
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