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Members of the CARE™ Gastroenterology Faculty recently attended the DDW 2018 conference held in Washington, DC (June 2nd-5th, 2018). At this conference, the 10th annual CARE™ at DDW education meeting was held. Attendees included academic and community specialists, and residents. This meeting brought together a pan-Canadian Faculty of KOLs who highlighted cutting-edge content that was presented during this year’s DDW conference, framed from a Canadian perspective.

The CARE™ Perspectives Conference Report from DDW 2018 provides a summary of the participating faculty presentations and other storylines relevant to the Canadian gastroenterology landscape. Content is written in the language in which it was presented, including abstract content and summaries of plenary sessions from DDW 2018.

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This section reviews abstracts on UC with CARE™ Faculty Perspectives provided by Dr. Remo Panaccione. What follows are clinical trial results for novel targeted oral small molecules, and an update on use of currently available biologics.

The Canadian UC treatment landscape is changing as innovation continues to drive the development of new molecules that build on the success of current therapies. Figure 1. Below provides a snapshot of the current treatment landscape and where we may be headed with innovative options.
TARGETED ORAL SMALL MOLECULES

Oral small molecules will offer an attractive option for mild-to-severe UC given their improved safety profiles and the potential for intermittent dosing strategies (resulting from an absence of immunogenicity). It will be interesting to see where these agents will fit into existing Canadian treatment paradigms with data indicating there may be benefit to both pre- and post-biologic positioning.

**DDW Sa1753. Tofacitinib achieves symptomatic improvement within 3 days in moderately to severely active ulcerative colitis, regardless of prior tumour necrosis factor inhibitor treatment status: results from OCTAVE induction 1 & 2**

Stephen B. Hanauer et al.

**Results:** At baseline, the mean Mayo subscores for the placebo and tofacitinib groups were 2.5 for stool frequency and 1.6 for rectal bleeding. By Day 3, significantly more patients achieved each of the binary efficacy endpoints with tofacitinib vs placebo (all p<0.05). Among patients with prior tumour necrosis factor inhibitor failure, 117 (26.8%) tofacitinib-treated patients had reduction from baseline stool frequency ≥1 at Day 3, vs 16 (14.0%) with placebo, and 133 (30.6%) tofacitinib-treated patients had reduction from baseline rectal bleeding ≥1 at Day 3, vs 14 (12.5%) with placebo. Subgroup analyses demonstrated generally consistent effects of tofacitinib treatment vs placebo, regardless of prior tumour necrosis factor inhibitor treatment failure status, baseline C-reactive protein, and corticosteroid use at baseline.

**Conclusion:** Significant symptomatic improvements were observed with tofacitinib vs placebo as early as Day 3. A consistent treatment effect was observed regardless of whether patients had prior tumour necrosis factor inhibitor treatment failure. These results support the rapid onset of tofacitinib efficacy previously reported based on significant improvement vs placebo at 2 weeks in partial Mayo score, and extend this result to response at Day 3.

**Related Abstract:**

**DDW 905. Efficacy and safety of tofacitinib retreatment for ulcerative colitis after treatment interruption: results from the OCTAVE clinical trials**

Julian Panes et al.

**Conclusion:** In patients with prior response to tofacitinib, retreatment with 10 mg BID following a period of treatment interruption was efficacious and well-tolerated, with clinical response recaptured in approximately three-quarters of patients by Month 2 and generally sustained at Month 12 with no new safety signals. Interpretation of adverse event rates is limited due to the small sample size.

**CARE™ FACULTY PERSPECTIVE**

Tofacitinib is currently under review by Health Canada and has recently been approved by the FDA and EMEA. These trial results are promising and an oral molecule will be a welcome addition to our therapeutic armamentarium. Discussion moving forward will focus positioning as well as on appropriate dosing in maintenance and appropriate monitoring/management of adverse events if they occur.
DDW 813. Apremilast for active ulcerative colitis: a phase 2, randomized, double-blind, placebo-controlled study

Silvio Danese et al.

Results:

<table>
<thead>
<tr>
<th>Week 12 Study Endpoints</th>
<th>PBO n=58</th>
<th>APR30 n=57</th>
<th>APR40 n=55</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMS clinical remission(a)</td>
<td>13.8%</td>
<td>31.6%*</td>
<td>21.8%</td>
</tr>
<tr>
<td>MMS clinical remission(b)</td>
<td>19%</td>
<td>43.9%*</td>
<td>27.3%</td>
</tr>
<tr>
<td>TMS clinical response(c)</td>
<td>46.6%</td>
<td>61.4%</td>
<td>67.3%*</td>
</tr>
<tr>
<td>Decrease from baseline MES of at least 1 point</td>
<td>41.4%</td>
<td>73.7%*</td>
<td>47.3%</td>
</tr>
<tr>
<td>MES ≤1</td>
<td>24.1%</td>
<td>56.1%*</td>
<td>34.5%</td>
</tr>
<tr>
<td>Geboes score &lt;2</td>
<td>29.3%</td>
<td>43.9%</td>
<td>41.8%</td>
</tr>
<tr>
<td>Mucosal healing(d)</td>
<td>15.5%</td>
<td>33.3%*</td>
<td>21.8%</td>
</tr>
</tbody>
</table>

\(a\) TMS ≤2 with no individual subscore >1.
\(b\) MMS ≤2 with no individual subscore >1.
\(c\) Decrease from baseline TMS of 3 and 50% with a reduction of at least 1 point in rectal bleeding score or absolute rectal bleeding score ≤1.
\(d\) MES ≤1 with Geboes <2.

Conclusion: In this 12-week, phase 2 study, patients with active UC treated with APR30 had clinically meaningful improvements in symptoms, endoscopy, biomarkers, and mucosal healing compared with PBO. The observed adverse events were consistent with those expected in UC patients and were also consistent with the known safety profile of apremilast.

CARE™ FACULTY PERSPECTIVE

Apremilast was first approved for psoriasis, where it has since proven long-term safety and efficacy with over 200,000 patients treated worldwide. In UC there is currently a therapeutic gap between 5-ASA and prednisone and prednisone and biologic therapy. With all major primary and secondary endpoints of this Phase II trial being met and results indicating a trend towards histological remission, it is anticipated that this agent may be able to fill those gaps especially in the mild to moderate patients as a pre-biologic.

Phase III trials to confirm these findings and trials investigating this agent in the mild-moderate setting are ongoing and eagerly awaited.
**BIOLOGIC UPDATE**

While it is exciting to focus attention on the benefits that novel agents in development may offer, we must continue to consider how current treatment paradigms can be further optimized with agents available to us now.

Vedolizumab, a humanized IgG1 monoclonal antibody, entered the UC market in 2016. With multiple biologic options available (i.e. infliximab and adalimumab) and little comparative data between them, optimal use of vedolizumab remains unclear. This section will review trials presented at DDW that look to provide insight on this concept.

**DDW 328. Comparative effectiveness of Vedolizumab and tumour necrosis factor-antagonist therapy in ulcerative colitis: a multicenter consortium propensity score-matched analysis**

David Faleck et al.

**Study Design:**

- Data
- Consortium
- Outcomes
  - 3-6 months
  - De-identified
  - Data re-coded
  - Compiled
  - Compiled
  - Analyzed
  - Effectiveness
  - Safety
  - Predictions
  - Comparisons

**Results:** The propensity score model accurately predicted treatment status (area under curve 0.73). Of 646 UC patients, 334 were included after matching (n=167 VDZ; 49% male; median age 36 years). After adjusting for concomitant steroid use, concomitant immunomodulator (azathioprine, 6-mercaptopurine, methotrexate) use, and number of prior TNF-antagonists used, VDZ-treated patients had statistically significant higher 12-month cumulative rates of clinical remission (54% vs 37%; HR 1.54, 95% CI 1.08-2.18) and endoscopic healing (50% vs 42%, HR 1.73, 95% CI 1.10-2.73). Cumulative 12-month rates for steroid-free remission were numerically higher for VDZ-treated patients, but not statistically significant (49% vs 38%; HR 1.43, 95% CI 0.79-2.60). These findings were consistent when stratified by disease extent and prior TNF-antagonist exposure.

**Related Abstract:**

**DDW 227. Comparative safety profile of Vedolizumab and tumour necrosis factor-antagonist therapy for inflammatory bowel disease: a multicenter consortium propensity score-matched analysis**

Dana J. Lukin et al.

**Conclusion:** In clinical practice, rates of SI and SAE were lower in patients treated with VDZ than with TNF-antagonist therapy. Concomitant immunosuppressive use was associated with an increased risk for both SI and SAE, and rates were similar between VDZ and TNF-antagonist therapy when using concomitant immunosuppressive therapy. Further studies are needed to understand the importance of concomitant immunosuppressive therapy for VDZ as this has significant implications on its safety profile.

**CARE™ FACULTY PERSPECTIVE**

Results of these statistical comparison studies favoured vedolizumab in terms of clinical remission, steroid-free remission, and endoscopic healing. Vedolizumab also appears to be superior in terms of safety outcomes, but it should be noted that there was an increased risk of SI and SAE in both arms with concomitant immunosuppressive use. These studies drew data from the largest real-world IBD registry with over 1000 vedolizumab treated patients with UC or CD. While overall methodology that was used is the best for this type of analysis, results should be taken with a grain of salt until head-to-head randomized controlled trials confirm these findings.
CROHN’S DISEASE

This section reviews abstracts on Crohn’s Disease (CD) with CARE™ Faculty Perspectives provided by Dr. Alain Bitton. What follows provides a snapshot of IBD epidemiology in Canada, clinical trial updates for novel biologic therapies, and disease activity and therapeutic drug monitoring.

EPIDEMIOLOGY

Canada has one of the highest incidences of Crohn’s and colitis in the world with 0.5% population (~233,000 people in 2012) affected. It is anticipated that prevalence will rise to 1% by 2030 (DDW abstract Tu1698, Coward et al.).

The rising prevalence of IBD will have an impact on Canadian practices and the healthcare system. Healthcare providers and payers should be aware of this and aim at providing appropriate resources, access to effective care, and better optimization of therapy.
NOVEL BIOLOGIC THERAPIES

**DDW Sa1758. Upadacitinib improves steroid-free clinical and endoscopic endpoints in patients with Crohn’s Disease: data from CELEST study**

Remo Panaccione et al.

**Results:** Among 220 randomised patients, 96 (43.6%) received CS at BL: median (min-max) age 38.5 (19.0-69.0) years, CDAI 291.0 (162-599), CD duration 9.4 (0.1-44.7) years and 95 (99.0%) had failed one or more TNFi. More patients taking UPA were able to discontinue CS and achieve endoscopic endpoints at 12/16 weeks and clinical endpoints at 16 weeks than patients on PBO (Figure). Patients on 24 mg BID achieved a statistically significant difference from PBO in all clinical remission endpoints. The rates of any AEs were similar between patients with or without CS use in the UPA (85.2% and 80.4%, in all UPA arms, respectively) and PBO groups (73.3% and 72.7%).

**Figure:** Proportion of subjects who discontinued corticosteroid and achieved clinical endoscopic endpoints at 16 Weeks

**Conclusion:** Patients with long-standing CD refractory to conventional/TNFi therapy who received CS at BL achieved statistically significant steroid-free endoscopic and clinical improvements at 16 weeks of treatment with UPA. The safety profile of UPA in patients taking CS at BL was consistent with the overall study population.

**CARE™ FACULTY PERSPECTIVE**

The CELEST study is a multicenter, randomized, double blind, placebo-controlled study of upadacitinib (UPA) an oral JAK-1 inhibitor for the induction of remission in patients with moderately to severely active CD who have inadequately responded (or are intolerant) to immunomodulators or anti-TNF therapy.

This sub-analysis assessed the efficacy of UPA as a steroid sparing agent in CD. Results in this population indicate a dose-dependent benefit in all maintenance endpoints including endoscopic remission. Importantly, no dose-dependent effect on safety were found. This agent shows promise in this refractory population on corticosteroids. Data on longer steroid sparing effect and safety of UPA is warranted before we can determine the full impact this agent will have in Canadian practice.

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*Endoscopic remission: SES-CD≤4 and ≥2-point reduction from BL, who subscore ≥1.*

*Endoscopic response: SES-CD reduction >50% from BL or endoscopic remission.*

*Clinical remission: SF≤1.5 and AP≤1.0, and both not worse than BL.*

*Modified clinical remission: SF≤2.8 and AP≤1.0, both not worse than BL.*

*Modified clinical remission was analysed in patients with SF≥4.0, AP≥2.0 at BL; other endpoints were analysed in all randomised patients.*

*†Significant at ≤0.05 and ≤0.1 level. †The follow-up ileocolonoscopy was performed at either week 12 or 16, per randomization schedule.*
DDW Sa1746. Long-term safety and efficacy of the anti-madcam monoclonal antibody SHP647 for the treatment of Crohn’s Disease: the OPERA II study
Geert R. D’Haens et al.

Results: In total, 268 patients (mean age 36.5 years; 56.3% women) were enrolled and entered the treatment period; 149 completed the study. Mean±SD HBI score at OPERA II baseline was 4.9±3.01. A total of 1150 and 461 AEs were reported during the treatment and follow-up periods, respectively. The most common treatment-related AEs during treatment were nasopharyngitis (5.6%), arthralgia (6.0%) and headache (5.2%). No patient experienced progressive multifocal leukoencephalopathy. Eighty patients experienced SAEs; these were considered treatment-related in 10 patients. Among patients who had AEs leading to discontinuation (n=54) the most common AE was CD flares. Two patients died: one (75 mg) of multiple organ failure after postoperative aspiration following a resection of the terminal ileum. The second (225 mg) died of metastatic neoplasm of unknown primary, with adenocarcinoma identified on cytology. Neither death was considered drug-related. HBI remission and response rates showed no unexpected decay over time.

Conclusion: SHP647 was well-tolerated. The sustained HBI response rate suggests efficacy of SHP647 over 72 weeks of treatment. These results add to evidence for the long-term safety and efficacy of SHP647.

DISEASE ACTIVITY

Mucosal healing has been associated with improved outcomes in Crohn’s disease (CD) and is considered a target for therapy. Biomarkers including Fecal Calprotectin (FC) and C-Reactive Protein (CRP) are widely used in the clinical setting as surrogate markers of endoscopic disease and help guide CD management. Previous studies have shown that endoscopic outcomes in patients whose treatment was escalated based on a tight control algorithm using symptoms and biomarkers were superior to those who were managed conventionally.

The CALM study (Su1796) presented below looked to further explore optimal biomarker cut-offs (FC and CRP) to predict mucosal healing, while DDW abstract SU1811 investigated the usability of IBDoc®, a home-based FC test intended to improve patient adherence and the sample return rate.

DDW SU1811. Home based fecal Calprotectin testing: a Canadian user performance evaluation study of IBDOC®
Alice C. Moore et al.

Results: 61 participants were enrolled in the study of which 34% (21) were male with an average age of 34.8 +/- 9.0 years. 51 patients had both IBDoc® and ELISA measurements available for comparison, resulting in agreement across values 88% of the time and which was highly correlated (r=0.88). Using the qualitative comparison, there were no false positives or negatives.

The patients extracts and reference ELISA measurements demonstrated an 89% agreement between values, which was also highly correlated (r=0.97) and with no false positives or negatives in the qualitative comparison. 97% (59/61) positively responded that they had understood the instruction in the App with the mean rating of 4.8+/-.50. 79% (48/61) of patients agreed that the IBDoc® was easy to use with an average rating of 4.4+/-1 with 85% (52/61) of patients strongly agreeing that they were willing use the home kit in the future and an average rating of 4.5+/-.89.

Conclusion: The FC measurements produced by patients using the IBDoc® were strongly correlated with the standard FC ELISA measurements. The majority of patients found the IBDoc® home kit easy to use and a product that they would likely to use in the future. Further studies are needed to determine whether patients adopt the device for use beyond the clinical trial setting and to assess its impact on patient care for IBD
**DDW Su1796.** Biomarker correlation with endoscopic outcomes in patients with Crohn’s Disease: data from CALM

Walter Reinisch et al.

**Table:** Proportion of patients meeting endoscopic endpoints by biomarker status at 48 Weeks.

**Results:** Association between the two endoscopic endpoints and CRP and FC cut-offs at 48 weeks is shown in Table.

<table>
<thead>
<tr>
<th>Biomarker Cut-off</th>
<th>Mucosal Healing and No Deep Ulcers, n (%)</th>
<th>P value</th>
<th>Endoscopic Response, n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CRP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 mg/L, n=98</td>
<td>65 (66.3)</td>
<td>33 (33.7)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>≥5 mg/L, n=69</td>
<td>21 (30.4)</td>
<td>48 (69.6)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>FC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;250 μg/g, n=97</td>
<td>72 (74.2)</td>
<td>25 (25.8)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>≥250 μg/g, n=59</td>
<td>8 (13.6)</td>
<td>51 (86.4)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>CRP and FC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 mg/L, &lt;250 μg/g, n=10</td>
<td>55 (78.6)</td>
<td>15 (21.4)</td>
<td>56 (80.0)</td>
<td>14 (20.0)</td>
</tr>
<tr>
<td>≥5 mg/L, &lt;250 μg/g, n=18</td>
<td>3 (16.7)</td>
<td>15 (83.3)</td>
<td>9 (50.0)</td>
<td>9 (50.0)</td>
</tr>
<tr>
<td>&lt;5 mg/L, ≥250 μg/g, n=25</td>
<td>16 (64.0)</td>
<td>9 (36.0)</td>
<td>17 (68.0)</td>
<td>8 (32.0)</td>
</tr>
<tr>
<td>≥5 mg/L, &gt;250 μg/g, n=41</td>
<td>5 (12.2)</td>
<td>36 (87.8)</td>
<td>12 (29.3)</td>
<td>29 (70.7)</td>
</tr>
</tbody>
</table>

**Conclusion:** Correlation of biomarker cut-offs with endoscopic outcomes is an important finding for future management of CD. Additional studies are needed to further define the biomarker cut-offs.

**CARE™ FACULTY PERSPECTIVE**

Interestingly, a greater proportion of patients had endoscopic endpoints associated with certain combinations of FC and CRP suggesting that future studies should evaluate composite indices that include more than one biomarker.
**BIOSIMILARS IN IBD**

In IBD, biologic therapy has revolutionized treatment and significantly improved patient outcomes. Some biologic therapies used in the treatment of IBD have or are going off patent, and competitive molecules like biosimilars are being introduced. The CARE™ Faculty has been looking at the role and impact of biosimilars on healthcare since 2015 across different medical specialties.

The one-year study results in Crohn’s Disease presented at the DDW conference add to previous non-inferiority findings for maintenance and switching.

**DDW 814. Phase III randomized controlled trial to compare biosimilar infliximab (CT-P13) with no innovator infliximab in patients with active Crohn’s Disease: 1-year maintenance and switching results**

Byong Duk Ye et al.

**Results:** Of 220 patients randomized, 180 patients completed Week 30 visit and 166 patients completed the study. CDAI-70, CDAI-100 response and clinical remission rates were similar between CT-P13 and INX up to Week 30. At Week 54, clinical remission as well as CDAI-70 and CDAI-100 response rates were well maintained and similar in all treatment groups even after switching of study drug. In addition, mucosal healing by colonoscopy was similar among all treatment groups at Week 54. Furthermore, SIBDQ scores increased and were similar among all treatment groups up to Week 54 even following switching of study drug. One-year safety including adverse drug reactions, serious adverse events and infections was similar among all treatment groups and all safety profiles were also similar after Week 30 in maintenance and switching groups. At Week 30, only 1 infusion-related reaction (IRR) was reported from CT-P13 to INX group after switching of study drug and this patient was anti-drug antibody (ADA) positive at Week 30. No further IRR was reported for switching groups after Week 30. There were no clinically meaningful differences in immunogenicity results throughout the study period among treatment groups up to Week 54.

**Conclusion:** Efficacy, safety and immunogenicity of CT-P13 and INX were comparable during 1-year treatment. Both switch groups were comparable to CT-P13 or INX maintenance groups in terms of efficacy and safety profiles. CT-P13 and INX treatment resulted in high and durable remission rates in this population (disease duration around 4 years).

**CARE™ FACULTY PERSPECTIVE**

There is increasing support in the medical community for switching from reference products to biosimilars on several indications, including IBD and rheumatic diseases. These longer-term data are promising. However, when considering the biosimilar trial designs, results should be accepted with caution and there should be continued commitment to conducting clinical trials that evaluate switching.

**WHEN CONSIDERING THE BIOSIMILAR TRIAL DESIGNS, RESULTS SHOULD BE ACCEPTED WITH CAUTION AND THERE SHOULD BE CONTINUED COMMITMENT TO CONDUCTING CLINICAL TRIALS THAT EVALUATE SWITCHING.**
PERSPECTIVES - DDW 2018

RECENT AND UPCOMING 2018 CARE™ PROGRAMS:
BIOSIMILARS AND ACCESS TO INNOVATION

CARE™ NATIONAL AND REGIONAL CONGRESSES

The second National CARE™ Congress: Update on Biosimilars and Access to Innovation was held at the Shangri-La Hotel in Toronto on April 6th, 2018. The meeting addressed questions and considerations regarding biosimilars in Canada and how they build towards a larger discussion on access to innovative medicine. The meeting included discussion and provided a platform for medical specialists and key stakeholders across multiple fields to meet, collaborate, and discuss concepts that have a practical impact on the Canadian healthcare landscape. See more info on the National Congress and meeting highlights: CAREeducation.ca/congress-2018

Recognizing the importance of this discussion across Canada and understanding systemic and practical differences seen at a regional level, the CARE™ Faculty will be hosting regional CARE™ meetings to extend the reach and impact of the National meeting.

PRIMER ON BIOSIMILARS

After review and feedback in 2017 and given the varying needs of different specialty groups, CARE™ Gastroenterology Faculty updated the CARE™ Primer on Biosimilars (available for download on the CAREeducation.ca website) to reflect the changing landscape of biosimilars in gastroenterology. This iteration of the Primer will consider clinical trial developments in IBD, and what the complexity of TNF-Alpha Inhibitors means for biosimilar use in gastroenterology, and can be found as a supplement to this report.

CARE™ BIOSIMILARS IN IBD DISCUSSION SERIES

How existing and future clinical trials are shaping the use of biosimilars in Canada has been discussed at length in the first 2 iterations of the CARE™ Biosimilar discussion series interviews involving Drs. John Marshall, Brian Feagan, and Vipul Jairath. Both can be found on the CARE™ Youtube channel.

Biosimilars Switching Interview #1- Dr. John Marshall and Dr. Brian Feagan focus on the limitations, interpretation, and implications of the NOR-SWITCH study results.

Biosimilars Switching Interview #2- Dr. John Marshall and Dr. Vipul Jairath discuss the NOR-SWITCH Trial in greater detail and look at what is needed with future trials to validate efficacy and safety of biosimilars prior to incorporation in practice.

Coming in Fall 2018! Biosimilar Switching in Interview #3- This next video segment in the biosimilars series will look at future clinical trials and the potential economic impact that biosimilars will have in Canada.
PPI-REFRACTORY HEARTBURN

Up to 40% of patients with GERD symptoms have persistent symptoms on PPI therapy that could be attributed to:

- Inadequate acid reflux control by PPIs
- Persistent non-acid reflux
- Other esophageal diseases (e.g., EoE, achalasia)
- Functional disorders

There are currently limited medical options for PPI-refractory patients with evidence indicating antireflux surgery is effective only if non-GERD disorders are excluded. At DDW Spechler et al. presented 2 trials that investigated the impact of rigorous pre-randomization evaluation of patients with heartburn refractory to PPIs prior to surgery (DDW 444) and the use of medical vs. surgical therapy in this patient population (DDW 615).

DDW 444. Characterization of conditions underlying heartburn refractory to proton pump inhibitors (PPIs) in a VA cooperative study of median and surgical treatments for PPI-Refractory Heartburn

Stuart J. Spechler et al.

Results: 366 patients (280 men, mean age 48.5 years) enrolled, and 288 (78.7%) were excluded by pre-randomization procedures (Figure 2). These procedures identified a non-GERD disorder (by endoscopy or manometry), or excluded GERD (by normal MII-pH results) in 122 patients (33.3%). 70 (19.1%) patients were unwilling or unavailable to complete the procedures, and 54 (14.8%) were excluded for technical reasons (preliminary exclusions, omeprazole intolerance, unable to tolerate manometry, unacceptable for surgery). Strong evidence of GERD was found in 120 patients (32.8%); the 2-week omeprazole trial resulted in ≥50% improvement in 42 of those (11.5% of the total group), leaving only 78 patients (21.3%) eligible for randomization.

Conclusion: In our study of patients with heartburn refractory to PPIs, rigorous pre-randomization evaluation revealed that at least one-third did not have GERD as the cause of heartburn. Evidence of GERD underlying heartburn was identified in almost one-third of patients, but heartburn was relieved in a number of those simply with instruction on how to take PPIs properly, often combined with a switch to another PPI. Our findings emphasize the importance of rigorous evaluation before considering invasive antireflux treatments for patients with PPI-refractory heartburn.

DDW 615. A VA cooperative, randomized trial of medical and surgical treatments for patients with heartburn that is refractory to proton pump inhibitors

Stuart J. Spechler et al.

Results: 366 patients enrolled, and 288 (78.7%) were excluded by pre-randomization procedures (described in an accompanying abstract). Among the remaining 78 (64 men; 54 white, 9 African-American, 14 other or mixed, 1 unknown; mean age 45.4 yrs), MII-pH showed +SAP alone in 37, abnormal acid reflux alone in 15, and both +SAP and abnormal acid reflux in 25 (1 missing data). The 78 were randomized to surgery (27), active medical (25) and placebo medical (26) groups. During follow-up, SAEs occurred in 4 surgical, 4 active medical and 3 placebo patients. Success rates at 12 months were 18/27 (66.7%) in the surgical group, 7/25 (28.0%) in the active medical group, and 3/26 (11.5%) in the placebo group. The success rate for surgery was significantly better than active medical (p=0.007) and placebo (p<0.0001) treatments; there was no significant difference between active medical and placebo (p=0.17).

Conclusion: For patients with heartburn refractory to PPIs who had rigorous pre-randomization procedures to exclude non-GERD disorders and who had abnormal esophageal MII-pH monitoring, laparoscopic Nissen fundoplication was significantly better at 12 months than active medical therapy, which did not differ significantly from placebo therapy in relief of heartburn. Careful work-up will exclude most patients with PPI-refractory heartburn from surgery but, for appropriate candidates, surgery is significantly superior to medical therapy.
Cryoballoon ablation of dysplastic Barrett’s Esophagus causes shorter duration and less severe post-procedural pain as compared to radiofrequency ablation

Sanne Noortje van Munster et al.

Figure: Images of a typical case in our study.

Results:
A: Barrett’s esophagus with the indicated treatment area for this dose escalation study, between the 7 and 1 o’clock position (between black lines and arrows).

B: Watching through the balloon, we see the emission of cryogen over a 90° section of the esophageal circumference. The diffuser is automatically pulled back over 3cm length.

C: Ice patch formation directly after treatment.

D: Follow-up endoscopy at 8 weeks shows a median BE regression of 99% as assessed by the 2 independent expert endoscopists.

Conclusion: Our open, pilot, multicenter study shows that 90°-SCBA is feasible, safe and well tolerated in patients with flat dysplastic BE. At the dose of 0.7mm/sec, it results in a median BE regression of 85% and is a promising new modality for endoscopic eradication. The latter will be confirmed in a consecutive study.

CARE™ FACULTY PERSPECTIVE

More RCT data are needed on the long-term efficacy in NDBE, LGD, HGD & long segment BE as well as the symptomatic benefit in long segment BE and after multiple treatments.
DUODENAL MICROBIOME & GASTRIC MOTILITY

**DDW 146.** Duodenal Mucosa-Associated Microbiota (MAM) and gastric emptying: Veillonella in the duodenal MAM linked to slow gastric emptying

Erin R. Shanahan et al.

**Results:**

![Graph showing the relationship between Veillonella abundance and gastric emptying lag time.](image)

Figure: A significant negative correlation between the relative abundance of the genus Veillonella in the duodenal MAM and gastric emptying lag time was observed (Spearman’s rho = -0.59, p<0.005, FDR q<0.05) in the overall patient cohort (FD and controls, n=36).

**Conclusion:** We observed a significant negative correlation between the relative abundance of the genus Veillonella in the duodenal MAM and gastric motility, which suggests microbes and/or microbial products may contribute to control of gastric motility. Further studies are required to explore the role and therapeutic potential of the MAM in motility disorders.

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**CARE™ FACULTY PERSPECTIVE**

It is known that microbes and/or their metabolites can modulate gastrointestinal (GI) motility. This study investigated the potential relationship between the mucosa-associated microbiota (MAM) and delayed gastric emptying often observed in subgroups of patients with FD.

Results were not able to establish a causal relationship. More clinical trial data is needed.

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HELICOBACTER PYLORI

**DDW 52.** Efficacy of high-dose dual therapy versus bismuth quadruple therapy for rescue treatment of Helicobacter Pylori— an interim report of multi-center, randomized control study

Chi-Tan Hu et al.

**Results:** The intention-to-treat eradication rates were 92.3% (144/156; 95% CI 88.1-96.5) with HDDT and 87.1% (135/155; 95% CI 81.8-92.4) with BQT and the per protocol eradication rates were 93.5% (144/154; 95% CI 89.6-97.4) and 87.7% (135/154; 95% CI 82.5-92.9), respectively. There was a trend towards a higher eradication rate in HDDT compared to BQT. The frequency of adverse events was significant higher in BQT (68%) compared to HDDT (29%), p<0.001. The resistance rates to amoxicillin, metronidazole, tetracycline, clarithromycin, and levofloxacin were 0.4%, 40.7%, 0.8%, 59.3%, and 38.7%, respectively. Resistance to metronidazole reduced the eradication rate in BQT group by 17% (from 95% to 78%). Frequent intake of acid and spicy foods, heavy alcohol or tea during treatment was associated with treatment failure in HDDT group. CYP2C19 genotypes did not affect the treatment outcome in these groups.

**Conclusion:** HDDT achieves a comparably high eradication rate to BQT. HDDT is also better tolerated than BQT and more widely available thus it is an excellent global option for H. pylori rescue therapy.

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**CARE™ FACULTY PERSPECTIVE**

Bismuth quadruple therapy (BQT) is recommended in most current treatment guidelines despite being associated with a high rate of adverse events that may decrease efficacy. HDDT is appealing because it is a simpler and widely available regimen with low antibiotic resistance.

Results from this study are promising but more information on local H. pylori antibiotic resistance is needed. When considering use in practice it is important to note that HDDT is not an option for penicillin allergic patients.
This section reviews abstracts on Functional GI Disorders with CARE™ Faculty Perspectives provided by Dr. Louis Lui. What follows provides an update on chronic constipation, IBS-D, and IBS epidemiology.

CHRONIC CONSTIPATION TREATMENT UPDATE

There has been little change to Canadian chronic constipation treatment paradigms since the incorporation of Linaclotide in routine practice. The CARE™ Chronic Constipation Algorithm (below), published in the Canadian Journal of Gastroenterology and Hepatology in 2017, provides clinical guidance in the management of IBS-C and CIC in Canada. The approach outlined in this algorithm remains highly relevant.

One update from DDW worth noting investigated the efficacy and safety of a higher dose of linaclotide used in clinical practice in IBS-C and CC patients in Japan (DDW Tu1627). Results were encouraging and help validate the efficacy and safety of higher dose of linaclotide used in clinical practice in IBS-C and CC patients.

Figure: CARE™ Chronic Constipation Treatment Algorithm
**CHRONIC CONSTIPATION TREATMENT UPDATE**

**DDW Tu1627.** Linaclotide is effective and safe for patients with chronic constipation in Japan: a phase III randomized, double-blind, placebo-controlled study with a long-term open-label extension study

Shin Fukudo et al.

Results:

Part 1: Change in weekly mean SBM frequency at the 1st week in the linaclotide group (4.02) was significantly higher than the placebo group (1.48, p < 0.001). The responder rate of CSBM at the 1st week in the linaclotide group (52.7%) was also significantly higher than the placebo group (26.1%, p < 0.001). Most of the secondary endpoints, including changes in stool consistency and straining severity score, were also significantly greater in the linaclotide group compared to the placebo group. The incidence of diarrhea in the linaclotide group (13.0%) was significantly higher than that in the placebo group (1.1%).

Part 2: Patients switched from placebo to linaclotide showed a rapid onset of response within the 1st week for change in SBM frequency, similar to that in patients who continued to receive linaclotide. The most common drug-related adverse event was mild or sometimes moderate diarrhea.

Conclusion: This study suggests that a linaclotide dose of 0.5 mg/day is effective and safe for CC patients in Japan.

**NOVEL THERAPY FOR IBS-D: RIFAXIMIN**

Rifaximin is a non-systemic antibiotic used for patients suffering from IBS-D. Three important trials investigating rifaximin use for IBS-D were presented at DDW (abstract information and study conclusions below).

While all trials reported positive results that are consistent with previous experience, long-term effects/AEs in recurrent/chronic uses remain uncertain and will need ongoing monitoring. It is expected that rifaximin will receive Health Canada NOC for this indication in December of this year and will become available in Canada in spring 2019.

**DDW Su1190.** Characterization of long-term rifaximin responders from a phase 3, randomized, double-blind, placebo-controlled repeat treatment trial for diarrhea-predominant irritable bowel syndrome (IBS-C)

Leonard Weinstock et al.

Conclusion: Patients with IBS-D with more severe symptoms appeared more likely to maintain long-term response to short-course rifaximin.

**DDW Su1191.** Efficacy of rifaximin on bloating in patients with IBS-D: a pooled analysis of three phase 3, randomized, placebo-controlled trials

Brian E. Lacy et al.

Conclusion: Rifaximin 550 mg three times daily for 2 weeks provided significant and durable improvement in bloating in patients with IBS-D.

**DDW Su1194.** Efficacy of rifaximin in patients with IBS-D and prior use of IBS medications

Anthony J. Lembo et al.

Conclusion: Repeat rifaximin treatment was efficacious in improving abdominal pain and stool consistency in patients with IBS-D with prior antidiarrheal or antispasmodic use.

**DDW Su1195.** Rifaximin repeat treatment for IBS-D and impact on clostridium difficile infection development

Mark Pimentel et al.

Conclusion: Repeat treatment with rifaximin did not predispose patients to infection with C. difficile, a finding that is consistent with the well-established safety profile for rifaximin.
IBS EPIDEMIOLOGY AND PATHOPHYSIOLOGY

**DDW Su1196. Trends in irritable bowel syndrome related hospitalizations and financial burden in United States**
Mohammad Arsalan Siddiqui et al.

**Results:**
The hospitalization rate for patients with IBS is significantly high and has been uptrending. Interestingly, the number of hospitalization with IBS as principal diagnosis has down trended. Some factors associated with high hospitalization rates are; age groups 45-64 and 65-84, female gender, Medicare patients and southern regions.

**Conclusion:** The hospitalization rate for patients with IBS is significantly high and has been uptrending. Interestingly, the number of hospitalization with IBS as principal diagnosis has down trended. Some factors associated with high hospitalization rates are; age groups 45-64 and 65-84, female gender, Medicare patients and southern regions.

**Number of ED visits and hospitalizations over time**

<table>
<thead>
<tr>
<th>Year</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of ED visits</td>
<td>292,750</td>
<td>310,815</td>
<td>317,857</td>
<td>337,552</td>
<td>375,146</td>
<td>410,488</td>
<td>432,393</td>
<td>452,393</td>
<td>481,038</td>
</tr>
<tr>
<td>Total discharged from ED</td>
<td>140,734</td>
<td>154,011</td>
<td>154,357</td>
<td>172,354</td>
<td>204,948</td>
<td>231,896</td>
<td>264,432</td>
<td>277,826</td>
<td>286,455</td>
</tr>
<tr>
<td>Total hospitalized</td>
<td>152,017</td>
<td>156,805</td>
<td>163,500</td>
<td>165,197</td>
<td>170,199</td>
<td>178,592</td>
<td>167,961</td>
<td>173,285</td>
<td>194,583</td>
</tr>
<tr>
<td>Total number admitted with IBS as principal diagnosis</td>
<td>15,594</td>
<td>14,074</td>
<td>13,496</td>
<td>12,381</td>
<td>12,373</td>
<td>12,037</td>
<td>9,830</td>
<td>8,100</td>
<td>7,755</td>
</tr>
</tbody>
</table>

**CARE™ FACULTY PERSPECTIVE**

While this is a US-centric study, there is applicability and learning in the Canadian context. There are currently 6 million Canadians living with IBS. With this high prevalence comes immense financial burden on the Canadian health care system and society. The annual health care direct cost for treating IBS exceeds $6.5 billion (not including over-the-counter medication or prescriptions), and on average a patient with IBS misses 13 work days per year accounting for $8 billion in lost productivity annually. This impacts policy makers, resource distribution and utilization by private and public payers.

**DDW 454. Stressful life events in adulthood increase risk for irritable bowel syndrome and symptom severity**
Colleen H. Parker et al.

**Results:**
A. average number of negatively perceived life events in adulthood.
B. negative event impact score.
C. negative total event impact score.

**Conclusion:** Negatively perceived life events in adulthood are associated with increased odds of having IBS, worse symptom severity and QOL. They are normally associated with increased HPA response, but this is blunted in IBS. Chronic stress likely contributes to GI dysfunction and symptom exacerbations. The blunted ACTH response in IBS may be due to increased hypothalamic CRF secretion and resulting downregulation of CRF1 receptors in the pituitary gland. Positive life events appear to mitigate adverse effects in IBS.

**CARE™ FACULTY PERSPECTIVE**

Much of the information we understand on the impact of stress on IBS symptoms is limited to patients < age 18, and those that were reported in clinical trials within 3-12 months of study enrolment. The association of life events in adulthood with IBS and dysregulated hypothalamic-pituitary-adrenal (HPA) function has not been extensively studied.

Results from this trial will help to educate and validate to patients the important association of stress and IBS symptoms, thus reinforcing the utility of CBT and psycho- and non-pharmacological therapy.
The CARE™ (Community, Academic, Research, Education) Faculty is a pan-Canadian group of leaders in their field who gather, discuss and address gaps in knowledge, to develop education initiatives that frame news from a Canadian perspective.

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