Abstract PWE-253 Table 1 Improvement in IBDQ

<table>
<thead>
<tr>
<th></th>
<th>PBO (N=246)</th>
<th>ADA (N=248)</th>
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</thead>
<tbody>
<tr>
<td>IBDQ at baseline (mean± SD)</td>
<td>123±33</td>
<td>128±29</td>
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<tr>
<td>IBDQ (mean±SD)</td>
<td></td>
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<tr>
<td>Week 8</td>
<td>20±.36</td>
<td>29±.36*</td>
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<tr>
<td>Week 32</td>
<td>20±.41</td>
<td>28±.41*</td>
</tr>
<tr>
<td>Week 52</td>
<td>19±.41</td>
<td>27±.42*</td>
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<tr>
<td>IBDQ response, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Week 8</td>
<td>112 (45.5)</td>
<td>144 (58.1)†</td>
</tr>
<tr>
<td>Week 32</td>
<td>54 (22.0)</td>
<td>86 (34.7)†</td>
</tr>
<tr>
<td>Week 52</td>
<td>40 (16.3)</td>
<td>65 (26.2)†</td>
</tr>
<tr>
<td>Weeks 8, 32, and 52</td>
<td>30 (12.2)</td>
<td>58 (23.4)†</td>
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*p < 0.05. p Values from ANCOVA with treatment and prior anti-TNF status as factors and baseline value as covariate.
†p < 0.05. p Values from Cochran-Mantel-Haenszel test stratified for prior anti-TNF use.

Conclusion For pts with moderate to severe UC who failed conventional therapy, ADA was more effective than PBO for inducing and maintaining improvements in HRQOL, as measured by IBDQ through 52 wks.


PWE-254 IMPACT OF INDUCTION DOSING ON MAINTENANCE OUTCOME WITH ADALIMUMAB IN CROHN’S DISEASE

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Introduction Two induction regimens of adalimumab are used in Crohn’s disease (CD): 160/80 mg or 80/40 mg at Weeks 0/2. We compared long-term efficacy for patients who received 160/80 mg vs 80/40 mg as induction therapy followed by eow maintenance therapy.

Methods Data were from two randomised, double-blinded, placebo-controlled efficacy and safety trials in moderate to severe CD. EXTEND, a 52-week study in patients with mucosal ulceration, used the 160-/80-mg induction regimen. CHARM, a 56-week study for maintenance of clinical remission, used the 80-/40-mg induction regimen. All patients who started with induction dose and were randomised to eow plus dropouts prior to Week-4 randomisation were included. Missing Crohn’s Disease Activity Index (CDAI) scores were imputed with both non-responder imputation (NRI) and last observation carried forward (LOCF). Remission (CDAI <150) and hospitalisation were compared between induction regimens. To incorporate the correlation between visits for a patient, a logistic regression with the patient-level random intercept using all the time points after Week 4 was constructed to compare likelihood of remission, controlling for baseline CDAI, fistula, prior use of an anti–tumour necrosis factor therapy, concomitant medications, CD duration, and other factors.

Results 70 patients in the 160-/80-mg group were compared with 336 patients in the 80-/40-mg group. Baseline characteristics were similar except for greater rates of rectal/anal CD in the 160-/80-mg group and greater use of concomitant steroids in the 80-/40-mg group. Compared with the 80-/40-mg group, the 160-/80-mg group had a greater percentage of time in remission from Week 0–52 (36% vs 25%; p<0.05, NRI), significantly fewer hospitalisations per patient (0.09 vs 0.25; p<0.05), and significantly fewer CD-related hospitalisations (0.07 vs 0.18; p<0.05). Patients in the 160-/80-mg group were significantly more likely to be in remission during Weeks 4 to 52 than were patients in the 80-/40-mg group after adjusting for baseline characteristics (adjusted OR 4.8; p<0.001). LOCF results for remission analysis were consistently similar. The 160-/80-mg regimen did not appear to lead to a higher rate of AEs.

Conclusion The 160-/80-mg induction regimen of adalimumab was associated with a greater likelihood of remission, more time in remission, and fewer hospitalisations during eow maintenance therapy compared with the 80-/40-mg regimen.


PWE-255 5-ASA ENHANCES DUOX2 EXPRESSION IN ACTIVE ULCERATIVE COLITIS: A RISK FOR COLORECTAL CANCER?

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Introduction Colonic DUOX2 expression produces hydrogen peroxide, a reactive oxygen species (ROS), which is up-regulated in active ulcerative colitis (UC). Overproduction of hydrogen peroxide amplifies ROS-induced genetic damage and causes cellular transformation which may explain the increased colorectal cancer (CRC) risk associated with chronic UC. Mescalazone (5-ASA) has been shown to be chemo-preventative for UC associated CRC and scavenges ROS. Here, we aimed to identify and investigate the effect of 5-ASA on DUOX2 expression using human rectal cancer cell lines and mucosal tissue biopsies.

Methods Mucosal biopsies were taken from 35 patients with UC and 24 patients with normal colons for in vivo experiments, and 24 patients with UC and 14 patients with normal colons for ex vivo experiments. Total RNA was extracted and quantitative real-time PCR used to calculate expression of DUOX2. Cytometric bead array technology was used on ex vivo culture supernatants to measure cytokine profiles. In situ hybridisation for DUOX2 expression was performed on sections from eight matched pairs of non-inflamed/inflamed biopsies and five matched pairs of non-inflamed/inflamed/dysplasia biopsies from UC patients. Human rectal cancer cells were
used for quantitative real-time PCR, with multiparameter flow cytometry utilised to measure hydrogen peroxide levels, apoptosis, DNA damage and cell proliferation.

Results DUOX2 is expressed throughout the colonic epithelium, is upregulated in active compared to quiescent ulcerative colitis and also in areas of UC associated dysplasia. In the setting of intestinal inflammation, but not in quiescent disease, 5-ASA enhances DUOX2 expression in vivo and ex vivo. As expected, 5-ASA was found to suppress cytokine (IL-6 and IL-8) production during an inflammatory flare and to maintain low cytokine levels during remission. The addition of 5-ASA in vitro led to upregulation of DUOX2 and elevated levels of hydrogen peroxide, DNA damage and apoptosis. These effects were further enhanced in a setting of hypoxia.

Conclusion We have shown that 5-ASA over stimulates DUOX2 expression in the setting of inflammation and hypoxia, but not in quiescent disease. Importantly, this suggests that during a flare 5-ASA could act as a carcinogen rather than a chemo-preventative drug. Further investigations to confirm the functional relevance of DUOX2 up-regulation in the colonic mucosa of patients with active UC is indicated.

Competing interests None declared, R Jeffery: None declared, R Poulsom: None declared, J Lindsay

PWE-256

INTESTINAL INFLAMMATION REGULATES RETINOIC ACID DEPENDENT IMPRINTING OF GUT TROPISM BY DENDRITIC CELLS INDEPENDENTLY OF RALDH

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Introduction In the mouse, tissue-specific expression of retinaldehyde dehydrogenase (RALDH) enzymes by CD103+ intestinal dendritic cells (DC) enables them to generate all-trans retinoic acid (RA) and thereby imprint a gut-tropic phenotype on T cells via induction of homing receptors including $\beta_7$ integrin. In health, RA from CD103+ also enhances their generation of Treg, contributing to intestinal homeostasis. In murine models of inflammatory bowel disease (IBD) RALDH expression by CD103+ DC is reduced but little is known about the function of RA in the human intestine. The aim of this study was to determine whether factors present in the healthy and inflamed human intestine regulate RA generation and activity.

Methods Conditioned media (CM) were generated by culture of intestinal biopsies from healthy individuals and IBD patients (inflamed/non-inflamed regions). DC were differentiated from monocytes using GM-CSF and IL-4 in the presence or absence of CM. Expression of RA-generating enzymes was assessed by qRT-PCR and RALDH activity determined using the Aldeflour assay. Induction of $\beta_7$ following activation of naïve allogeneic CD4+ T cells was determined by flow cytometry.

Results Activation of naïve CD4+ T cells by human monocyte-derived DC resulted in RA-dependent upregulation of $\beta_7$. These DC possessed retinal-inhibitable Aldefluor activity and expressed both alcohol dehydrogenase (RDH10) and RALDH (RALDH1,2,3) enzymes required for the generation of RA from retinol via retinal. Aldefluor activity was regulated by GM-CSF and RA, and reflected predominately the activity of RALDH2 as suggested by qRT-PCR analysis of sorted Aldefluor+ DC. CM significantly suppressed Aldefluor activity (p<0.0001) irrespective of whether generated from healthy or IBD tissue (inflamed or non-inflamed). The inhibitory effect of CM generated from healthy tissue could be partially reversed with the prostaglandin E2 (PGE2) EP-2 receptor antagonist AH6809 but this effect was less marked with CM from IBD tissue suggesting the involvement of distinct RALDH regulators. Although the effects of inflamed and non-inflamed CM on Aldefluor activity were similar, DC differentiated in the presence of inflamed CM induced significantly higher (p<0.05) levels of CD4 T cell $\beta_7$ expression.

Conclusion Factors generated in the human intestinal mucosa limit RALDH activity in DC and may thereby impact upon their generation of RA. Factors other than PGE2 are involved particularly in inflamed tissue. Intestinal mediators influence the imprinting of gut tropism independently of effects on RA-generating enzymes. Manipulation of RA availability may offer new therapeutic options in IBD.

Competing interests None declared.