Conference Report on Gastroenterology
Commentary and content provided by the CARE Gastroenterology Faculty

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UNITED EUROPEAN GASTROENTEROLOGY WEEK 2015 · BARCELONA, SPAIN · OCTOBER 24-28
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Conference Report on Gastroenterology

HIGHLIGHTS FROM ACG AND UEGW 2015

Members of the CARE Gastroenterology Faculty recently attended and reviewed the ACG 2015 conference held in Honolulu, Hawaii (October 16th-21st) and UEGW 2015 in Barcelona, Spain (October 24th-28th).

The annual CARE at ACG education meeting was run on October 17th and was attended by community specialists and residents from across Canada. The CARE Gastroenterology Faculty, led by Dr. John Marshall, presented on a number of key topics in the field.

The CARE Perspectives Conference Report from ACG 2015, augmented with content from UEGW 2015, provides a summary of the most compelling stories and news presented at these events. Additional perspectives from the CARE Gastroenterology Faculty is also included.

CARE GASTROENTEROLOGY FACULTY CONTRIBUTING TO THIS REPORT:

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The content that follows is written in the language in which it was presented, and is adapted from the presentations made at the ACG 2015 meeting. It is augmented with content and perspectives from members of the CARE Gastroenterology and Liver Disease Faculties.
IBS- Constipation

**DIAGNOSTIC AND TESTING**

**UEGW 2015. P0434.** Diagnosis and Management of Moderate-to-Severe Irritable Bowel Syndrome with Constipation [IBS-C] in Europe: Pooled Results from the IBIS-C Study.

- Jan Tack, Vincenzo Stanghellini, Flemming Mortensen, Yan Yannakou, Peter Layer, Benoît Coffin, Magnus Simrén, Jonathan Mackinnon, Jordan Bertisch, José Portea

**Results:** 525 patients were included (60% severe, mean age [±SD] 45.3±15.8 years old, 86.9% female). Mean time since diagnosis: 3.0±5.2 years; mean symptom duration: 12.8±13.1 years. Diagnostic procedures since the onset of symptoms were highly variable: the most common were blood tests (71.6%; range: 88.9% Sweden–57.6% France); colonoscopy (62.9%; range: 78.4% Germany–41.1% Italy); abdominal ultrasound (54.7%; 62.7% Germany–36.1% Sweden). The main associated comorbidities were anxiety (34.1%), dyspepsia (31.0%), headache (30.4%), and insomnia (27.0%). 62.1% (74.1% Italy–57.6% France) of patients had an average of 4.0±2.7 diagnostic tests (4.5±3.0 Italy–3.4±2.7 France) during follow-up and 65.3% took prescription drugs for their IBS-C (90.4% UK–41.1% Italy). The most commonly prescribed medications were laxatives (48.8%), antispasmodics (19.8%), and prokinetics (18.9%). 20.4% took other medications. Specifically, laxatives were prescribed as a monotherapy (14.1%), in combination with antispasmodics (6.3%) or with another drug that was not an antispasmodic, antidepressant, or prokinetic (10.7%). Overall, 67.2% of patients took non-prescription medication for their IBS-C (82.1% Italy–56.3% Spain) (33.0% laxatives; 24.2% pre/probiotics, 19.6% herbal medicine) and 33.0% of patients sought complementary therapies (44.4% Sweden–27.5% Germany). Overall, marginal improvement was noted in symptom severity (IBS-SSS total score ± SD) between baseline (323.2 ± 84.3) and the 6-month visit (253.9 ± 105.6, 76.1% moderate-to-severe; 85.4% France–67.3% Italy).

**Conclusion:** IBS-C symptoms remain undiagnosed for an average of almost 10 years and there is a high degree of variability in diagnostic and management procedures between European countries. Over half of the patients continued to undergo diagnostic tests after a diagnosis has been reached and the degree of control did not improve over time despite a high level of prescription and non-prescription medication use. At the end of the study over three quarters of patients still suffered from moderate-to-severe IBS-C.

**CARE FACULTY PERSPECTIVE:** Conducting more tests and procedures is very costly and doesn’t appear to help reassure patients or relieve their symptoms. Better treatment strategies are needed to manage challenging IBS symptoms such as abdominal pain and bloating.

**MANAGEMENT**

**ACG 2015. P1001.** A National Survey and Needs Assessment on Choices of Therapeutic Agents for Chronic Idiopathic Constipation and Constipation Predominant Irritable Bowel Syndrome: A Canadian Perspective

- Yvonne Tao, BSc; MD; Louis WC. Liu, MD, PhD; Christopher Andrews, MD, MSc; David Armstrong, MA, MB, BCH; FACG

**Results:** The response rate to the survey was 15% (n=52). Almost all (96%) responders follow a standard, stepwise approach for managing patients with CIC and IBS-C. However, they believe that only 23% of referring physicians follow the same approach. Reported first-line therapy (osmotic laxatives) was similar for IBS-C and CIC but second-line therapy differed for CIC (bulk agents) and IBS-C (GCC agonist). Nearly 80% of responders indicated that GCC agonists were the most satisfactory therapy for IBS-C and CIC; despite this, 61% of responders and 64% of referring physicians (reported by the responders) are reluctant to move from over-the-counter to prescription agents. Among the 68% of responders who are aware of the 2 published guidelines, only 51% found the guidelines helpful in prioritizing treatment choices, and 69% of responders indicated that a treatment algorithm, applicable to Canadian practice, would be valuable.

**Conclusions:** This survey demonstrates a need for an education program to standardize and enhance the treatment of CIC and IBS-C. The majority of Canadian GIs would welcome a practical management algorithm to translate new published guidelines and the role of new therapeutic agents into clinical practice. Based on this needs assessment, a comprehensive treatment algorithm has been developed and will be evaluated for the management of IBS-C and CIC in Canadian practice. (see opposite page)

**CARE FACULTY PERSPECTIVE:** This study was conducted by members of the CARE Gastroenterology Faculty, led by Dr. Louis Liu. The survey that was conducted provided insight into the practical management of CIC and IBS-C in Canada, and led to the development of a Canadian-centric management algorithm. This is meant to be an iterative piece, with continual updates based on advances that occur in research.

"THIS SURVEY DEMONSTRATES A NEED FOR AN EDUCATION PROGRAM TO STANDARDIZE AND ENHANCE THE TREATMENT OF CIC AND IBS-C."
ASSESS ALARM FEATURES

ALARM FEATURES IDENTIFIED

SPECIALIST ASSESSMENT RECOMMENDED (REFER)

NO ALARM FEATURES IDENTIFIED

STILL CONSTIPATED

TYPE OF CONSTIPATION?

LIFESTYLE MODIFICATIONS (E.G. DIETARY FIBRE, FLUID, EXERCISE)

INADEQUATE FIBRE INTAKE

FIBRE SUPPLEMENTS

e.g., Milk of magnesia, lactulose or PEG titrate to efficacy and tolerability +/- fibre supplements

Eight-week trial at a reasonable dose prior to reassessment of maintenance or escalation to step-up therapies

SLOW TRANSIT

OSMOTIC LAXATIVES

e.g., Linaclotide

PROSECRETORY AGENTS

e.g., Prucalopride

Additional agents

- Stimulants
- Osmotic laxatives

RESCUE THERAPY

- Glycerine suppository
- Stimulant laxatives (e.g., bisacodyl)
- Enema

PROSECRETORY OR PROKINETIC AGENTS

- Linaclotide or Prucalopride Eight to twelve-week trial prior to reassessment for maintenance or consideration of referral for specialist assessment

INSATISFACTORY RESPONSE OR INTOLERANT TO SIDE EFFECTS

SPECIALIST ASSESSMENT RECOMMENDED (REFER)

HISTORY & PHYSICAL INCLUDING CAREFUL PERINEAL/RECTAL EXAMINATION

ADDRESS SECONDARY CAUSES

ADDRESS SECONDARY CAUSES

PRIORITY USAGE DEPENDANT ON PATIENTS' TOLERABILITY AND AFFORDABILITY

STILL CONSTIPATED

FUNCTIONAL ABDOMINAL PAIN

Predominant IBS-C

Eight-week trial at a reasonable dose prior to reassessment of maintenance or escalation to step-up therapies

ADDITIONAL AGENTS

- Stimulants
- Osmotic laxatives

PHARMACOLOGICAL

e.g., TCA, SSRI, SNRI, antipasmodic

NON-PHARMACOLOGICAL

e.g., Meditation, relaxation, hypnosis

SPECIALIST ASSESSMENT RECOMMENDED TO CONSIDER ANORECTAL MANOMETRY, DEFECOGRAPHY AND POSSIBLE BIOFEEDBACK THERAPY.
IBS-Diarrhea

ACG 2015. P1007. Effect of Eluxadoline on Abdominal and Bowel Symptoms Over Time in Phase 3 Clinical Trials in Patients With Irritable Bowel Syndrome With Diarrhea

Lucinda Harris, MD; Susan Lucak, MD; Lin hang, MD; Leonard S. Dave, PhD; Paul S. Covington, MD; 1. Mayo Clinic, Phoenix, AZ; 2. Columbia University Medical Center, New York, NY; 3. David Geffen School of Medicine at UCLA, Los Angeles, CA; 4. Furiex Pharmaceuticals, a subsidiary of Actavis PLC, Orthwood, TX; 5. Clinical Dynamic, Wilmington, NC

Results: 2428 pts with IBS-D were enrolled across both trials. In both studies, daily abdominal discomfort and bloating scores decreased from baseline within the 1st wk, with greater reductions seen for ELX. Abdominal discomfort scores were significantly lower (p < 0.05) than PBO for ELX 100 mg at all time points through Wk 24 in both studies (except Wk 4 in IBS 3002), while bloating was significantly lower (p < 0.05) than PBO for ELX 100 mg from Wk 16 onward in both studies. BM frequency and episodes of urgency and incontinence were also reduced from baseline. Both ELX doses significantly reduced (p < 0.05) episodes of urgency compared to PBO at all time points through Wk 24 in both studies. Similarly, ELX significantly reduced BM frequency compared to PBO through 24 wks (data not shown). Episodes of incontinence were significantly lower (p < 0.05) than PBO for both ELX doses from Wk 16 onward in IBS-3002.

Conclusions: ELX significantly improves abdominal discomfort and bloating, and significantly reduces BM frequency, and episodes of urgency and incontinence; effects are sustained through 6 months of treatment.

CARE FACULTY PERSPECTIVE: This abstract is interesting because it looks at abdominal symptoms (eg. bloating and abdominal discomfort) which we know are very bothersome to patients. This agent shows significant improvement for these symptoms and helps to reduce bowel frequency.

ACG 2015. P313. Eluxadoline Demonstrates Efficacy for the Treatment of Irritable Bowel Syndrome (IBS) With Diarrhea (IBS-D) Among Multiple Clinically Relevant Patient Subgroups

Brian E. Lacy, MD; PhD1; William Chey, MD; Anthony J. Lembo, MD; Leonardi S. Dave, PhD; Paul S. Covington, MD; 1. Dartmouth-Hitchcock Medical Center, Lebanon, NH; 2. University of Michigan, Ann Arbor, MI; 3. Beth Israel Deaconess Medical Center, Boston, MA; 4. Furiex Pharmaceuticals, a subsidiary of Actavis PLC, Driftwood, TX; 5. Clinical Dynamic, Wilmington, NC

Results: 2423 patients with IBS-D were included in the pooled ITT set. The majority of patients were female (66%), aged < 65 years (90%), and had baseline WAP scores of 5 to < 8. Histories of GERD and depression were reported for 31% and 25% of patients, respectively, and 20% of patients had a prior cholecystectomy. In both males and females, and in patients aged < 65 and > 65 years, significantly more patients (p < 0.002) receiving eluxadoline 75 and 100 mg were composite responders than patients receiving PBO. Also, significantly greater responder proportions were seen with eluxadoline treatment among patients with histories of GERD (75 and 100 mg) and depression (100 mg), or among patients with a prior cholecystectomy (75 and 100 mg). When stratified by baseline WAP, responder proportions were significantly higher for both eluxadoline groups (p < 0.001) vs. placebo.

Conclusions: Overall, treatment with eluxadoline is effective in both male and female patients with IBS D and multiple relevant subgroup populations based on composite response.
**Bacterial Overgrowth**


Jonathan Pourmorady, MD, Eric Shah, MD, Ali Rezaee, MD, Mark Pimentel, MD, Cedars-Sinai Medical Center, Los Angeles, CA

**Results:** Nine studies were included in the final meta-analysis. The estimated prevalence of a positive breath test in IBS subjects was 36% (CI=16-55%) while in controls, the estimated prevalence was 15% (CI=8-22%). The odds ratio of a positive breath test was higher in IBS subjects versus healthy controls (OR=3.32, 95% confidence interval (CI) = 2.42-4.56). The studies were further analyzed based on geographical location (see figure 1) and stratified into North America (OR=1.83, 95% CI=1.09-3.08), Asia (OR=3.86, 95% CI=2.41-6.2), and Europe (OR=6.92, 95% CI=2.97-16.15). Significant heterogeneity was noted among the North American studies. Glucose was the most commonly used substrate in the nine studies (see figure 2) and had the highest odds of a positive breath test in IBS subjects versus healthy controls (OR=5.6, 95% CI=3.4-9.23). Studies that used glucose were more homogenous as compared with lactulose.

**Conclusions:** In this meta-analysis of 1,641 patients in 9 case-control studies, we demonstrated that positive breath tests are more common among IBS patients in comparison to healthy controls. Our findings suggest that small intestinal bacterial overgrowth is more prevalent in an IBS population and are consistent with the bacterial overgrowth hypothesis for IBS.

**Care Faculty Perspective:** Due to the non-invasive nature of breath testing, it is a mainstay clinical tool in diagnosing small intestinal bacterial overgrowth (SIBO) in IBS. Based on hydrogen breath testing, this meta-analysis confirmed its hypothesis that SIBO is more prevalent in IBS patients compared to control populations.

This study highlights the importance of the role of microbiome, and this will help to advance future therapeutic options. More research is necessary to better understand this concept.

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**Other abstracts of interest**

**Peppermint Oil**

**ACG 2015. P327.** Patient Satisfaction With IBS Symptom Relief Using a Novel Peppermint Oil Delivery System in a Randomized Clinical Trial and by the General Patient Population

Michael S. Epstein, MD, FACG1, Brooks D. Cash, MD, FACG2, Syed Shah, PhD3

1. Digestive Disorders Associates, Annapolis, MD; 2. University of South Alabama, Mobile, AL; 3. IM HealthScience, Boca Raton, FL

**Results:** 35 subjects randomized to peppermint oil (PO) in the RCT and 285 patients in the general population completed the surveys. Dosage frequency in the general population was much lower (60.8% used only 1 to 2 capsules per day) compared to 6 capsules per day in the RCT. There was a very high satisfaction rate (>80%) with the novel PO delivery system in both surveys. The response for all questions from patients in each trial was remarkably similar despite the lower capsule intake by patients in the general population.

**Conclusions:** The novel PO delivery system showed a high rate of patient satisfaction in an RCT and the general patient population. Patients recruited for IBSREST had moderate to severe IBS symptoms. Their overall satisfaction rate of greater than 80% for all questions is encouraging since patients with severe IBS are historically not satisfied even with improvement of individual IBS symptoms. In the general IBS patient population the overall satisfaction was also high (85%), even with much lower usage of capsules.

**Care Faculty Perspective:** It has been shown in the past that peppermint is effective in relieving symptoms for IBS, however the dosage that is required is not well tolerated by patients because of its taste. This study is interesting because it offers patients a novel way to delivery peppermint oil. As symptom relief can positively affect a patient’s quality of life, it is encouraging to see that patients’ have a very high overall satisfaction rate (80%) with this new delivery system.
Esophagus/Endoscopy


Nicholas Horton, MD1, Ani Garber, MD, EdD2, Mazen Alaldawi, MD3, Johnathon Markus, MD4, Rocio Lopez, MPH, MS5, Jessica Barry, MD6, Mohammad A. Hanouneh, MD7, Ibrahim A. Hanouneh, MD7, Maged Rok, MD7, John Vargo, MD, MPH4, Sunguei Jang, MD4

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Results: 249 patients (64 ± 13 years, 38% female, average BMI of 30) presented with non-variceal upper gastrointestinal bleeding (NVUGIB) and had initial EGD for management. The most common indication was melena (51%) and 83% had an ulcer in the stomach. 107 patients (43%) had recurrent NVUGIB. 51% had EGD treatments to manage their bleeding. Average ICU length of stay was 18.2 days with a mortality rate of 22%. Subjects receiving repeat EGD were 3.5 times more likely to achieve hemostasis after 1st recurrent event (p=0.025). For every 1-unit increase in Hemoglobin and 25-unit increase in platelet count at time of recurrent bleed, the odds of achieving hemostasis increased by 50% (OR=1.5; p=0.012) and 10% (p=0.046), respectively. Subjects who had EGD+IR or Surgery were more likely to have more recurrent events than those who had EGD treatment only (p < 0.001). No mortality benefit was recognized.

Conclusions: This study is the first of its kind to directly compare the effectiveness of EGD vs. angiographic embolization in recurrent NVUGIB. Subjects who received EGD for the first recurrent bleeding episode were 3.5 times more likely to achieve hemostasis. This is noteworthy and underscores the possibility of endoscopic hemostatic superiority and validates consensus recommendations of repeating upper endoscopy as the next step after initial successful hemostasis.

CARE FACULTY PERSPECTIVE: This study emphasizes the utility of repeat endoscopy and hemostatic intervention, compared with interventional radiology and embolization in preventing further recurrent bleeding.

Further analyses will be helpful to determine whether there are clinical features that may identify patients who will, nonetheless, benefit from angiographic embolization.

Barrett’s Esophagus

ACG 2015. PRESIDENT’S PLENARY SESSION 2. ABSTRACT 6. Impact of Histology Confirmation by GI Pathologist Panel on Progression Rates in Barrett’s Esophagus With Low-Grade Dysplasia: Results From a Multicenter Prospective BE Registry.

Rajesh Krishnamoorthy, MD1, Muri Krishna2, Jason Lewis, MD1, Nicholas R. Crewel3, Michele Johnson3, Ross Dierkhising1, Brenda Gregg4, Kenneth K. Wang, MD5, FACG6, Yvonne Romeo, MD5, FACG6, David Katzka1, Nautej Buttar, MD1, Prasad G. Iyer, MD6, FACG6


Results: 352 BE-LGD subjects were identified, of which 249 subjects had biopsy slides available for review. The mean (SD) age was 64.3 (11.4) years. 201 (80.7%) were males. The mean follow up of subjects was 7.8 years. 15 subjects progressed to HGD/EAC with an annual risk of progression of 0.8 %. Following review by the pathologists’ panel, the histologic diagnosis was LGD (92 patients) or IND (91 patients) in 73.5%, and NDBE (66 patients) in 26.5% of study subjects. The progression risk in subjects with additional confirmation of LGD/IND was significantly higher than those downstaged to NDBE group [log-rank p=0.027]. After adjusting for age, sex and BE length, the difference in progression risk stayed intact (HR 9.1, 95% CI 1.2-70.4, p=0.034).

Conclusions: In this large well-defined cohort of BE-LGD patients, all with expert GI pathologist confirmation, progression risk increases 9 fold when an additional panel of expert GI pathologists confirm a LGD/IND diagnosis. These BE subjects may be candidates for endoscopic therapy.

CARE FACULTY PERSPECTIVE: This is an important study which supports recent recommendations that a diagnosis of dysplasia in Barrett’s esophagus should be confirmed by 2 pathologists who have expertise in GI pathology.

In this study, review of reported dysplasia concluded that > 25% of patients did not, in fact, have dysplasia requiring more aggressive follow up and intervention. Implementation of specialist GI pathologist review may be difficult to implement but it offers the prospect of reduced utilization of resources for patients who do not, in fact, have dysplasia; resources should then be available for the management of patients with dysplasia who have a significantly greater risk of progression.
ACG 2015. ORAL ABSTRACT 55. Transepithelial Brush Biopsies With Computer-Assisted 3-Dimensional Analysis Markedly Improve Detection of Barrett’s Esophagus and Dysplasia: Interim Analysis From a Prospective Multi-Center Community Based Study.

Erkanda P. Ikonomi, MD 1, Rajiv Bhuta, MD 1, Natalya Iorio, MD 2, Rahul Kataria, MD, FACG 3, Vivek Kaul, MD, FACG 4, Seth A. Gross, MD, FACCF 5, Michael S. Smith, MD, MBA 5
1. Temple University Hospital, Philadelphia, PA; 2. Jackson Memorial Hospital, Miami, FL; 3. University of Rochester Medical Center, Rochester, NY; 4. New York University Langone Medical Center, New York, NY; 5. Temple University School of Medicine, Philadelphia, PA

Results: From June 2013 to May 2015, 7649 prospectively enrolled cases had FB and WATS3D results available for analysis (39% male, mean age 56 years). The most common endoscopic indications were reflux and BE. Esophagitis was the most frequent finding, followed by salmon-colored mucosa. FB found 972 cases of non-dysplastic BE (NDBE, 13%) and 33 cases of dysplastic BE (0.43%). WATS3D found an additional 1536 NDBE cases and 134 cases with dysplasia that were missed on FB (127 indefinite/low grade dysplasia, 7 high grade dysplasia or carcinoma). Adding WATS3D to FB increased the yield for all BE by 1602 cases (20.9%, NNT 4.77) and for dysplasia by 1.75% (NNT 57.1). The augmented yield of adding WATS3D to FB was 159% for all BE and 406% for dysplasia/neoplasia.

Conclusions: WATS3D greatly improves detection of both BE and dysplasia when added to FB in a community setting. Fewer than 5 WATS3D cases were required to diagnose an additional case of BE, and fewer than 60 WATS3D were needed to identify an additional dysplastic case. This study, the largest WATS3D sample to date, underscores the importance of using WATS3D to identify disease missed by standard sampling methods.

CARE FACULTY PERSPECTIVE: Application of wide area sampling using WATS3D has the potential to significantly improve the diagnosis of Barrett’s dysplasia compared with routine four quadrant biopsies; however, the cost-effectiveness of this technique should be investigated before widespread adoption. In addition, it will be important to determine whether the higher detection rates are associated with improved outcomes or whether WATS3D is superior to strategies based on advanced endoscopic imaging and targeted biopsy of abnormal mucosa.

"WATS3D GREATLY IMPROVES DETECTION OF BOTH BE AND DYSPLASIA WHEN ADDED TO FB IN A COMMUNITY SETTING."


Daniel K. Chan, MD, Cadman L. Leggett, MD, Lori L. Lutzke, CCRP, Prasad G. Iyer, MD, FACG, Kenneth K. Wang, MD, FACG
Mayo Clinic, Rochester, MN

Results: We reviewed 3,114 EMR sessions which were associated with 1,312 unique patients and found 41 (1.3%) total episodes of bleeding. Aspirin or clopidogrel use was not significantly associated with bleeding (OR 0.5, 95% CI 0.23-1.19, p = 0.11), nor was warfarin use alone associated with bleeding (OR 0.42, 95% 0.06-3.12, p = 0.33). Though the absolute risk was low, combination blood thinner therapy was associated with the highest risk of bleeding. Aspirin and clopidogrel use (OR 4.30, 95% CI 1.44-12.84, p = 0.03), and bridging therapy using low molecular weight heparin (OR: 41.6, 95% CI 3.51-493.17, p = 0.03) were significantly associated with bleeding.

Conclusions: Esophageal EMR for the treatment of dysplastic BE is a safe procedure with a low risk of bleeding. Our overall bleeding rate was 1.3%, which is much less than other prior estimates. This may be due to our practice of with-holding antiplatelet agents for five days prior to EMR and maintaining INR < 1.5. Aspirin or clopidogrel use alone is not significantly associated with bleeding, however dual antiplatelet therapy carries the highest risk of bleeding.

CARE FACULTY PERSPECTIVE: This study suggests that EMR for dysplasia in Barrett’s esophagus is a safe procedure. Avoidance of post-EMR bleeding complications appears to be possible with close attention to pre-procedural anti-coagulation management. Further analysis to identify other risk factors such as lesion size and operator-dependent factors will be helpful in guiding optimal management of Barrett’s dysplasia.
Gastroesophageal Reflux

ACG 2015. ORAL ABSTRACT 57. IW-3718, a Novel Gastric-Retentive Bile Acid Sequestrant, Improved Symptoms of Refractory GERD in a Double-blind, Placebo-controlled Phase 2a Study

Michael F. Vaezi, MD, PhD, MSc, FACG 1, Ronnie Fass, MD 2, David Reasner, PhD 3, Michael Hall, MD, MBBCh 3, Tracy Dixon, PhD 3, Mark Cunne, PhD 3, Bernard J. Lavins, MD 3

1. Vanderbilt University Medical Center, Nashville, TN; 2. MetroHealth Medical Center, Cleveland, OH; 3. Ironwood Pharmaceuticals, Cambridge, MA

Results: ITT Population included 93 patients (33 pathological bile reflux (PBR), 19 normal bile reflux (NBR), 41 unknown bile reflux (UBR)). Demographics were generally similar between the IW-3718 and placebo groups within each stratum. Overall, the percent of patients free of regurgitation (RG) at Week 4 was significantly higher among patients on IW-3718 compared with placebo (p=0.03), with greater improvement seen in PBR patients (p=0.01). Degree of relief for overall GERD symptoms (p=0.07) and % of patients free of HB (p=0.25) were numerically greater for IW-3718 vs placebo. Change from baseline in severity of daytime HB, severity of daytime RG, and percent of days free of HB and RG were also improved at Week 4 for IW-3718 patients (vs placebo) in the overall population and in the PBR subgroup. AEs were reported by 48% and 32% of IW-3718 and placebo patients, respectively; the most common AE was constipation (13% vs 0%, respectively).

Conclusions: IW-3718 was well tolerated and improved RG and HB in GERD patients with continued symptoms while taking SD PPIs. The results of this study support the hypothesis that bile acid sequestration can reduce rGERD symptoms.

CARE FACULTY PERSPECTIVE: Refractory GERD symptoms (rGERD), despite proton pump inhibitor therapy, remain a clinical challenge. The potential causes include inadequate PPI dosing, esophageal hypersensitivity, functional heartburn and non-acidic gastroesophageal reflux.

This preliminary study suggests that rGERD patients have a high prevalence of bile reflux, detected by esophageal luminal bilirubin monitoring (Bilitec). These ‘bile refluxers’ derive symptomatic benefit from the administration of a bile acid sequestrant formulated to remain resident in the upper GI tract and bind to gastric bile acids, thereby reducing their reflux into the esophagus. If this benefit is confirmed in larger, phase 2 studies, challenges will include (1) how to determine which rGERD patients have significant bile reflux, (2) whether bile acid sequestrants will reduce esophageal injury and prevent or heal erosive esophagitis or Barrett’s esophagus and (3) whether the benefit is due to binding of bile acids or to another mechanism.


Nadim Mahmud, MD, MS, MPH 1, Julia McNabb-Baltar, MD 2, Walter W. Chan, MD, MPH 1

1. Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; 2. Center for Pancreatic Disease, Brigham and Women’s Hospital, Division of Gastroenterology, Hepatology, and Endoscopy, Boston, MA

Results: 2,723,541 patients (mean age 70.2 yrs, 53% F, mean CCI 1.067) were included in the analysis, with 9,064 (70.4 yrs, 57% F, CCI 1.074) with reflux esophagitis, 335,760 (69.7 yrs, 60% F, CCI 1.014) with GERD alone, and 2,378,717 (70.3 yrs, 52% F, CCI 1.075) without any reflux disease. The overall intubation rate was 6.1% and mortality was 4.5%. After adjusting for potential confounders, there were independent positive associations between GERD and both intubation (OR 1.725, p < 0.0001) and death (OR 1.716, p < 0.0001). Reflux esophagitis was also independently associated with increased intubation (OR 1.739, p < 0.0001) and mortality (OR 1.724, p < 0.0001). Subgroup analyses showed no significant differences in outcomes between patients with a diagnosis of reflux esophagitis and those with GERD alone.

Conclusions: A diagnosis of GERD or reflux esophagitis is independently associated with increased rate of intubation and mortality in patients hospitalized for AECOPD. Further prospective studies are needed to assess the benefit of aggressive anti-reflux therapy on AECOPD outcomes.

CARE FACULTY PERSPECTIVE: This study provides important data to indicate that gastroesophageal reflux disease is associated with adverse outcomes in patients with acute exacerbations of chronic obstructive disease; that is, GERD itself is associated with respiratory disease and thus, the reported association between proton pump inhibitor therapy and community acquired pneumonia may not be attributable to the PPIs themselves but rather to the underlying reflux disease.

"GASTROESOPHAGEAL REFLUX DISEASE IS ASSOCIATED WITH ADVERSE OUTCOMES IN PATIENTS WITH ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE DISEASE."
**Esophageal Cancer**

**ACG 2015. P1672. The Evolving Landscape of Esophageal Cancer: A Four-Decade Analysis**

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**Results:** Since 1973 there has been an 8-fold increase in the number of patients with esophageal cancer (r=0.9, p < 0.0001). While squamous cell cancers have increased 3-fold, they have relatively decreased in incidence due to a 52-fold increase in adenocarcinoma, especially in the distal esophagus (r=0.98, p≤0.0001). Unlike squamous cell carcinoma, stage of presentation for adenocarcinoma has progressively decreased, with 25% of patients now presenting with localized disease (p ≤ 0.0001).

**Conclusions:** There has been a notable increase in esophageal cancer over the past 40 years. This increase is the result of a dramatic, even alarming, increase in adenocarcinoma of the esophagus. In addition, increased obesity rates and endoscopic surveillance have led to increased incidence of esophageal cancer. Patients with adenocarcinoma are presenting at an earlier stage, but only in a minority of patients, with potential implications of a better prognosis. While many factors undoubtedly play a role in the “epidemic” of adenocarcinoma of the esophagus (especially the distal esophagus), GERD and the widespread application of H-2 blockers and, more recently, PPIs must be evaluated as causative agents. Furthermore, surgeons must be fully prepared to offer the full spectrum of operations for esophageal diseases including cancer.

**UEGW 2015. OP241. Long-Term Outcomes of Endoscopic Resection and Additional Therapy to Superficial Esophageal Cancer with MM or SM Invasion**

Toshiyuki Yosha, Tomohiro Tsuchida, Akiyoshi Ishiyama, Toshiaki Hirasawa, Yorimasa Yamamoto, Junko Fujisaki, Masahiro Igarashi

**Results:** In 141 cases (male/female 128/13, median age 66), we resected 76 cases by EMR and 65 cases by ESD, and pathological depth of invasion was MM/SM1/SM2 85/20/36. Median observation period was 41 months (2-140). En-bloc resection rate and local recurrence rate for EMR /ESD was 47.3% /100%, 11% /0% respectively. Of 85 cases of T1a-MM, 69 cases were observed with no additional therapy because of LI (-) and DI (-). One patient had recurrence as lymph node (LN) metastasis and received operation and CRT, surviving with no re-recurrence. The rest of 16 cases were recommended additional therapy because of LI (+) or DI (+) and 7 cases were performed additional therapy (operation/CRT 3/4). No one died of EC in T1a-MM. Of 20 cases of T1b-SMI, 11 cases were observed with no additional therapy because of LI (-) and DI (-). Of them, 2 cases had recurrence (LN metastasis and lung metastasis) and died of EC. Nine cases were recommended additional therapy, because of LI (+) or DI (+). And 5 cases were performed additional therapy (operation/ CRT 1/4), although one case had recurrence (liver metastasis) and died of EC. Of 35 cases of T1b-SM2, all cases were recommended additional therapy which 23 cases were performed (operation/CRT/RT 13/6/4). Three had recurrence (2 cases of intramucosal metastasis and 1 case of LN metastasis). They were performed operation or CRT and 1 case were died of EC. Overall survival (OS) for MM/SM1/SM2 were 84.6%/71.1%/84.6% in 3 year and 81.5%/64.6%/84.6% in 5 year. In OS, additional therapy group was significantly superior to no additional therapy group (p<0.05) among the cases we recommended additional therapy. Comparing OS, survival benefit was not different between operation and CRT as additional therapy. In total 7 cases had metastatic recurrence during the observation period and 4 cases died of EC.

**Conclusions:** The long term outcomes of ER with additional therapy was satisfactory. With appropriate consideration for additional therapy, ER will be a good therapeutic choice for MM or SM invasive EC.

**CARE FACULTY PERSPECTIVE:** This study confirms other observations that the incidence of esophageal adenocarcinoma (EAC) has increased dramatically over the last 40 years; as the authors indicate, this appears to parallel the increasing incidence of gastroesophageal reflux disease (GERD). The authors’ inference that the increase in EAC is due to acid suppression therapy, is not an appropriate conclusion to be drawn from their data; association does not prove causation.

**CARE FACULTY PERSPECTIVE:** This study highlights the technical advances being made in the endoscopic treatment of early, superficial esophageal cancer. There is an increasing number of options open to patients with esophageal dysplasia and neoplasia, emphasizing the importance of effective surveillance for Barrett’s esophagus to detect early lesions. In a Canadian context, there is a need to develop centres that have the expertise and funding to provide advanced endoscopic therapy for early upper gastrointestinal malignancy.
Conclusions: In this prospective study of patients with Crohn’s disease, no significant correlation was found between FC, an objective biomarker of disease activity, and a clinical index of disease activity, HBI, as evident by cross-referencing them with the findings of CT enterography. Although questionnaires such as HBI may not be completely reliable to assess Crohn’s disease activity, further research is needed to confirm the utility of FC as a more objective measure of Crohn’s disease activity than indices such as HBI.

CARE FACULTY PERSPECTIVE: This abstract further stresses that clinical symptoms are not a reliable way to assess patients with Crohn’s disease, and objective measures such as fecal calprotectin should be used when deciding to change or escalate therapies for Crohn’s disease.

Results: Of 103 patients, 46% were male with average age of 43.6 +/- 15.7 years. Using a Spearman’s correlation coefficient graph, no significant correlation was found between HBI and FC levels (rs = - 0.070 (p = 0.484, 95 CI, -0.2664, 0.1319)). Average HBI was 4.4 +/- 4.5 for active disease and 5.3 +/- 4.9 for inactive disease, showing a statistically non-significant difference between the 2 groups (p=0.28). Average FC was 556 +/- 596.8 for ug/g for active disease and 181.6 +/- 222.3 for inactive disease (p=0.001). In order to assess the validity of FC against CTE findings, any value greater than 150 ug/g was considered to represent active disease. Using this cutoff, FC had a sensitivity of 0.61, specificity of 0.79, PPV of 0.76, and a NPV of 0.62 for detecting active disease, as defined by CTE.

Figure 2. Scatter plot of Fecal Cal and HBI showing a lack of correlation between HBI and Fecal Cal
ACG 2015. PLENARY SESSION 1, ABSTRACT 25. Serum Amyloid a as a Surrogate Marker for Mucosal and Histologic Inflammation in Patients With Inflammatory Bowel Disease
Andres Yarur, MD1, Anjali Jain, PhD2, Maria Quintero, MD, MPH3, Jamie Barkin, MD, MACG4, Maria T. Abreu, MD4

Results: 94 patients were included (43% were women, 92% had CD). 59 (62.8%) had active endoscopic disease and 71 (75.5%) had active microscopic inflammation. All patients were receiving a biologic, 23% were on prednisone and 39% were on combination therapy (biologic plus immunomodulator). SAA was the test that best predicted mucosal inflammation. When stratifying by location of disease, SAA predicted inflammation in both isolated small bowel disease (ROC: 0.8) and colonic disease (ROC=0.78). High SAA levels (≥ 2.4 mg/mL) identified 83% (19/23) and 81% (13/16) of those patients with microscopic and macroscopic inflammation but normal CRP (< 4mg/mL).

Conclusions: High circulating SAA levels can accurately predict endoscopic and microscopic inflammation and may be used as a surrogate marker for disease activity, especially on those patients in which CRP levels do not correlate with their disease activity. Further studies looking into how SAA can predict response to treatment and its role in long-term disease monitoring are warranted.

CARE FACULTY PERSPECTIVE: Biomarkers of disease activity such as C-reactive protein (CRP) and fecal calprotectin provide cheaper and non-invasive methods of assessing patients with IBD. CRP does not correlate well with mucosal inflammation and is not made by 15-20% of patients. Serum amyloid A (SAA) (an acute phase protein) may be a useful biomarker in IBD.

This study is of cross-sectional design; longitudinal studies are needed to examine if SAA can predict response to treatment, its role in disease monitoring, correlation with endoscopic inflammation, etc.

ACG 2015. P1068 - Inflammatory Bowel Disease Patients With High-Grade Cytomegalovirus Infection May Benefit From Antiviral Therapy
Jonathan Pourmorady, MD1, Minh Nguyen, MD2, Christopher McPhaul, MD2, Bradley Morganstern, MD2, Dhall Deepti1, Phillips Flacherec, MD1, Erin Vakilzadeh, MD1, Ol Fatimeed, MD, MS1, Andrew Ippoliti, MD2, Stephen Targan, MD, Dermot McGovern, MD, PhD1, David Shoh, MD1
1. Cedars-Sinai Medical Center, Beverly Hills, CA; 2. Cedars-Sinai Medical Center, Los Angeles, CA

Results: Figure 3.

<table>
<thead>
<tr>
<th># of Pts</th>
<th>CMV PCR (copies)</th>
<th>ESR (MM/HR)</th>
<th>CRP (MG/DL)</th>
<th>LOS (Days)</th>
<th>Colectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated High Grade CMV</td>
<td>15</td>
<td>216.1±79.70</td>
<td>39.2±6.48</td>
<td>6.5±1.62</td>
<td>20.6±3.60</td>
</tr>
<tr>
<td>Untreated High Grade CMV</td>
<td>9</td>
<td>23.2±22.62</td>
<td>48.0±13.43</td>
<td>6.6±1.96</td>
<td>20.1±3.43</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>0.10</td>
<td>0.26</td>
<td>0.47</td>
<td>0.47</td>
</tr>
<tr>
<td>Treated Low Grade CMV</td>
<td>12</td>
<td>18.5±9.75</td>
<td>38.3±8.76</td>
<td>7.6±2.21</td>
<td>10.2±2.29</td>
</tr>
<tr>
<td>Untreated Low Grade CMV</td>
<td>8</td>
<td>9.7±9.43</td>
<td>55.0±19.38</td>
<td>4.4±1.68</td>
<td>12.8±5.21</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>0.29</td>
<td>0.19</td>
<td>0.15</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Conclusions: Our study indicates that serum CMV PCR correlates with colonic CMV burden and may be used to predict CMV colitis with “high grade” CMV infection. Our data suggests that treating patients with high CMV burden (≥5 CMV inclusion cells) may improve important clinical outcomes, notably colectomy. Further studies are warranted.

CARE FACULTY PERSPECTIVE: This is an important study that suggests treating patients with high CMV burden may improve outcomes including colectomy. On the other hand, those with low grade CMV infection (<5 inclusion bodies) do not appear to benefit from treatment with antivirals. Pathologists should always be asked to rule out CMV infection when reviewing biopsies from patients with active IBD.

STAY TUNED FOR THE CARE PERSPECTIVES CDDW CONFERENCE REPORT AVAILABLE IN 2016 ON WWW.CAREEDUCATION.CA
UEGW 2015. P0317. Use of Faecal Calprotectin Pathway in Primary Care to Distinguish Irritable Bowel Syndrome from Inflammatory Bowel Disease

Amritpal Dhaliwal, Joanne Orourke, Vandana Sagar, Jake Burdsall, Rupert Ransford, Andrew Milestone

Results: Nineteen GP surgeries (19/22) referred 277 patients via FC pathway over 24 months (Jan 2013-Jan 2015). Forty-five samples rejected as inappropriate.

Figure 4. Faecal Calprotectin Results (received to date)

<table>
<thead>
<tr>
<th>FCP Interpretation</th>
<th>FCP Result (μg/g)</th>
<th>Patients (n=232)</th>
<th>Pathway Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal &lt;50</td>
<td>&lt;50</td>
<td>62.1% (144/232)</td>
<td>IBD excluded. Retain in primary care</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>50-150</td>
<td>22.4% (52/232)</td>
<td>Repeat after 4-6 weeks, if repeat &gt;50μg/g refer to secondary care</td>
</tr>
<tr>
<td>Elevated</td>
<td>&gt;150</td>
<td>15.5% (36/232)</td>
<td>Refer to secondary care</td>
</tr>
</tbody>
</table>

Diagnosis outcomes were available on 175/232 patients at the time of presented data analysis: Elevated 13.7%(24), Indeterminate 19.4%(34) & Normal 66.8%(117). In Elevated FC clinic attenders, IBD was detected in 50%(11/22). Indeterminates were repeated in only 68%: normal repeat 52.2%(12/23), 2 IBD cases detected. After a normal FC, 12.8% were referred to secondary care anyway, but no IBD detected. In the normal FC group alone, assuming a normal FCP avoided a secondary care referral in 87.2% (102/117), the potential cost savings =£73,468 (assuming new patient clinic + 1 colonoscopy=£741.68).

Conclusions: Preliminary data suggests a structured FC pathway is effective in distinguishing IBD & IBS in Primary Care with significant cost savings. Further refinement is required for age ranges & FC cut-off points. Based on this pilot data & latest NICE Diagnostic Appraisal 11, the local Clinical Commission Group have commissioned a secondary care supervised FC service for primary care.

CARE FACULTY PERSPECTIVE: Fecal calprotectin is a reasonable test for primary care physicians to use in order to risk stratify whether patients have diarrhea due to inflammatory bowel disease. However, normal fecal calprotectin values do not necessarily mean a diagnosis of IBS, and clinicians must remember other common causes of diarrhea such as celiac disease or bile-salt diarrhea may also be associated with a normal calprotectin levels.

Novel Agents

ACG 2015. P1764. Efficacy and Safety of Vedolizumab With Advancing Age in Patients With Crohn’s Disease: Results From the GEMINI 2 Study

Vijay Yagnik1, Nabeel Khan2, Marla Dubinsky3, Jeffrey Axler4, Alexandra Green5, Brihad Abhyankar5, Karen Lasch6

1. Massachusetts General Hospital, Harvard Medical School, Boston, MA; 2. University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA; 3. Mount Sinai Hospital, New York, NY; 4. Toronto Digestive Disease Associates, University of Toronto, Toronto, ON, Canada; 5. Takeda Development Centre Europe Ltd, London, United Kingdom; 6. Takeda Pharmaceuticals International Inc, Deerfield, IL

Results: At baseline, 178 (48%), 161 (44%), and 29 (8%) pts in the induction and 246 (53%), 179 (39%), and 36 (8%) pts in the maintenance ITT populations were aged 55 years, respectively. At week 6, 31 (28%) VDZ-treated pts aged 55 years had an enhanced clinical response (≥100-point reduction in CD Activity Index [CDAI] score from baseline). Clinical remission (CDAI total score ≤150) was achieved by 16 (14%), 15 (16%), and 1 (8%) VDZ-treated pts in each age category, respectively. At week 52, remission was achieved by 65 (38%), 42 (37%), and 9 (41%) VDZ-treated pts aged 55 years, respectively. AEs occurred at similar rates across the ages. Three malignancies (<1%) were reported in VDZ-treated pts aged 20 years (carcinoid tumor of the appendix), 45 years (breast cancer), and 52 years (squamous cell carcinoma [skin]). Five deaths were reported: 3 VDZ-treated pts aged <35 years (myocarditis; CD and sepsis; septic shock), 1 VDZ-treated pt aged 46 years (intentional overdose), and 1 PBO-treated pt aged 75 years (bronchopneumonia).

Conclusions: These data suggest that the safety and efficacy of VDZ were generally similar in CD pts across all the age categories analyzed. Data interpretation is limited by the small pt population aged >55 years; these findings should be further evaluated in prospective studies.

"THESE DATA SUGGEST THAT THE SAFETY AND EFFICACY OF VDZ WERE GENERALLY SIMILAR IN CD PATIENTS ACROSS ALL THE AGE CATEGORIES ANALYZED."
ACG 2015. PLENARY SESSION 2, ABSTRACT 54: A Multicenter, Randomized, Double-Blind, placebo-Controlled phase 3 Study of Ustekinumab, a Human Monoclonal Antibody to IL-12/23p40, in Patients With Moderately- to Severely-Active Crohn’s Disease Who Are Naive or Non-Refractory to Anti-TNF (UNITI-2)

Brian Feagan, MD, FACG 1, Chris Gasink 2, Yinghua (Grace) Lang 2, Joshua R. Friedman, MD, PhD, Jewel Johanning 2, Long-Leong Gao, MD, MF, FACG 3, Stephen B. Hanauer, MD, FACG, Paul Rutgeerts, MD, PhD 5, Stephan Targan, MD 6, Willem J.S. de Villiers, MD, PhD, Jean-Frederic Colombel, MD 3, Zsolt Tulassay 9, Ursula Seidler, MD 10, William J. Sandborn, MD, FACG 11

1. Robarts Clinical Trials, Robarts Research Institute, University of Western Ontario, London, ON, Canada; 2. Janssen R&D, Spring House, PA; 3. Icahn School of Medicine at Mount Sinai, New York, NY; 4. Feinberg School of Medicine, Northwestern University, Chicago, IL; 5. University of Leuven, Leuven, Belgium; 6. Cedars-Sinai Medical Center, Los Angeles, CA; 7. University of Calgary, Calgary, AB, Canada; 8. University of Cape Town, South Africa; 9. Semmelweis University, Budapest, Hungary; 10. Medizinische Hochschule, Hannover, Germany; 11. University of California San Diego and UC San Diego Health System, La Jolla, CA

Results: Of the 628 patients randomized, the median disease duration was 6.4 years and the baseline mean CDAI was 303; 39% were receiving steroids (including budesonide) and 35% were receiving immunomodulators; 69% were naïve to anti-TNFs, whereas 31% had previously been exposed to anti-TNFs but had not failed anti-TNF therapy. At Week 6, 55.5% and 51.7% in the ~6 mg/kg and 130 mg UST groups were in clinical response, respectively, vs 28.7% in the PBO group (p<0.001). At Week 8, 40.2% and 30.6% of patients in the ~6 mg/kg and 130 mg UST groups were in clinical remission, respectively, vs. 19.6% in the PBO group (p<0.009). Both UST doses also resulted in significant improvements vs PBO in CDAI, IBDQ, CRP, as well as fecal lactoferrin and calprotectin. Proportions of patients with AEs, SAEs, and infections (including serious infections) were similar in the UST and PBO groups. No malignancies, deaths, opportunistic infections or TB occurred in UST-treated patients. In a broad population of moderate-severe CD patients not previously failing TNF-antagonists (69% anti-TNF naïve), IV UST induced clinical response and remission and was well-tolerated throughout induction.

CARE FACULTY PERSPECTIVE: Ustekinumab was previously demonstrated effective in Crohn’s disease patients with anti-TNF failures. This study now supports its use in patients prior anti-TNF failure. Although these data are very promising, there are outstanding questions that need to be answered:

• Is it effective for maintenance therapy?
• What is the impact on endoscopic healing?
• What is the impact on fistula closure? Immunogenicity?

We eagerly await the results of IM-UNITI (maintenance study) for further insights.
Results: The cohort included 493 pts with UC. Seventeen pts were found to have osteoporosis prior to UC diagnosis (dx); of the remaining 476 UC pts, 42.6% were women, and the median age at dx of UC was 34.3 years (range, 1-87). The cumulative incidence of osteoporosis after UC dx by fractures or BMD testing was 7.6% at 10 years (95% confidence interval [CI], 4.9%-10.1%), 16.4% at 20 years (12.1%-20.5%), 21.8% at 30 years (16.1%-27.5%), and 36.8% at 40 years (23.2%-51.1%). Among the 110 pts with BMD testing, the cumulative incidence of osteoporosis after UC dx was 13.6% at 10 years (95% CI, 6.7%-20%), and 35.6% at 30 years (22.3%-46.9%). Older age at UC dx was significantly associated with risk for osteoporosis (ages 40-64 HR relative to < 40 years, 7.4; 95% CI, 3.9-14.1; p < 0.0001 and age ≥65 HR, 29.7; 95% CI, 14.0-62.9; p < 0.0001). Female gender (HR, 1.2; 95% CI 0.8-2.0; p=0.37), number of surgeries (HR, 1.0; 95% CI, 0.7-1.4; p=0.95), cumulative duration of steroid use (HR per year of use, 1.0; 95% CI 0.8-1.2; p=0.57), tobacco use (HR 1.2; 95% CI 0.7-1.9; p=0.48), and alcohol use (HR 0.9; 95% CI 0.5-1.5; p=0.43) were not associated with increased risk of osteoporosis.

Conclusions: Older age was a risk factor for osteoporosis in our population-based cohort of UC. The cumulative incidence of osteoporosis was close to 1 in 10 patients after 10 years of UC dx, and increased to about 1 in 5 patients after 30 years of UC dx. Even though we found older age to be the only significant risk factor for osteoporosis, evaluation of bone density should be a consideration in the health maintenance strategy for UC patients.

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Results: Mayo endoscopy subscores of 0 or 1 were associated with the lowest concentrations of Lac & fCal. Baseline fLac & fCal were poor predictors for endoscopic healing at Wk6 (AUCs<0.63). Area under the ROC curve analysis showed that fLac & fCal at Wk6 are poor predictors for endoscopic healing at Wk6 (AUCs<0.63). Area the lowest concentrations of Lac & fCal. Baseline fLac & fCal were endoscopic improvement.

Conclusions: At Wk6, Mayo endoscopy subscores were positively associated with levels of fLac & fCal. Cut-offs of fLac<50µg/ml & fCal <250µg/kg at Wk6 demonstrated reasonable sensitivity & specificity for normal/endoscopic disease activity. Overall these data suggest that fecal inflammatory marker levels might be useful surrogates for endoscopic improvement.
**5-ASA**

**UEGW 2015. P1624. Efficacy of Concomitant Mesalamine Suppository in Patients with Active Ulcerative Colitis Who Showed Inadequate Response to an Oral 5-Aminosalicylic Acid Preparation: A Prospective Study**

Naoki Yoshimura, Ryu Tanaka, Minako Sako, Masakazu Takazoe

**Results:** At week 4, the average UC-DAI fell from 3.2±0.7 at entry to 1.4±1.7 (n=192, P<0.001). Of the 192 patients, 90 (46.9%) achieved clinical remission, and 43 (22.4%) achieved response level. The bleeding sub-score fell from 1.0±0.2 to 0.4±0.5 (P<0.001). Regarding the response rate vs extent of UC, the UC-DAI fell from 3.2±0.7 to 1.4±1.7 in patients with proctitis (n=171, P<0.001) and from 3.1±0.5 to 1.3±1.5 in patients with left-sided colitis (n=20, P<0.001). One patient with pancolitis worsened. Further, by concomitant Pentasa suppository, the bleeding sub-score in patients who did not respond well to oral 5-ASA preparations alone (n=129) fell from 1.0±0.1 to 0.3±0.5 (P<0.001); in sulfasalazine-treated subgroup (n=49, mean dose 3.7±1.0g/day, range 1.5-6.0/day) fell from 1.0 ± 0.1 to 0.3±0.5 (P<0.001); in Pentasa (n=20), 2.3±0.8g/day, range 1.5-3.0/day fell from 1.0±0.0 to 0.2±0.4 (P<0.001); in Asacol (n=60),3.4±0.4g/day, range 2.4-3.6/day fell from 1.0±0.1 to 0.4±0.6 (P<0.001), reflecting significant efficacy for concomitant Pentasa suppository in patients who did not respond well to high dose oral 5-ASA preparations alone. No serious adverse event was observed.

**Conclusions:** This is the first study in Japan that has investigated the efficacy of Pentasa suppository in patients who did not respond well to an oral 5-ASA preparation. Based on the outcomes of the present investigation, we believe that patients with distal UC who have active disease while on an oral 5-ASA preparation alone should benefit from concomitant Mesalamine Suppository.

**Related Abstract**

**ACG 2015. P1787. Remission Status Predicts Health-Related Quality of Life for Patients With Mild-to-Moderate Ulcerative Colitis Receiving Short-Term and Long-Term Daily Therapy With Multimatrix Mesalamine**

Aaron Yarlas1, Geert D’Haens, MD, PhD2, Deborah Willshire3, Megan Teynor4
1. Optum, Lincoln, RI; 2. Academic Medical Center, Amsterdam, Netherlands; 3. Shire, North Ryde, Australia; 4. Shire, Lexington, MA

**Results:** Of 197 patients in the induction period, 103 (52.3%) entered the MP and 91 (88.3%) completed. At Week 32 clinical remission occurred in 14/67 (20.9%), HD (p=0.0108 vs. PBO), 17/65 (26.2%), LD (p=0.0021), and 4/65 (6.2%), PBO; clinical response occurred in 34/67 (50.7%), HD (p=0.0002), 23/65 (35.4%), LD (p=0.0571), and 13/65 (20.0%), PBO; mucosal improvement (Mayo endo-subscore ≤ 1) occurred in 22/67 (32.8%) for HD (p=0.0046), 21/65 (32.3%), LD (p=0.0064), and 8/65 (12.3%), PBO. The improvement in total Mayo score at Week 32 from baseline was 3.4, HD (p=0.0004), 2.2, LD (p=0.1932), and 1.6, PBO. During the MP, adverse events (AEs) were most common in PBO. AEs occurred in 11/42 (26.2%), HD; 4/36 (11.1%), LD; 8/25 (32.0%), PBO. The most common were: worsening of UC (HD, n=1; LD, 0; PBO, n=2) and UTI (HD, 0; LD, n=1; PBO, n=1). No AEs of special interest (cardiac, pulmonary, ophthalmologic, hepatic, malignancy or serious infections) were reported during the MP.

**Conclusions:** Patients with moderate to severe UC who continued treatment with ozanimod were more likely to achieve and maintain clinical remission, clinical response and mucosal improvement than those receiving placebo. These data support the longer term efficacy and safety/tolerability profile of ozanimod in the treatment of moderate to severe UC.

**Novel Agents**

**ACG 2015. PLENARY SESSION 1. ABSTRACT 19. A Randomized, Double-Blind, Placebo-Controlled Trial of Ozanimod, an Oral S1P Receptor Modulator, in Moderate to Severe Ulcerative Colitis: Results of the Maintenance Period of the TOUCHSTONE Study**

Stephen B. Hanauer, MD, FACG1, Brian Feagan, MD, FACG2, Douglas C. Wolf, MD3, Geert D’Haens, MD, PhD4, Severine Vermeire, MD, PhD5, Subratia Ghosh, MD6, Heather Smith7, Matt Cravets, PhD7, Paul Frithua, MD, PhD, PharmD7, Richard Aranoda, MD7, Sheila Gupta, MD7, Allan Olson, MD7, William J. Sandborn, MD, FACG8.
1. Division of Gastroenterology, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL; 2. Robarts Clinical Trials, Robarts Research Institute, University of Western Ontario, London, ON, Canada; 3. Atlanta Gastroenterology Associates, Atlanta, GA; 4. Academic Medical Center, Amsterdam, Netherlands; 5. University Hospital Gasthuisberg, Leuven, Belgium; 6. University of Calgary, Calgary, AB, Canada; 7. Receptos, Inc., San Diego, CA; 8. University of California San Diego, Division of Gastroenterology, La Jolla, CA

**Results:** This is the first study in Japan that has investigated the efficacy of Pentasa suppository in patients who did not respond well to oral 5-ASA preparations alone. Based on the outcomes of the present investigation, we believe that patients with distal UC who have active disease while on an oral 5-ASA preparation alone should benefit from concomitant Pentasa suppository.

**Related Abstract**

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Aaron Yarlas1, Geert D’Haens, MD, PhD2, Deborah Willshire3, Megan Teynor4
1. Optum, Lincoln, RI; 2. Academic Medical Center, Amsterdam, Netherlands; 3. Shire, North Ryde, Australia; 4. Shire, Lexington, MA

**Results:** Of 197 patients in the induction period, 103 (52.3%) entered the MP and 91 (88.3%) completed. At Week 32 clinical remission occurred in 14/67 (20.9%), HD (p=0.0108 vs. PBO), 17/65 (26.2%), LD (p=0.0021), and 4/65 (6.2%), PBO; clinical response occurred in 34/67 (50.7%), HD (p=0.0002), 23/65 (35.4%), LD (p=0.0571), and 13/65 (20.0%), PBO; mucosal improvement (Mayo endo-subscore ≤ 1) occurred in 22/67 (32.8%) for HD (p=0.0046), 21/65 (32.3%), LD (p=0.0064), and 8/65 (12.3%), PBO. The improvement in total Mayo score at Week 32 from baseline was 3.4, HD (p=0.0004), 2.2, LD (p=0.1932), and 1.6, PBO. During the MP, adverse events (AEs) were most common in PBO. AEs occurred in 11/42 (26.2%), HD; 4/36 (11.1%), LD; 8/25 (32.0%), PBO. The most common were: worsening of UC (HD, n=1; LD, 0; PBO, n=2) and UTI (HD, 0; LD, n=1; PBO, n=1). No AEs of special interest (cardiac, pulmonary, ophthalmologic, hepatic, malignancy or serious infections) were reported during the MP.

**Conclusions:** Patients with moderate to severe UC who continued treatment with ozanimod were more likely to achieve and maintain clinical remission, clinical response and mucosal improvement than those receiving placebo. These data support the longer term efficacy and safety/tolerability profile of ozanimod in the treatment of moderate to severe UC.

**CARE FACULTY PERSPECTIVE:** This study introduces a novel oral agent targeting a different mechanism of action important in the immunopathogenesis of IBD. Ozanimod was effective in maintaining clinical efficacy in ulcerative colitis.

**Based on the outcomes of the present investigation, we believe that patients with distal UC who have active disease while on an oral 5-ASA preparation alone should benefit from concomitant Mesalamine Suppository.**
ACG 2015. PLENARY SESSION 1. ABSTRACT 20. First Trough Level of Infliximab at Week 2 Predicts Future Outcomes of Induction Therapy in Ulcerative Colitis: A Post-hoc Analysis of a Multicenter Prospective Randomized Controlled Trial

Taku Kobayashi1, Yasuo Suzuki2, Satoshi Motoya3, Fumihito Ogata4, Haruhiko Ito5, Hiroaki Ito6, Noriko Sato7, Kunihiko Ozaki8, Mamoru Watanabe9, MD, FACG; Toshifumi Hibi, MD, PhD, FACG; 1. Center for Advanced IBD Research and Treatment, Kitasato University Kitasato Institute Hospital, Tokyo, Japan; 2. Toho University Sakura Medical Center, Department of Internal Medicine Sakura, Sakura, Japan; 3. Inflammatory Bowel Diseases Center, Sapporo-Kosei General Hospital, Sapporo, Japan; 4. Department of Gastroenterology, Fukukawa University Chikushi Hospital, Chikushino, Japan; 5. Center for Diagnostic and Therapeutic Endoscopy, Keio University, Tokyo, Japan; 6. Digestive Disease Center, Kitano Hospital The Tazuke Kofukan Medical Research Institute, Osaka, Japan; 7. Pharmacovigilance & Quality Assurance Division, Mitsubishi Tanabe Pharma Corporation, Osaka, Japan; 8. Development Division, Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan; 9. Department of Gastroenterology and Hepatology, Tokyo Medical and Dental University, Tokyo, Japan

Results: Week 2 TL was significantly associated with a 14-week CAI remission. The optimal cut-off value for predicting 14-week CAI remission was 21.3 μg/mL (area under the curve: 0.65, 95% Confidence Interval [CI]: 0.52–0.77) in receiver operating characteristic curve analysis. The week 2 TL/CAI ratio (TL/CAI) also correlated with 14-week CAI remission (the optimal cut-off value for predicting 14-week CAI remission: 4.3; area under the curve: 0.76, 95% CI: 0.65–0.86). In multiple logistic regression analysis which included patient background factors, CAI remission at week 2, week 2 TL ≥ the median value, and week 2 TL/CAI ≥ the median value as the explanatory variables, the week 2 TL/CAI was an independent factor correlating with 14-week CAI remission (odds ratio 8.07; 95% Confidence Interval 2.84–27.07, p < 0.001). The week 2 TL and TL/CAI were also significantly associated with 30-week mucosal healing.

Conclusions: Our results suggest that the first TL at week 2, in combination with clinical evaluation, is useful for predicting both short- and long-term outcomes, allowing an earlier decision between continuing IFX or switching to other options.

CARE FACULTY PERSPECTIVE: This study may enable us to identify individuals treated with infliximab who could benefit from early dose escalation or switching therapy.

ACG 2015. PLENARY SESSION 1. ABSTRACT 21. Efficacy of Vedolizumab Maintenance Therapy With and Without Continued Immunosuppressant Use in GEMINI 1 and GEMINI 2

Brian Feagan, MD, FACG1, Corey A. Siegel, MD2, Gil Meexclusiveaka, MD, MS3, Kim Isaacs, MD, PhD, FACG4, Karen Lasch5, Maria Rosando5, Alexandra Green6, Brihad Abhyankar7; 1. Robarts Clinical Trials, Robarts Research Institute, University of Western Ontario, London, ON, Canada; 2. Dartmouth-Hitchcock Medical Center, Lebanon, NH; 3. Cedars-Sinai Medical Center, Los Angeles, CA; 4. University of North Carolina School of Medicine, Chapel Hill, NY; 5. Takeda Pharmaceuticals International Inc, Deerfield, IL; 6. Takeda Pharmaceuticals International Co, Cambridge, MA; 7. Takeda Development Centre Europe Ltd, London, United Kingdom

Results: At week 52, rates of clinical remission, clinical response, mucosal healing (UC), and corticosteroid-free remission were numerically higher with VDZ, irrespective of baseline immunosuppressant (IS) use. Mean trough concentrations were similar between patients who discontinued IS (US) versus those who didn’t (non-US).

Conclusions: Discontinuing immunosuppressants did not appear to substantially affect the clinical efficacy of VDZ maintenance therapy. Interpretation of these post hoc analyses is limited by the cross-regional comparison and the relatively small sample sizes.

CARE FACULTY PERSPECTIVE: With vedolizumab now available in Canada for the treatment of ulcerative colitis there remains many questions relating to optimization of efficacy with this agent. This post-hoc analysis of GEMINI 1 and II suggests that concomitant therapy with vedolizumab and immunosuppressants was no better than vedolizumab alone in maintaining efficacy. However, given the limitations of this analysis (sample size, post-hoc analysis) further prospective studies are required to better define the role of combination therapy with vedolizumab.
Cost of Healthcare in IBD

**ACG 2015. P1029. The Rising Burden of Inflammatory Bowel Disease in North America from 2015 to 2025: A Predictive Model.**

Stephanie Coward, MSc¹; Fiona Clement, PhD¹; Tyler Williamson, PhD¹; Glen Hazlewood, MD¹; Siew Ng, PhD²; Steven Heitman, MD, MSc¹; Cynthia Seow, MBBS, MSc¹; Remo Panaccione, MD¹; Subrata Ghosh, MD¹; Gilaad G. Kaplan, MD, MPH¹

1. University of Calgary, Calgary, AB, Canada; 2. Chinese University of Hong Kong, Shatin, NT, Hong Kong

**Results:** In 2015 the prevalence of IBD is 0.52% and 1,870,181 are estimated to be living with IBD in North America (Figure 6). Over the next decade the prevalence of IBD in North America will increase by 2.39% per year (95% CI: 1.39%, 3.41%) (Figure 6). Between 2015 and 2025 the prevalence of CD will rise significantly in Canada (APC=3.75; 95% CI: 2.57, 4.93) and the US (APC=3.30; 95% CI: 0.17, 6.53); however, the prevalence will remain stable for UC (Figure 6). By 2025 approximately 0.9% of Canadians and 0.6% of Americans will have IBD. In 2025 the number of individuals with IBD in North America is estimated to be 2,571,653 with direct healthcare costing over $27 billion (Figure 6).

**Conclusions:** The prevalence of IBD will rise dramatically over the next decade such that 0.65% of individuals living in North America will have a diagnosis of IBD. The rise in prevalence will be dominated by Crohn’s disease, whereas the prevalence of ulcerative colitis has plateaued in North America. In 2025 over 2.5 million individuals will have IBD and over $27 billion will be spent on direct healthcare costs. The substantial burden of IBD in North America in the next decade necessitates multifactorial solutions including innovating the delivery of healthcare and studying interventions that prevent the development of IBD.

**Figure 6.**

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Annual Percentage Change (95% CI)</th>
<th>Prevalence per 100,000 in 2015</th>
<th># of people with IBD in 2015</th>
<th>Total cost in 2015</th>
<th>Prevalence per 100,000 in 2025</th>
<th># of people with IBD in 2025</th>
<th>Total cost in 2025</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada CD</td>
<td>3.75 (2.57, 4.93)</td>
<td>400</td>
<td>143,645</td>
<td>$761,387,855</td>
<td>578</td>
<td>227,795</td>
<td>$1,494,819,111</td>
</tr>
<tr>
<td>Canada UC</td>
<td>1.74 (-0.02, 3.54)</td>
<td>260</td>
<td>93,163</td>
<td>$493,809,045</td>
<td>309</td>
<td>121,566</td>
<td>$797,730,230</td>
</tr>
<tr>
<td>Total with IBD in Canada</td>
<td>2.79 (1.68, 3.91)</td>
<td>660</td>
<td>236,807</td>
<td>$1,255,196,900</td>
<td>887</td>
<td>349,361</td>
<td>$2,292,549,341</td>
</tr>
<tr>
<td>USA CD</td>
<td>3.30 (0.17, 6.53)</td>
<td>268</td>
<td>862,523</td>
<td>$9,094,843,300</td>
<td>371</td>
<td>1,290,006</td>
<td>$17,732,975,363</td>
</tr>
<tr>
<td>USA UC</td>
<td>0.68 (-1.25, 2.64)</td>
<td>240</td>
<td>770,851</td>
<td>$3,982,162,740</td>
<td>257</td>
<td>891,319</td>
<td>$7,510,103,557</td>
</tr>
<tr>
<td>Total with IBD in the USA</td>
<td>1.72 (-0.48, 3.96)</td>
<td>508</td>
<td>1,633,373</td>
<td>$14,077,006,039</td>
<td>628</td>
<td>2,181,325</td>
<td>$25,243,078,919</td>
</tr>
<tr>
<td>Total with IBD in North America</td>
<td>2.39 (1.39, 3.41)</td>
<td>524</td>
<td>1,870,181</td>
<td>$15,332,202,939</td>
<td>654</td>
<td>2,530,686</td>
<td>$27,535,628,260</td>
</tr>
</tbody>
</table>
PRIMER ON SUBSEQUENT ENTRY BIOLOGICS (SEBs)

Health Canada definition: An SEB is biologic drug that enters the market subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug. SEBs are also known as ‘follow-on biologics’ (USA), biosimilars (Europe), and similar biotherapeutic products (WHO).

Generics and SEBs are not the same. Figure 7 provides an overview of their differences.

CURRENT STATE OF SEBs IN CANADA

Currently, a number of SEBs exist globally. International regulatory authorities have developed standards and guidelines (FDA, EMA, Health Canada). Presently, no SEBs are approved under FDA guidelines in US, five are approved in Europe and only one in Canada. There is no SEB currently in use or approved for the treatment of IBD in North America.

Summary of Health Canada Guidelines

- An SEB can only be considered if there is an existing approved reference biologic drug (RBD)
- The SEB can be judged to be similar to the RBD by meeting predetermined criteria (ie. similar biochemical structure, similar pharmacokinetic and pharmacodynamic properties, demonstration of similarity in clinical studies)
- SEBs are not ‘generic biologics’
- Approval does not declare pharmaceutical or therapeutic equivalence to the RBD
- An SEB is to be considered a new biologic drug and is regulated no differently than the RBD. The SEB should not be used as the RBD for a later SEB submission (eg. if an SEB was approved for one indication, the SEB cannot be defined as the RBD for the SEB seeking approval for a different indication).
- SEBs will not be labelled as interchangeable with the RBD.
- An SEB should not be automatically substituted in place of a RBD by dispensing pharmacies.

POTENTIAL IMPACT FOR SEBs IN CANADIAN PRACTICE

Biologics have improved patient wellbeing, reduced hospitalization and surgical rates, and may have the potential to alter natural history of disease however cost burden is associated. Provided SEBs enter market at substantially lower cost, there is a potential opportunity to reduce cost to patients and payers/ enhance availability of this class of therapy. However, this is contingent on SEBs for IBD having clear, demonstrated efficacy and safety record comparable with RBDs.
POTENTIAL CHALLENGES FOR SEBs IN CANADIAN PRACTICE

Challenges: Interchangeability & Substitutability

“Interchangeability” generally refers to the requirement to “interchange” a lower cost generic version of a brand name drug (a financial decision).

“Substitutability” or “therapeutic substitution” generally refers to substituting an altogether different drug as functionally equivalent to a prescribed drug for treating the same condition (a medical decision).

Interchangeability and/or substitutability must be carefully considered:

• SEBs and RBDs are not the same, and could lead to clinically meaningful differences
• Complexity and impurity profile of an SEB could lead to consequences
• Immunogenicity of SEBs cannot be fully predicted using preclinical/clinical studies
• Not all indications of an RBD are authorized for the SEB

Challenges: Data Extrapolation

“Data extrapolation” refers to the evaluation by Health Canada of a proposal to grant additional indications held by the reference biologic drug to the SEB, in the absence of such clinical data.

Extrapolation may be justified based on:

• Mechanism of action
• Pathophysiological mechanism(s) of the disease(s) or conditions involved
• Safety profile in the respective conditions and/or populations
• Clinical experience with the reference biologic

CONCLUDING REMARKS:

The complexity of these SEBs, together with factors related to their manufacturing, have the potential to translate into clinically relevant differences in efficacy, safety, and immunogenicity in biosimilar agents. It is important for the Canadian gastroenterology community to gain a full understanding of the important issues in the context of the development and entry into the marketplace of such biologic agents.

PATIENT SAFETY AND EFFICACY MUST ALWAYS REMAIN THE HIGHEST PRIORITY.

REFERENCES:

i. Health Canada Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs), 2010/03/05.

ACG 2015. P1126. Treatment of Hepatitis C Infection: Single-Center, Real World Experience With Sofosbuvir-Based Therapies

Nyan L. Latt, MD, Vincent Louie, PharmD, Derenik Gharibian, PharmD, Amandeep Sahota, MD; Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA

Results: Mean age is 59 years; 65% were male. There were 55% genotype 2, 34% genotype 1 and 19% genotype 3 patients. 44% had cirrhosis, 38% had prior treatment failures and 9.7% were liver transplant recipients. Overall SVR at 12 weeks (SVR12) was 80%. Overall SVR 12 for genotype 1 was 69%; treatment naive: 84%, prior treatment failure: 62%, non-cirrhotic: 89% and cirrhotic: 68% respectively. Overall SVR 12 for genotype 2 was 90%; treatment naive: 92%, prior treatment failure: 87%, non-cirrhotic: 93% and cirrhotic 84%. Overall SVR 12 for genotype 3 was 53%, treatment naive: 43%, prior treatment failure: 58%, non-cirrhotic: 40% and cirrhotic: 57%. Overall SVR 12 among liver transplant recipients were 75%. The most common side effects were fatigue, arthralgia and nausea. 3% discontinued treatment due to intolerable side effects. Serious adverse events requiring hospitalizations were due to pneumonia, abdominal wall abscess, chest pain and syncope.

Figure 9. Sustained Virological Responce at 12 weeks (SVR12)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Genotype 1</th>
<th>Genotype 2</th>
<th>Genotype 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cirrhotic</td>
<td>89%</td>
<td>85%</td>
<td>93%</td>
<td>40%</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>68%</td>
<td>59%</td>
<td>84%</td>
<td>57%</td>
</tr>
<tr>
<td>Treatment History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naive</td>
<td>84%</td>
<td>75%</td>
<td>92%</td>
<td>43%</td>
</tr>
<tr>
<td>Experienced</td>
<td>75%</td>
<td>62%</td>
<td>87%</td>
<td>58%</td>
</tr>
<tr>
<td>HIV Co-infection</td>
<td>66%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Liver Transplant</td>
<td>75%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Liver Cancer</td>
<td>64%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 10. SVR Comparison to Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>Observed</th>
<th>Reported*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1</td>
<td>69%</td>
<td>89%**</td>
</tr>
<tr>
<td>Naive</td>
<td>75%</td>
<td>89%</td>
</tr>
<tr>
<td>Non-cirrhotic</td>
<td>93%</td>
<td>92%</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>62%</td>
<td>80%</td>
</tr>
<tr>
<td>Experienced</td>
<td>62%</td>
<td>-</td>
</tr>
<tr>
<td>Non-cirrhotic</td>
<td>73%</td>
<td>-</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>57%</td>
<td>-</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>90%</td>
<td>93%</td>
</tr>
<tr>
<td>Non-cirrhotic</td>
<td>93%</td>
<td>98%</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>88%</td>
<td>91%</td>
</tr>
<tr>
<td>Experienced</td>
<td>87%</td>
<td>86-94%</td>
</tr>
<tr>
<td>Non-cirrhotic</td>
<td>93%</td>
<td>76-96%</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>80%</td>
<td>60-78%</td>
</tr>
<tr>
<td>Side Effects</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td>3%</td>
<td>1-5%</td>
</tr>
<tr>
<td>Discontinuation Rate</td>
<td>2.6%</td>
<td>0-2%</td>
</tr>
</tbody>
</table>

*Reported values taken from NEUTRINO, FISSION, POSITRON, and FUSION clinical trials
** NEUTRINO overall genotype 1 SVR rate in treatment naive patients

Conclusions: It was observed that real-world SVR rates are lower compared to clinical trials. Patient characteristics that influence SVR rates are male gender, cirrhosis, prior treatment failure and high baseline viral load. Rate of side effects, serious adverse events were comparable to clinical trials. Overall, patients appear to be compliant and tolerate treatment well. In conclusion, our study highlights the differences in outcomes between clinical trials and real-world clinical practice.

ACG 2015. PLENARY SESSION 2: ABSTRACT 67. Sofosbuvir-Based Treatment Is Safe and Effective in Patients With Chronic Hepatitis C Infection and End-Stage Renal Disease

Naim Alkhouri, MD1, John Gurguis, MD2, Sumi Anthony1, John Rivas3, Ibrahim A. Hanouneh, MD1
1. Cleveland Clinic, Cleveland, OH; 2. Cleveland Clinic Foundation, Cleveland, OH; 3. Department of Gastroenterology, Cleveland Clinic, Cleveland, OH

Results: Eight patients (6 female, 6 with GT1, one with GT4, and one with GT3), mean age 56.8 ± 20 years, mean time on dialysis of 5.5 years, and mean fibrosis stage of 1.625 ± 1.4 (two with cirrhosis) were included in the study. Seven patients were HCV treatment naive and one was a prior null responder to interferon-based therapy. Four patients were started on sofosbuvir/simeprevir and 4 patients were started on sofosbuvir/ledipasvir for 12 weeks. Therapy was well tolerated overall with pruritus/ headache developing in one patient each. No patient discontinued therapy due to side effects. Baseline hemoglobin was at 10.8 ± 2.4 g/dL with no significant change during treatment (10.9 ± 1.7 g/dL). Similarly, there was no significant change in platelet count or bilirubin levels with sofosbuvir/ simeprevir or sofosbuvir/ledipasvir treatment (198 ± 164 k/uL at baseline and 188 ± 165 on treatment for platelets; 0.3 ± 0.4 mg/dL and 0.25 ± 0.15 for bilirubin). 4 out of 4 patients who completed treatment (100%) achieved SVR 12, 4 patients are still currently on treatment of these 3 achieved undetectable HCV RNA at week 4 of therapy.

Conclusions: Full dose sofosbuvir/simeprevir or sofosbuvir/ledipasvir therapy for HCV-infected patients with ESRD was well-tolerated with no discontinuation due to side effects and no significant hematological adverse events.

"FULL DOSE SOFOSBUVIR/SIMEPREVIR OR SOFOSBUVIR/LEDIPASVIR THERAPY FOR HCV-INFECTED PATIENTS WITH ESRD WAS WELL-TOLERATED WITH NO DISCONTINUATION DUE TO SIDE EFFECTS AND NO SIGNIFICANT HEMATOLOGICAL ADVERSE EVENTS."
ACG 2015. P413. Efficacy of Ombitasvir/Paritaprevir/and Dasabuvir +/-Ribavirin in Patients Receiving Concomitant Acid-Reducing Agents in Phase 3 Trials
Mitchell Shiffman 1, Vinod Rustgi 2, Michael Bennett 3, Xavier Forns 4, Tarek Asselah 5, Ramon Planas-Vila 6, Marcos Pedrosa 7, Guy Neff 7, Ronald D’Amico 7, Greg Ball 7, Juan Carlos Lopez-Talavera 7, Nancy Reau, MD 8
1. Liver Institute of Virginia, Bon Secours Health System, Richmond, VA; 2. Thomas E. Starzl Transplantation Institute, Pittsburgh, PA; 3. Medical Associates Research Group, San Diego, CA; 4. Liver Unit, Hospital Clinic, CIBERHID, IDIBAPS, Barcelona, Spain; 5. Centre de Recherche sur l’Inflammation, Inserm UMR 1149, Université Paris Diderot, APHP Hôpital Beaujon, Clichy, France; 6. Hospital Germans TriasPujol, CIBERehd, Badalona, Spain; 7. AbbVie Inc., North Chicago, IL; 8. University of Chicago Medical Center, Chicago, IL

Results: 2053 patients were enrolled and dosed with 3D+/-RBV in phase 3 trials. 410 patients (20.0%) were receiving a concomitant ARA; of these, 308 (15.0%) were receiving a PPI. SVR12 rates were 95.9% (393/410, 95% CI: 93.5-97.4) among patients receiving an ARA and 96.3% (1583/1643, 95% CI 95.3-97.2) among patients not receiving an ARA. SVR12 rates were 95.1% (293/308, 95% CI: 92.1-97.0) among patients receiving a PPI and 96.4% (1683/1745, 95% CI 95.5-97.2) among patients not receiving a PPI. SVR12 rates were also comparably high irrespective of whether patients were receiving a concomitant ARA/PPI by treatment regimen (3D+RBV or 3D), and among patients receiving a standard or high dose of PPIs (Figure 11).

Figure 11.

<table>
<thead>
<tr>
<th>SVR12 by baseline factors, n/N (%)</th>
<th>GT1a with no cirrhosis 3D+RBV for 12 weeks</th>
<th>GT1a with cirrhosis 3D+RBV for 24 weeks</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>569/593 (96)</td>
<td>115/121 (95)</td>
<td>684/714 (96)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>353/370 (95)</td>
<td>84/89 (94)</td>
<td>437/459 (95)</td>
</tr>
<tr>
<td>Female</td>
<td>216/223 (97)</td>
<td>31/32 (97)</td>
<td>247/255 (97)</td>
</tr>
<tr>
<td>Treatment-naïve</td>
<td>403/420 (96)</td>
<td>53/56 (95)</td>
<td>456/476 (96)</td>
</tr>
<tr>
<td>Prior PegIFN/RBV non-response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>47/50 (94)</td>
<td>13/13 (100)</td>
<td>60/63 (95)</td>
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<tr>
<td>Partial response</td>
<td>36/36 (100)</td>
<td>10/10 (100)</td>
<td>46/46 (100)</td>
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<tr>
<td>Null response</td>
<td>83/87 (95)</td>
<td>39/42 (93)</td>
<td>122/129 (95)</td>
</tr>
</tbody>
</table>

Conclusions: In phase 3 trials of 3D+/-RBV in HCV genotype 1-infected patients, SVR12 rates were high regardless of ARA/PPI use or PPI dose. These data support the co-administration of 3D with ARAs including PPIs.

UEGW 2015. P0668. Sustained Virologic Response Rate of 96% of HCV Genotype 1A-Infected Patients Treated with Ombitasvir/Paritaprevir/R and Dasabuvir with Ribavirin
Heiner Wedemeyer, Paul Pockros, Samuel S Lee, Edward Gane Christophe Moreno, Simone Strasser, Victor De Ledinghen, Andreas Maseron, Wangang Xie, Roger Trinh, Yan Luo, Fernando Tatsch, Vinod Rustgi

Results: Among 714 HCV GT1a-infected patients treated with the label-recommended 3D+RBV regimen, 64% were male, 33% were treatment-experienced, 17% had cirrhosis, and 85% had baseline viral loads ≥800,000 IU/mL. Sustained virologic response was achieved in 96% (95% CI, 94-97%) of patients (Figure 12). Response rates were similar regardless of the presence or absence of cirrhosis (95 versus 96%, respectively). Virologic failure was observed in 18 (2.5%) patients, 5 (0.7%) with on-treatment breakthrough and 13 (1.8%) with post-treatment relapse. Seven patients (1.0%) discontinued treatment due to AEs, 4 of whom subsequently achieved SVR12. The most common AEs were fatigue (41%), headache (33%), nausea (23%), and insomnia (17%). Grade 3+ laboratory abnormalities were infrequent for ALT (0.9%), AST (0.6%), haemoglobin (0.3%), and total bilirubin (2.8%).

Figure 12.

<table>
<thead>
<tr>
<th>n/N (%)</th>
<th>3D+RBV</th>
<th>3D</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant ARA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>321/332 (95.8)</td>
<td>72/75 (96.0)</td>
<td>393/410 (95.9)</td>
</tr>
<tr>
<td>No</td>
<td>1170/1213 (96.5)</td>
<td>413/430 (96.0)</td>
<td>1583/1643 (96.3)</td>
</tr>
<tr>
<td>Concomitant PPI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>238/250 (95.2)</td>
<td>55/58 (94.8)</td>
<td>293/308 (95.1)</td>
</tr>
<tr>
<td>No</td>
<td>1253/1298 (96.5)</td>
<td>430/447 (96.2)</td>
<td>1683/1745 (96.4)</td>
</tr>
<tr>
<td>PPI dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard*</td>
<td>162/169 (95.9)</td>
<td>37/39 (94.9)</td>
<td>199/208 (95.7)</td>
</tr>
<tr>
<td>High</td>
<td>52/54 (96.3)</td>
<td>14/15 (93.3)</td>
<td>66/69 (95.7)</td>
</tr>
</tbody>
</table>

*Standard dose was ≤20 mg for omeprazole and esomeprazole, ≤30 mg for dexlansoprazole, ≤15 mg for lansoprazole, and ≤40 mg for pantoprazole.

Conclusions: In HCV GT1a-infected patients, the label-recommended 3D regimen with RBV achieved high SVR12 rates, including historically difficult-to-cure subgroups of patients with prior PR null response and/or cirrhosis.
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.

The vision of the CARE Faculty is to share opinions and update Canadian specialists with news and developments from key conferences framed in a Canadian perspective.

The mission of the CARE Faculty is to enhance medical education, with the explicit goal of improving patient outcomes.