Trends-in-Medicine

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by Lynne Peterson

SUMMARY

Diet is effective in **eosinophilic esophagitis**, but almost impossibly difficult for patients to maintain. Biologics may offer the best hope, but experts weren't particularly enthusiastic about any of them yet.

♦ Both XenoPort's arbaclofen placarbil and AstraZeneca's AZD-3355 look promising as add-on therapy to a PPI for **GERD**.

♦ Salix's Xifaxin (rifaximin) is already being used off-label for **hepatic encephalopathy**, but cost – not insurance reimbursement – is a major issue, and general gastroenterologists do not believe that FDA approval will significantly increase their use of it. ♦ Data showed that Forest Labs/ Ironwood's linaclotide is effective in **IBS**, but the clinical significance of the effect is still somewhat uncertain. ♦ Several less invasive or non-invasive approaches to **bariatric surgery** are being tested, and this has been accompanied by a flattening to slight decrease in use of banding procedures.

Trends-in-Medicine
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DIGESTIVE DISEASE WEEK (DDW)

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DDW brings together experts in gastroenterology, hepatology, endoscopy, and gastrointestinal surgery. DDW this year conflicted with the American Society of Clinical Oncology meeting, so this is a look at new therapies for only a few selected conditions discussed at DDW – eosinophilic esophagitis, gastroesophageal reflux disease (GERD), hepatic encephalopathy, irritable bowel syndrome, and bariatric surgery.

EOSINOPHILIC ESOPHAGITIS (EoE)

What causes EoE? Dr. David Katzka of the University of Pennsylvania argued that EoE:

- **Is an allergy-based disease.** He said, "There is often an association with food allergies. Allergy seems to be the rule with EoE patients…Clearly, allergy, if not ***the*** player, is one of the major players in the development of EoE." In particular peanuts, oats, barley, and rice can be triggers, and withdrawal of those foods can be effective in EoE. Thus, medications effective in allergy can also be helpful in EoE, such as topical steroids (fluticasone).
- **Has a genetic predisposition.** Dr. Katzka said, "Most allergies are genetic, inherited, and related to an irregularity in the immune system, but the specific allergen is not…A gene can be identified in close to 50% of children of a parent with EoE. The gene is not just a marker; it is a major player in the generation of this disease as well…The hope is that we could use a genetic test to differentiate EoE from reflux, but there is still some overlap, so the test is not ready for prime time."
- **Is associated with GERD but may not be due to GERD.**

Diagnosis. Dr. Glenn Furuta of the University of Colorado School of Medicine, Chair of the Eosinophilic Disease Study Group for the World Congress of Pediatric Gastroenterology, said, "This is a good time to get into this field." He said the "magic number" of eosinophil count used to diagnosis EoE is highly inaccurate, urging standardization on how the numbers are arrived at and use of other measures, "There is no correlation between the (eosinophil) numbers and symptoms, making us wonder if we should get biopsies. This raises a very important point requiring further study, but today all we have are the numbers (or eosinophil count)...Numbers are important because we are at the infancy of this disease…We need to define the etiology, biomarkers, prevention, and prophylaxis."

Other possible diagnostic measures include:

- **Edema** – though this is a very non-specific finding.
- **Inflammatory infiltrate** – mast cells and markers of IgE.
- **Response to injury** – with EoE there is increased trichrome staining.
- **Biomarkers** – such as IL-1, cytokines-eotaxin-3, fibroblast growth factor-9, and eosinophil peroxidase (anti-EPO antibody) immunohistochemical staining/scoring system measuring both number and granulation that was developed by the Mayo Clinic, Scottsdale.

Therapies. Therapies described by speakers included:

- **Diet.** Diet can be an extremely effective therapy, with a very quick response, but it isn't an easy diet. For example, an elemental diet can result in a 90%+ improvement. The problem is that diet is extremely if not impossibly difficult to follow. A six-food elimination diet can result in about a 70% improvement (and even better in pediatric patients), but it is also difficult to maintain over time. A speaker said, "In adults, the 6-food diet has had very encouraging results, with a 52% near complete response and a 33% complete response…There was recurrence when foods were re-introduced. Dietary therapy is a very viable option in this condition."

- **Topical steroids pumped into the mouth and swallowed.** This can result in 75%-90% improvement, but it also tends to lead to relapse. A speaker said there has been an "explosion" of research in this area, and all the studies confirmed the effect. "There is good symptom response across all the studies; there is a dramatic response. But the studies were all retrospective or open-label and with relatively short treatment periods. More recently, there were three randomized trials, but in all these there was also symptom response and eosinophil counts either markedly decreased or normalized." There have also been some recent reports of herpes esophagitis with topical steroids.
  - **Budesonide.** This has been delivered in the sugar substitute Splenda, but Meritage Pharma has been granted orphan drug status by the FDA for its oral viscous budesonide for the treatment of pediatric EoE. A 36-patient randomized trial found that swallowing nebulized budesonide 1 mg BID was effective "in the vast majority of patients" over 15 days, but a 50-week maintenance trial is still on-going.
  - **Fluticasone.** A study at 4400 µg BID vs. placebo for three months showed ~50% histologic remission with fluticasone vs. ~18% with placebo, but a speaker pointed out that "fully 50% of patients did not respond." A study of patients previously treated with fluticasone found that 91% reported recurrent dysphagia (difficulty swallowing) with a mean time to recurrence after treatment of 9 months.

- **Oral (systemic) steroids.** The problem is that after treatment is stopped, symptoms recur and eosinophil counts go up. A comparison of oral prednisone vs. topical fluticasone showed patients with both treatments were almost symptom free at Week 6 and about 50% in both groups were symptom free at Week 24.

- **Biologics.** These include anti-IL-13, anti-IL-5 (**GlaxoSmithKline's Bosatria, mepolizumab**), and Johnson & Johnson's Remicade (infliximab). A speaker said the results with Remicade so far are "not impressive. There is no consistent response. There were two patients with a minor response but endoscopically no change." Mepolizumab was mentioned in passing, but **Cephalon's anti-IL-5, reslizumab**, was not mentioned directly at all.

- **Leukotriene antagonists.** These were described as relatively well tolerated, but, as the dose is pushed, nausea and myalgias have been reported.

- **Mast cell stabilizers** like cromolyn. A speaker said this doesn't seem to work.

- **Immunomodulators** like azathioprine. This is reported to be effective, but patients relapse when it is stopped.

- **Endoscopic therapy (dilation).** A speaker said there have been some concerning data about "relatively high levels of perforations, tears, and chest pain leading to hospitalization…There is a fairly high rate of symptomatic improvement…More recent data say there might be less risk in the modern era – no perforations, a few tears, and much lower chest pain, so maybe these results are a little more encouraging."

Relationship of GERD to EoE. A speaker said that, simplistically, proton pump inhibitor (PPI) responders have GERD; PPI non-responders have EoE, but there may be some acid-response form of EoE. The question is how are GERD and EoE related.

Dr. Stuart Spechler, chief of GI at Dallas VA Medical Center, said, "If EoE does not protect against GERD and vice versa, then you would expect ~20% of adults with EoE also to have GERD. It seems very unlikely one protects from the other… The American Gastroenterological Association (AGA) Institute's definition (of EoE) is untenable because it would exclude the patients with pathological GERD…EoE and GERD may be related, so a trial of PPI therapy is recommended for patients with EoE even though the disease appears clear-cut…It is possible that EoE can respond to PPI therapy …The hypothesis is that acid reducing medications might contribute to the development of EoE…PPIs have been the mainstay for GERD patients for two decades and have an excellent track record for safety…so the mere association (between GERD and EoE) doesn't establish cause and effect. And by no means is it clear that PPIs lead to food allergy, but this is an interesting theory that deserves further study…I strongly encourage the AGA Institute to change the definition (of EoE) from a primary disorder of esophagitis characterized

by upper GI symptoms and an esophageal biopsy showing ≥15 eosinophils/hpf (high power fields) to one in which GERD may have a role."

Dr. Spechler added, "It is hard to know the role of PPIs (in EoE)…but children now get treated with PPIs very frequently in the community…so a lot of kids are getting exposed, and it will be very difficult to tease out (any effect)…It is very hard for me to think we missed this disease in the past…It does seem to be a new disorder. I do think it is much more common since the 1990s." Asked if he would still treat EoE patients with a PPI, Dr. Spechler said, "Yes. We have no proof for this hypothesis, but it is also very clear that the esophagus responds very well to PPIs. I would still advocate treating these patients."

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

GERD develops when the contents of the stomach reflux into the esophagus, causing troublesome symptoms (e.g., heartburn and regurgitation) and/or complications. The standard therapy for GERD is a PPI, but studies have found that 20%-30% of patients still have persistent symptoms while on a PPI. Thus, companies are looking for new drugs that will help these patients.

ASTRAZENECA's AZD-3355, a gaba$_B$ agonist

Phase IIa data on this drug, which is likely to compete with XenoPort's arbaclofen placarbil, were presented in a series of posters at DDW. Researchers concluded that these data, which included a 244-patient, double-blind, randomized, placebo-controlled, multicenter, European, proof-of-concept study, warrant continued development. The key findings in the presentations were:

- Adding AZD-3355 to a PPI in GERD patients resulted in a 35% reduction in reflux episodes 0-24 hours after dose vs. placebo.
- Adding AZD-3355 to a PPI resulted in more symptom-free days for heartburn (36% vs. 21%) and regurgitation (37% vs. 23%) in patients with persistent symptoms despite daily PPI therapy.
- The most common adverse events were diarrhea, paresthesia, nausea, and fatigue.
- A pharmacokinetic (PK) study of three doses – (A) 100 mg modified-release (MR) capsule with a dissolution rate of 50% in 4 hours, (B) 100 mg MR capsule with a dissolution rate of 100% in 4 hours, and (C) a 100 mg oral solution – found that food intake did not significantly alter C_{max} for the capsules, but there was a slight decrease in C_{max} with the solution formulation. T_{max} showed a small numerical increase with both the solution formulation and the MR "A" capsule when taken with food.
- Half-life is 1.9-11.9 hours.
- A healthy volunteer study in 30 men concluded that AZD-3355 is bioequivalent to esomeprazole (AstraZeneca's Nexium).

Asked why doctors should choose AZD-3355 over baclofen or the XenoPort drug, an AstraZeneca researcher said, "There are differences between the peripheral and central effects of baclofen. We are mostly peripherally acting. Baclofen works because of its central effects, so the (major) side effect is lethargy." Another researcher pointed out, "Baclofen doesn't cross the blood brain barrier well; just fragments cross. And the therapeutic index of baclofen is not good. We wanted a gaba$_B$ with a better therapeutic index. AZD-3355 plateaus at around 50% at the low doses…It is extracellular action that causes the CNS (central nervous system) side effects (with baclofen). With baclofen, all the effect is in the CNS, even at low doses. I believe baclofen works centrally, not peripherally."

What's next? Researchers said a multidose Phase IIb trial has not yet started but has to be done before moving to a Phase III trial. The Phase IIb will also look at clinical endpoints. In

AZD-3355 in PPI-Refractory GERD Patients

Measurement	AZD-3355 n=21	Placebo n=21
Reflux episodes	-16 vs. placebo	---
Weekly acidic reflux	-6.5 vs. placebo	---
Weekly alkaline reflux	-0.64 vs. placebo	---
Number of symptomatic reflux episodes 24 hours following Dose 1	Nss difference	
Headache	8 patients	11 patients
Paresthesia (transient)	5 patients	3 patients
Nausea	2 patients	5 patients

AZD-3355 Add-on Therapy in PPI-Refractory GERD Patients

Measurement	AZD-3355 n=122	Placebo n=122	p-value
Primary endpoint: Response to treatment (≤1 24-hour period with heartburn or regurgitation of ≤mild intensity during the last 7 days of treatment)	16%	8%	0.026
Post hoc analysis: Response to treatment (≤1 24-hour period of heartburn or regurgitation of ≤very mild intensity during the last 7 days of treatment)	34%	15%	N/A
Symptom-free days during 4-week treatment period			
Heartburn	36%	21%	---
Regurgitation	37%	23%	---
Heartburn and regurgitations	19%	10%	---
Adverse events			
Any adverse event	45%	37%	---
Diarrhea	11%	3%	---
Paresthesia (transient)	8%	5%	---
Nausea	7%	3%	---
Fatigue	6%	6%	---

studies so far, a 65 mg BID dose was used, based on animal studies. A researcher said, "That is not the optimal dose. We could and should go higher."

AZD-3355 does not work in true PPI non-responders, but a researcher said it does work in partial responders.

There are no plans to develop AZD-3355 for spasticity because it doesn't act centrally. A researcher said, "We are not interested in spasticity; it is a small market."

XENOPORT's arbaclofen placarbil (AP, XP-19986)

Arbaclofen placarbil (AP) is a prodrug of the R-isomer of baclofen in a sustained release tablet designed for either QD or BID dosing. At DDW, Dr. Nimish Vakil of the University of Wisconsin School of Medicine and Public Health presented data from a randomized, double-blind, placebo-controlled, parallel group, Phase IIa trial of AP monotherapy in 156 patients with symptomatic GERD.

- The trial missed the primary endpoint, showing no statistically significant difference overall in heartburn events/week vs. placebo at any of the 4 doses tested (20 mg QD, 40 mg QD, 60 mg QD, and 30 mg BID).
- There was no apparent dose response curve.
- However, a preplanned secondary analysis of PPI-naïve and PPI-responder patients found:
  - A greater reduction in heartburn events/week and more complete relief of GERD symptoms in PPI-naïve patients with AP (-55.4%) vs. PPI-responders (-22.5%).
  - PPI-responsive patients showed a statistically significant ($p<0.05$) reduction in regurgitation events/week at Week 4 but only at the 30 mg BID dose.

This trial raises a number of issues/questions:

- *How much weight can you give to secondary analyses in a trial that fails its primary endpoint?* XenoPort CEO Ron Barrett said, "This is a Phase II study, and that is about learning the right patient population. The naïve patient population probably did not have GERD even though they had symptoms. The population we are most interested in, the relevant population, is those who are on a PPI and still have a symptom and at least a partial response to a PPI…Our intention in Phase III is not to do monotherapy but an adjunctive therapy study. We think that is the best way to use this drug. PPIs work; they are safe. We are really interested in patients still symptomatic despite being on a PPI."
- *How reliable are patient recorded symptoms?* In this case the symptoms were recorded by patients in electronic diaries.
- *Are there subgroups of patients who had better responses?* Barrett said, "These were all PPI responders. All of these patients had to have a response to a PPI." However, he suggested that AP may be particularly useful as monotherapy in patients taking Plavix (Sanofi-Aventis, clopidogrel) where PPIs are contraindicated since AP is not metabolized by the CYP450 pathway as PPIs are.
- *Is the side effect profile significantly better than baclofen?* Dr. Vakil said, "This (trial) doesn't give us direct evidence…We all have clinical experience with baclofen. It is my personal impression that there is a difference…

Phase IIa Dose-Ranging Trial of Arbaclofen Placarbil at Week 4

Measurement	Placebo n=31	Arbaclofen placarbil 20 mg QD n=30	40 mg QD n=33	60 mg QD n=32	30 mg BID n=30
Change in heartburn events/week from baseline	~ -6	(p=Nss)	(p=Nss)	***Primary endpoint #1:*** (p=Nss)	
			Primary endpoint #2: (p=Nss)		Nss
Safety					
>1 treatment-related adverse event	61.3%	43.3%	45.5%	68.8%	63.3%
Withdrawal due to treatment-related adverse event	6.5%	0	3%	9%	10%
Treatment-related serious adverse events	0	0	0	0	0
Somnolence	3%	3%	12%	16%	13%
Dizziness	10%	10%	6%	13%	20%
Headache	6%	3%	6%	13%	13%
Fatigue	6%	7%	6%	6%	13%
Nausea	6%	0	6%	6%	17%
Myalgia	0	0	3%	0	7%
Vomiting	3%	0	6%	3%	0
PPI-responsive patients					
Complete relief of heartburn (completers)	7%	21% (p=Nss)	29% (p=Nss)	35% (p=Nss)	64% **(p<0.05)**
Complete relief of heartburn (ITT)	6%	21% (p=Nss)	28% (p=Nss)	30% (p=Nss)	50% **(p<0.05)**
Complete relief of regurgitation (completers)	13%	53% **(p<0.05)**	39% (p=Nss)	47% **(p<0.05)**	58% **(p<0.05)**
Complete relief of regurgitation (ITT)	12%	53% **(p<0.05)**	35% (p=Nss)	41% (p=Nss)	47% (p=Nss)
Complete relief of heartburn and regurgitation (completers)	6%	16% (p=Nss)	37% (p=Nss)	25% (p=Nss)	50% **(p<0.05)**
Complete relief of heartburn and regurgitation (ITT)	6%	16% (p=Nss)	33% (p=Nss)	22% (p=Nss)	39% (p=Nss)

Especially at lower doses, we do not see the kind of symptoms that we see with baclofen. What the mechanism is is hard to say. There is a hypothesis that blood levels fluctuate…My impression is the side effect profile is somewhat lower with this (AP)." Barrett said AP has pretty much the same side effects as baclofen, but at a lower incidence level, "We are pleased that the level is manageable – 10%-20% at the highest dose. The severity is mild-to-moderate. Very few patients dropped out of the study. The completion rate was 90%."

- *Why did PPI-naïve patients have a much different response?* Since PPIs work in most naïve patients, why doesn't AP? Dr. Vakil suggested it is because the PPI-naïve patients are more difficult to identify, less likely to have a response, and a far more heterogeneous group. On the other hand, he said that PPI-responders are more similar to GERD patients, so treatments are more likely to work there, but he added, "That's pure speculation, of course."
- *Are there CNS side effects other than somnolence?* Yes, there is some dizziness and fatigue, but that was described as occurring "in the teens or single digits…and only at the highest doses."
- *Can patients "feel" when they are on arbaclofen?* Barrett said, "They have a reduction in symptoms…In principle, the adverse events can, in some cases, indicate to the patients that they may be on the drug, but the incidence level can't explain the results."
- *Is XenoPort looking to license this to a big pharma?* Barrett said, "We've been talking to big pharma about this program all along. When and if we partner, that will be determined by the progress we make and the business relationships offered to us."

Asked about potential advantages of AP over AstraZeneca's AZD-3355, Barrett said, "There are animal data that show to get the maximal effect on reflux you have to have central activation of the $gaba_B$ receptors…Our compound can activate both peripheral and central $gaba_B$ receptors while their compound is designed only to activate peripheral receptors… They believe that will lead to better tolerability, but I don't think the data distinguish their compound over our compound …but it is still early for both."

The next step for AP in GERD is for a Phase IIb trial as adjunct therapy to a PPI, which the company hopes to begin later this year. The dose for that Phase IIb trial has not yet been determined, and Barrett would not say how long the trial will be, though he noted that typically that type of trial is 4-8 weeks. Barrett commented, "The top dose here (30 mg BID) would be acceptable in terms of the adverse event profile. Remember, these patients have no good treatment option currently." Both the Phase IIb and the Phase III trial are planned as add-on therapy to a PPI, not as monotherapy, so will the patients in these trials be true incomplete PPI-responders? That is likely to be a sticky issue in the final analyses, particularly by FDA reviewers who may wonder if it is the PPI working, not AP.

XenoPort is in discussions with the FDA about endpoints and study design. Barrett commented, "One can't necessarily use the precedent of PPIs to know how to develop this drug because those drugs treat symptoms through acid suppression. Our drug works through a different mechanism. We can affect not only heartburn symptoms but also regurgitation, which PPIs have not used as an endpoint in the past."

Asked about FDA requirements for long-term safety data, Barrett said, "In order to meet the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) guidelines for chronic therapy, we need >100 patients for a year, >300 patients for 6 months, and >1,500 total patients, so our development program contemplates meeting all that." XenoPort is not following the Phase IIa patients, so the long-term data will need to come from either the Phase IIb or Phase III trials.

HEPATIC ENCEPHALOPATHY

SALIX's Xifaxin (rifaximin)

Dr. Thomas Boyer of Tucson AZ offered "Clinical Pearls for the Diagnosis and Management of Hepatic Encephalopathy," and he was extremely negative about rifaximin.

Pathogenesis. Dr. Boyer said the pathogenesis of hepatic encephalopathy "remains unclear," but the working hypothesis is that it is related to high serum ammonia levels, so all treatment is aimed at lowering ammonia levels. However, he noted that there is a huge amount of variability in ammonia levels in either arterial or venous blood in these patients, "Patients with no hepatic encephalopathy may have the same blood ammonia level as severely impaired patients with Grade 3 hepatic encephalopathy…And most labs don't really know how to draw blood ammonia levels." He recommended using a blood ammonia level to diagnose hepatic encephalopathy "only if you are confused about the cause of a coma," adding that "using ammonia in the absence of a mental status exam is of no use."

Types. Dr. Boyer identified three types of hepatic encephalopathy:

- Type A.
- Type B – which he said is extremely rare except in dogs.
- Type C – which can be further divided into: episodic, persistent, and minimal. The precipitating factors for this type of hepatic encephalopathy are:
  - GI bleeding.
  - Infection.
  - Hyponatremia.
  - Dietary.

- Sedatives/hypnotics/pain medications – which is increasing. He said, "It seems every patient with cirrhosis also has low back pain and is taking oxycodone, which contributes to the encephalopathy."
- Constipation. He said, "Many patients hate lactulose, stop taking it, and get constipated."
- Renal insufficiency. He noted, "Once renal insufficiency occurs, the problems with managing hepatic encephalopathy go up significantly."

Type C has 4 stages: trivial lack of awareness, lethargy, somnolence to semi-stupor, and finally coma. About 50% of patients with minimal encephalopathy develop overt hepatic encephalopathy within 3 years. Dr. Boyer said, "The new kid on the block is minimal encephalopathy…The clinical manifestations of minimal hepatic encephalopathy can be quite trivial – complaints of decreased energy, reversal of day/night sleep cycle, or impaired cognition or motor skills. On exam, they may have blunted affect, difficulty in doing performance tasks, RAM (rapid alternating movements), but not infrequently the same as normal…Minimal hepatic encephalopathy is common – far more common than any of us would like to believe."

To make the diagnosis of hepatic encephalopathy, doctors have to do more than just take a blood ammonia level, which can vary considerably. They can:

- Send patients for a formal neuropsychological assessment – which he said most doctors don't do.
- Do a short neurophysiologic battery (trails test). He said this is probably the best option for identifying patients.
- Give a computerized test (reaction time, flicker test).
- Do neurophysiological tests.

The impact on daily life is the biggest issue with hepatic encephalopathy, Dr. Boyer said, adding, "Clearly they are at increased risk of car accidents, and it is very difficult to convince them to stop driving, which puts you in an interesting bind if you make this diagnosis. And it can impact their work performance."

Treatment options. Dr. Boyer reviewed the treatment options, concluding that none are very good.

- **Lactulose, a non-absorbable disaccharide** – "The studies are terribly underpowered, with a small number of patients. The benefit of lactulose is not clear. It is still standard-of-care, but the data are poor. It is effective in minimal encephalopathy. One of the approaches to patients with minimal hepatic encephalopathy or symptoms suggestive of that is to place them on lactulose and see if they improve – a sort of proof by treatment."
- **Neomycin** – "This is misused. People give 3-4 grams, and you should not use >2 grams."
- **Rifaximin** – "There is really no clear advantage of rifaximin compared to other antibiotics in the treatment of hepatic encephalopathy other than one trial vs. neomycin where the blood ammonia level fell more with rifaximin…In the meta-analysis there is no advantage to rifaximin. They are equivalent therapies…For prevention of hepatic encephalopathy with rifaximin, again they were small studies…and no evidence of benefit in prophylaxis, at least in this small trial…It is difficult to justify the use of rifaximin when other agents are less expensive. The major problem with rifaximin is cost. Frequently insurance companies refuse to pay, and if that is the case, I suggest going to something like neomycin."

Comparison of Clinical Efficacy of Rifaximin vs. Lactulose

Trial	Rifaximin	Lactulose	Relative Risk
Mas A et al.	40/50	41/53	1.03
Massa P et al.	20/20	20/20	Not estimable
Giacomo F et al.	20/20	16/20	1.25
Loguercio C et al.	8/14	2/13	3.71 favoring lactulose
Pak et al.	27/31	21/22	0.88
Total patients	**135**	**128**	**1.08**
Total events	115	100	---

- **Protein restriction** – "No one has ever shown this to be effective."
- **Probiotics** – "These are as good as lactulose in treating hepatic encephalopathy."

Cost. Dr. Boyer said the cost of rifaximin is a big issue, "If you leave patients with hepatic encephalopathy untreated… they generate a lot of expense because they are in the hospital all the time…and that doesn't include the financial cost of the patient not being able to work…Lactulose improves quality of life and reduces the cost of caring for the patient…so it is clearly of some benefit. (The cost of) neomycin is about the same as lactulose. Rifaximin as a primary therapy comes at a huge increase in cost that is greater than if you left the patient untreated, but if you take patients who fail lactulose and add rifaximin to that combination, then the incremental cost effectiveness is not very great...So, to me this is the role of drugs like rifaximin or neomycin – additive, not primary therapy."

DDW physician perspective

Numerous gastroenterologists and liver experts at DDW were asked how they treat hepatic encephalopathy. General gastroenterologists typically treat only a handful of hepatic encephalopathy patients a year (<10), and about a quarter of these are on rifaximin already, with few reimbursement complaints. A few doctors said they refer all these patients to a liver specialist. Those who do treat hepatic encephalopathy patients said they primarily prescribe lactulose and, to a lesser extent, rifaximin as well as neomycin and, occasionally, other poorly absorbed antibiotics. Perhaps surprisingly, reimbursement was not a big complaint.

Other comments by these general gastroenterologists about rifaximin included:

- *Ohio:* "Cost is an issue. Not all insurance companies currently support its use, so it is really more or less being used now when lactulose fails. Lactulose is very cheap… Some patients can't tolerate lactulose. I give rifaximin to patients who fail lactulose."
- *New York #1:* "Lactulose has a lot of side effects…If it were my choice, I would use rifaximin over lactulose."
- "It is not revolutionary, but it is a little 'neater' than lactulose, and the nurses like it better."
- *Virginia:* "I use mostly lactulose and antibiotics – depending on the infection, if it is caused by an infection. I've looked at the rifaximin data here, which is to be published soon in ***Gastroenterology***, and it looked promising. I will read about it. Cost is not an issue if I believe it works, but there is no real problem with lactulose. I give it (lactulose) by tube if the patient doesn't take the pills."
- *California #1:* "I refer the few hepatic encephalopathy patients I get to liver specialists."
- *New York #2:* "If patients don't respond to lactulose, they get rifaximin…I treat 5-10 hepatic encephalopathy patients a year, and about 25% are on rifaximin. Reimbursement is never an issue. Compliance is good with both lactulose and rifaximin. When I give rifaximin, it is for indefinite, chronic use."
- *California #2:* "I have about 10 hepatic encephalopathy patients. I start with lactulose, and if it is effective, then I continue it. If it isn't effective or the patient can't tolerate it, then I use rifaximin, so about one-third of my patients get rifaximin. Insurance covers rifaximin…There is a small risk of side effects with neomycin, but you have to look at the cost of rifaximin vs. neomycin…Compliance with rifaximin is better than with lactulose; it's as good as any medication in hepatic encephalopathy patients… When I give rifaximin, it is until the patient no longer has symptoms – until transplant or a GI bleed, etc. Rifaximin is usually, but not necessarily, a chronic therapy…Even if rifaximin were FDA-approved for hepatic encephalopathy it wouldn't be first-line because of cost and effectiveness."
- *Indiana:* "I have 6-7 hepatic encephalopathy patients a year, but only about half of those need treatment. Currently, I have one on lactulose and two on rifaximin. In the clinic, about 5%-10% of patients get rifaximin. Lactulose is very, very good, and it is inexpensive. Neomycin works well, but the concern is resistance. Rifaximin is very expensive…When I prescribe rifaximin, it is generally for two weeks, and then I re-evaluate the patient (give a drug holiday). So, I tend to do one week on and one week off. Once a patient has hepatic encephalopathy, survival is <1 year…Compliance with lactulose is pretty good because the patients tend to have more supervised care – family – so someone gives it and monitors that the patient is taking it. But patients complain all the time about it…With rifaximin, about 50% of the time, the patient or pharmacy calls and says, 'Are you nuts prescribing something this expensive and BID.' At that high a cost, they cut the dose…Adherence is an issue with both lactulose and rifaximin."

IRRITABLE BOWEL SYNDROME (IBS)

An IBS Task Force has been formed to develop a consensus statement on IBS. Dr. Eamonn Quigley, president of the World Gastroenterology Organisation (WGO), president of the American College of Gastroenterology, and past-president of the American Gastroenterological Association (AGA), said the Task Force wants to establish a global definition of IBS and a new approach to IBS management. The Task Force met for the first time during DDW, and the next step will be a presentation of its conclusions at the Gastro 2009 meeting in London in November 2009. Dr. Quigley said, "That document will address not only the current status of where we are but where the gaps in knowledge are…We feel this is an area that is long overdue for emphasis. We feel that it is important not only that the issue of IBS and the impact of IBS be recognized in the U.S., Canada, and Europe, but that the global dimension be understood. The literature is incredibly dominated by data from Europe and North America, but we now know that IBS is almost as common everywhere in the world."

Dr. Quigley called IBS an unmet medical need that is finally getting the attention he believes it deserves, "Until recently we didn't have a lot of research in this area…It was an under-researched area. IBS was regarded by the medical community as a minor complaint…Pain and disruptions in bowel habits are the main symptoms, but the classic patient can fluctuate between diarrhea and constipation…Drug development has been hampered by a lack of understanding of the basic pathophysiology of the disease or the development of drugs that are effective but not sufficiently specific…Ten percent of adults have IBS-like symptoms, but the majority of them never see a doctor. Industry made a mistake. This is an enormous population, but they went about it too simply."

Several IBS drugs have been introduced to the market and then removed, such as Johnson & Johnson's Propulsid (cisapride) and Novartis's Zelnorm (tegaserod) because of side effects. Dr. Quigley said this has made regulatory officials leery of IBS drugs, and he believes regulatory officials don't consider IBS a serious disorder.

Examples of available therapies.

- For pain – anti-spasmodics.
- For constipation – lactulose.
- For diarrhea – loperamide.

Why emphasize IBS when there aren't good targeted drugs available yet? Dr. Quigley said the hope is that patients will

get a more appropriate assessment, "It appears a lot of these patients are inappropriately investigated in the sense that they get too many tests…Radiation exposure in IBS is substantial, and that is increasing with more access to CT (computed axial tomography). And there is very little data to support the use of CT in IBS. It is of no value."

DRUGS IN DEVELOPMENT FOR IBS

FOREST LABORATORIES/IRONWOOD PHARMACEUTICALS' linaclotide

Linaclotide is a first-in-class, minimally-absorbed, guanylate cyclase-C agonist that reduces visceral pain and promotes intestinal secretion and colonic transit. It is promising because it acts locally, not systemically, and it acts quickly – within a week or less. There were several presentations on linaclotide, but they were rehashing and slicing and dicing last year's Phase IIb trial. And experts at DDW were not convinced of the clinical significance of the linaclotide efficacy data.

Dr. Bernard Lavins of Ft. Washington PA briefly reviewed the top line safety and efficacy data from a Phase IIb trial in adults with chronic constipation that was presented at DDW last year, and he then offered new data on a quality of life analysis of that same trial. That Phase IIb trial was a 28-day, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in 304 patients. It compared four doses of linaclotide – 75 µg QD, 150 µg QD, 300 µg QD, and 600 µg QD, all administered in the morning – to placebo. The key findings were:

- The trial met the primary endpoint, showing a statistically significant decrease from baseline in the mean number of spontaneous bowel movements (SBMs) at each dose.
- Stool consistency, complete spontaneous bowel movements (CSBMs), straining, bloating, and constipation severity were all significantly improved vs. placebo.
- Adverse events were higher with linaclotide (29%-38%) vs. placebo (32%), with diarrhea 5%-14% (vs. 3% with placebo).

Quality of life data. The new quality of life data were based on the Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaire, a validated measure consisting of 28 questions in 4 categories (satisfaction, physician discomfort, worries/concerns, and psychosocial discomfort). Dr. Lavins emphasized that a 0.5 unit change from baseline at the group level constitutes the minimum for a clinically significant difference in quality of life measures.

Linaclotide did meet that hurdle in most measures, but just barely, and experts were not convinced the amount is sufficient. They pointed out that PAC-QOL uses a 5-point scale, a 0.5 point difference is minimally significant, and the difference was never >1.0. Dr. Anthony Lembo of Boston MA, a linaclotide investigator, said, "The 0.5 does indicate there is a difference, but whether that is clinically meaningful of not I can't tell you." Dr. Quigley agreed the benefit is small, but added, "It could be clinically meaningful for ***some*** patients…Within the large numbers (with IBS) we need to look at responders. Among responders, there may be a bigger benefit. And that may be what we've failed to do in the past – better select patients and target patients more effectively."

However, Dr. Lavins defended the results. He said, "When we looked at the data (on patients who were responders with a >1 unit change from baseline, we found)…where the group starts and ends up is determined by where they started at baseline. Where patients are bad, there is more room to improve. There may have been a potential floor effect on how much improvement you can get for the population."

Post hoc time-to-treatment-effect analysis. Both orally and in a poster, Dr. Lembo presented the results of a *post hoc* analysis of the time to onset of the linaclotide treatment effect on IBS-C (IBS with constipation) symptoms in patients in the

Correlation of PAC-QOL with Linaclotide to Other Efficacy Assessments

PAC-QOL score	PAC-QOL subscores			
	Constipation severity	CSBM rate	Straining	Bloating
Overall	0.49-0.64	0.38-0.54	0.41-0.58	0.41-0.51
Psychosocial discomfort	0.41	0.29	0.34	0.35

Quality of Life Results with Linaclotide

PAC-QOL change from baseline	Placebo n=68	Linaclotide				
		75 µg QD n=59	150 µg QD n=56	300 µg QD n=62	600 µg QD n=59	Notes
Overall	-0.41	-0.72 (p<0.05)	-0.80 (p<0.001)	-0.67 **(p=Nss)**	-0.83 (p<0.001)	300 µg dose not significant
Satisfaction	-0.62	-1.36 (p<0.01)	-1.48 (p<0.001)	-1.34 (p<0.01)	-1.49 (p<0.001)	All doses significant
Physical discomfort	-0.41	-0.71 (p<0.05)	-0.86 (p<0.01)	-0.75 (p<0.05)	-0.83 (p<0.00)	All doses significant
Worries/concerns	-0.40	-0.67 **(p=Nss)**	-0.72 (p<0.05)	-0.54 **(p=Nss)**	-0.85 (p<0.01)	No dose response
Psychosocial discomfort	-0.29	-0.40 **(p=Nss)**	-0.46 **(p=Nss)**	-0.36 **(p=Nss)**	-0.42 **(p=Nss)**	No dose significant, possibly due to floor effect

Phase IIb trial. Within the first week of treatment, linaclotide significantly improved abdominal symptoms, bowel habits (CSBMs, straining, and stool consistency), and global assessments (global relief, adequate relief). However:

- >50% of linaclotide patients had an SBM within 24 hours of the initial dose vs. 37% of placebo patients.
- There was no real dose effect.
- All but the highest dose (600 µg) had a similar effect.
- The correlation between Week 1 abdominal symptoms was high (pain and discomfort, r=0.88; bloating with abdominal pain and discomfort, r=0.69 and 0.76, respectively).
- By Day 7, there is little difference for any dose of linaclotide.
- Linaclotide was well tolerated. The most common adverse event was diarrhea.

Post hoc responder analysis. Dr. Jeffrey Johnston, a linaclotide investigator, presented the results of a *post hoc* responder analysis of the placebo and 300 µg linaclotide dose (the Phase III dose), evaluating the performance and correlation of two IBS-C symptom-specific composite endpoints vs. 5 IBS global endpoints. He reported that linaclotide 300 µg showed a statistically significant treatment effect for all 7 endpoints.

In most cases, the responder rates for linaclotide were 2- to 4-fold higher than those for placebo. There was a strong correlation of each composite endpoint with all global endpoints, except IBS-SSS. The correlation among the global endpoints, with the exception of IBS-SSS, was generally very strong (r>0.6). The correlation of abdominal pain/discomfort responders with constipation responders was only fair (r=0.39). The drug was well tolerated with diarrhea as the most common adverse event.

Time to Treatment Effect with Linaclotide

Measurement	Placebo n=68	Linaclotide 75 µg QD n=59	Linaclotide 150 µg QD n=56	Linaclotide 300 µg QD n=62	Linaclotide 600 µg QD n=59
SBMs within 24 hours of initiation	~37%	50% (p=Nss)	~54% (p<0.05)	~54% (p<0.05)	~76% (p<0.001)
CSBMs within 24 hours of initiation	~8%	~25% (p<0.05)	~13% (p=Nss)	~22% (p<0.05)	~36% (p<0.0001)
Median time to first CSBM	195 hours	141 hours	112 hours	96 hours	72 hours
Patients who were weekly SBM responders in the first week of treatment	~46%	~60% (p=Nss)	~67% (p<0.05)	70% (p<0.001)	~76% (p=Nss)
Patients who were weekly CSBM responders in the first week of treatment	~13%	20% (p=Nss)	21% (p=Nss)	~32% (p<0.001)	~37% (p<0.001)
Adverse events					
Any adverse event	31.9%	35.6%	32.1%	29.0%	38.1%
Any GI adverse event	13.0%	18.6%	23.2%	12.9%	23.8%
Diarrhea	2.9%	5.1%	8.9%	4.8%	14.3%
Abdominal pain	4.3%	3.4%	8.9%	3.2%	3.2%
Flatulence	5.8%	3.4%	5.4%	3.2%	3.2%
Nausea	1.4%	3.4%	3.6%	1.6%	3.2%

Asked about efficacy, Dr. Lavins said, "Our patients love the drug and want to stay on it. When they complete our studies, they are given the option of going into a long-term safety study. A large percentage of people are going into the long-term safety study and remaining in that, which gives an indication on safety and efficacy. And the physicians love it. They like the drug and are pleased with the effect they are seeing in their patients."

Asked about the apparent lack of a dose response, Dr. Lavins said, "When we looked at dose response for the primary endpoint, we saw an increasing effect for several endpoints… such as CSBM and stool consistency…So, we were somewhat surprised there was not as dramatic a dose response effect with PAC-QOL…It might have to do with what the PAC-QOL measures. The physical discomfort subscale looks at bloating and some abdominal pain and discomfort in that, and, in our Phase III trials with linaclotide, we didn't see a dose response in those endpoints. And that may be the result of patients having a low level of severity with respect to those symptoms when they entered the study." He also pointed out that each arm of the trial was small, so it may not have been powered sufficiently.

Asked if there have been any safety signals in the ongoing long-term safety trial, Dr. Lavins said, "There have been no signals of any concern which is what you would expect with a drug that is not absorbed and acts locally."

Asked how linaclotide compares to Zelnorm, Dr. Lavins said, "It is hard to make the comparison because Zelnorm is no longer on the market, and we didn't do a head-to-head study. Zelnorm is an absorbed drug and is a serotonin receptor agonist. Linaclotide is not absorbed and has no effect on serotonin."

How big is the market for a drug like linaclotide? The prevalence of chronic constipation is pretty high; Dr. Lavins estimated 20 million Americans suffer from it. Dr. Lavins doesn't believe that any competitors are nipping on their heels. He said, "I can't even think of anyone in Phase II."

What is the status of other trials?

- One 16-week, ~600-patient Phase III trial in IBS completed enrollment in May 2009. It is likely to be finished in fall 2009, but data probably won't be presented until DDW 2010. It is testing two doses: 150 µg and 300 µg.
- Another Phase III in IBS is about to start. This will be a 26-week trial testing only the 300 µg dose.

Asked how tough the FDA is being given the history with other constipation drugs such as Zelnorm, Dr. Lavins said, "So far the (FDA) requests seem pretty reasonable in terms of their need for safety information. I think that is because our drug is minimally absorbed, basically not absorbed. At the therapeutic doses we are giving, it is not detectable in the serum." The FDA is asking for one-year safety data, and Dr. Lavins said those studies are enrolling now. He would not speculate when they would be completed, but he said the goal is to file linaclotide with the FDA in 2011.

Asked to compare the results with the 600 µg dose to the results with the 300 µg dose, Dr. Johnston said, "The 600 µg data looked just as good as the 300 µg group…It is the 300 µg dose that we are taking into Phase III, and that is based on evaluating both efficacy and safety."

Asked why linaclotide was dosed once-daily in the morning, Dr. Johnston said, "When we started the program, we didn't have any data on food effect. We thought it made more sense to give it in the morning before breakfast. It is easier to remember to take it first thing in the morning."

Are there genetic markers that would help identify responders? Not yet, according to Dr. Quigley, who said, "Inflammatory bowel disease is working in that direction, but the basic genetics of IBS are only at the very start…I'm well aware of what is going on in the cancer area (with bio-markers), but we are a long way off from that. In a disorder as diverse and heterogeneous as IBS, it is unlikely we will find a single pathology…We now know for certain that ~10% of people who have gastroenteritis will go on to develop IBS, and we know a lot about post-infectious IBS. That is probably a minority of IBS, but we can learn a lot about it. There are interesting data from Canada suggesting one of the factors that pre-disposes getting IBS after gastroenteritis is your genotype. They have identified the genotype markers. It is complex, but at least it is a step forward."

MOVETIS's Resolor (prucalopride) for IBS-C

Resolor was submitted to European regulators in June 2008. Dr. Quigley said Movetis has three "good" trials in constipation, "It works. The next thing is looking at IBS-C… There is no question we need a pro-motility agent across a whole range of disorders, and we don't have one right now."

Movetis got the rights to prucalopride from J&J, which gave up on the drug. Movetis is a privately-owned European specialty pharmaceutical company founded in 2006 by former J&J senior managers and scientists, and its focus is on the GI system.

SALIX's Xifaxin (rifaximin)

Rifaximin is being investigated in IBS as well as hepatic encephalopathy. Dr. Quigley said the emerging concept is "that IBS is not just a gut-brain axis condition but may be a gut-brain-immune system-microbiota axis. That is where rifaximin and probiotics come in."

The cost of rifaximin is an issue in IBS as well as in hepatic encephalopathy. Dr. Quigley said, "In the trial a variety of doses were used, and some are going to be very expensive."

TAKEDA/SUCAMPO PHARMACEUTICALS' Amitiza (lubiprostone)

Dr. Quigley described this as good from a safety point of view because it is locally acting.

BARIATRIC SURGERY

Several new approaches to weight loss surgery were discussed at DDW, including the duodenal switch, four NOTES (natural orifice translumenal endoscopic surgery) procedures, and a device for cosmetic applications:

- **Duodenal switch.** This procedure currently accounts for ~10% of all weight-loss surgery. Dr. Vivek Prachand, a surgeon from the University of Chicago, made a non-randomized comparison of the duodenal switch and Roux-en-Y gastric bypass in patients ≥200 pounds above their ideal body weight. He found the duodenal switch was better, resulting in greater weight loss and a better effect on comorbidities. Three years after the surgery, patients with the duodenal switch were less likely to need medications for diabetes, hypertension, and dyslipidemia. However, malabsorption of vitamins and other nutrients is an issue with the duodenal switch, the switch procedure is more technically difficult, and patients are more likely to see their GERD resolved with gastric bypass.

Comparison of Duodenal Switch and Gastric Bypass at 3 Years

Patients with:	Duodenal switch n=198	Bypass n=152
Diabetes resolved	100%	60%
Hypertension resolved	70%	40%
Cholesterol resolved	70%	20%
Acid reflux resolved	50%	75%

- **Endoluminal vertical gastroplasty (EVG).** Dr. Roberto Fogel, a gastroenterologist from Venezuela, described his success with this transoral technique for pediatric obesity. In 21 patients with a BMI of 28-45, he puts 4 sutures in the stomach via the transoral route. He said the procedure is easy to do and takes just 25-30 minutes to do. However, patients have to be "really, really motivated." In adults, this approach has had some bleeding complications, but he said bleeding has not been a problem in children.
- **Transoral gastric volume reduction (TRIM).** Dr. Christopher Thompson of Brigham & Women's Hospital described an 18-patient, multicenter feasibility study of this procedure. In the first six patients with 9-month follow-up, mean weigh loss was 36.5 pounds, with a

reduction in waist circumference of 5.6 inches. In the 12 patients with 6-month follow-up, mean weight loss was 27.9 pounds, and waist circumference declined 4.7 inches.

- **Transoral gastroplasty (TOGA).** Dr. Kai Nishi of Cedars-Sinai Medical Center reported on the status of the U.S. pivotal trial of incision-less weight loss surgery with Bard's EndoCinch, a suturing device. All the procedures in this prospective, randomized, multicenter, sham-cross-over study in 275 patients were completed in May 2009, and one-year data will be available in May 2010, at which time the sham patients will be allowed to crossover and have the procedure performed if they want it. He said the device is "fairly large" and "somewhat complicated."
- **Transvaginal sleeve gastrectomy.** Dr. Santiago Hogan of the University of California, San Diego, described the initial human experience in the U.S. with this procedure, in which two incisions are made in the abdomen and one in the vagina to remove 70% of the patient's stomach. He commented, "The technology is not out there to do this fully NOTES."
- **BaroSense.** This company is developing an implantable, transoral, restrictive, non-surgical device that creates plications (folds) in the upper gastric wall to attach a small rubber plug with small holes in it. The removal device, which is in Phase I clinical trials, creates a small pouch to receive food. A surgeon suggested this may appeal to women seeking to lose 20 pounds for cosmetic reasons.

How do bariatric surgeons chose which procedure to use? Dr. Prachand said, "When I counsel patients, I think of three factors: the severity of the obesity…the nature of the medical problems related to obesity…and patient preference."

What do these newer approaches mean for the use of banding (Allergan's Lap-Band and Johnson & Johnson's Realize? On average, bariatric surgeons questioned at DDW estimated that their use of bands would remain flat or go down slightly over the next year, but there would be a shift to greater use of J&J's band. One surgeon said, "We use Lap-Band now, but we are in active discussion with our hospital to change because the technical aspects of the J&J band are good. There is no evidence one band is better than the other, and I am credentialed on both, but the port placement is better with Realize." Another surgeon said, "We used to use both bands, but we now do Realize 100%. The port is easier to put in, and the Realize website is phenomenal, just extremely good."

Outlook for Bariatric Surgery Approaches

Patients with:	Patient population	June 2009	June 2010
Duodenal switch/sleeve	BMI>50	22%	27%
Banding	BMI 35-45, no metabolic comorbidities	18%	15%
Gastric bypass	BMI 35-50, good for metabolic comorbidities	60%	58%

MISCELLANEOUS

A number of studies were highlighted at DDW as having the potential to change clinical practice. Among these were:

➢ **ADDEX PHARMACEUTICALS' ADX-10059, an mGluR5 blocker** – showed proof-of-concept in GERD. In a first-in-man, single-blind, placebo-controlled study, two doses were tested (50 mg TID and 250 mg TID). The high dose met the primary endpoint – a statistically significant reduction in 24-hour esophageal pH. However, the adverse events – particularly dizziness and nausea – were very high in the high dose (92% overall vs. 8% with placebo and 17% with low dose). The drug was given as a powder in a capsule in this trial, and a speaker suggested this caused very rapid absorption. A modified-release formulation which slows absorption, reduces C_{max}, and has improved tolerability is being used in the Phase IIb studies. The speaker said, "The lower dose did not appear effective, but there was large inter-patient variability, and we are investigating that (with a new formulation)." The Phase IIb trial is testing 25 mg, 50 mg, 100 mg, 120 mg, and 150 mg all BID and modified-release.

➢ **Anticoagulation** – more is not always better. Dr. Neena Abraham of Baylor College of Medicine presented the results of a retrospective study of 78,084 VA patients, including 1,061 with upper GI events (UGIE). She found that younger patients (age 60-69) who are on a complex antithrombotic regimen (e.g., aspirin + Plavix + warfarin) are at highest risk of UGIE, with a stepwise increase in risk as the therapy got more complex: a 70% increase in risk at one year with dual therapy, a four-fold increase with triple therapy. She said, "We know these drugs are helpful for the heart in preventing future heart attacks and stroke, but now doctors need to consider the short-term risk of GI bleeds…It boils down to short-term risk for long-term benefit…Triple therapy is not indicated for beyond a year with a drug-eluting stent, but often these drugs get prescribed in perpetuity. The first thing I recommend for people at risk of a drug-related bleed is to ask their cardiologist to downgrade from triple to dual to mono-therapy. A lot of it is conversations with the cardiologists… and minimizing other risk factors for a GI bleed, which can sometimes involve a PPI."

➢ **Colonoscopies in Crohn's disease** – should be done more often than are currently being done. In the SONIC trial everyone got a colonoscopy, and it turned out that in ~25% of patients the diagnosis of Crohn's disease was not verified by the colonoscopy; the inflammation was not verified. Thus, those ~25% of patients presumably don't need the therapy, but the evidence for therapy is even stronger in the other ~75% of patients.

➢ **GILEAD'S Viread (tenofovir)** – two-year data from an ongoing trial indicated that HBV patients on Gilead's Hepsera (adefovir) can be safety and effectively switched to tenofovir, either as monotherapy or in combination with emtricitabine (Emtriva) – Gilead's Truvada.

➢ **HORIZON THERAPEUTICS' HZT-501 (8000 mg ibuprofen + 26.6 mg famotidine)** – significantly reduces pain from NSAID-induced upper GI ulcers. Data from two 24-week Phase III trials – REDUCE-1 and REDUCE-2 – showed that patients with mild-to-moderate pain treated with a fixed dose tablet of HZT-501 developed 50% fewer NSAID-induced upper GI ulcers vs. ibuprofen alone.

➢ **JOHNSON & JOHNSON's Remicade (infliximab)** – is better than azathioprine in moderate-to-severe Crohn's disease. Standard-of-care has been to start with azathioprine and reserve an anti-TNF for azathioprine failures. That is likely to change now. Dr. William Sandborn of the Mayo Clinic presented the 1-year results of the SONIC trial, concluding, "We believe these data…show a substantial benefit for anti-TNF-based therapy over azathioprine. That effect is most pronounced in patients who received combination therapy. We hear a lot about comparative effectiveness in the media, and this is a good example of a comparative effectiveness trial."

➢ **MERCK's CDA1 and CDB1**, two fully-human monoclonal antibodies licensed from Medarex and MassBiologics – showed very good results in preventing recurrence of *C. difficile* infections in a 200-patient, double-blind, randomized, placebo-controlled Phase II trial. They are administered IV.

Dr. Donna Ambrosino, an infectious disease specialist from the University of Massachusetts School of Medicine, said, "*C. diff* used to be a bug that only the very young and very old got, but for reasons not clear this has become an increasingly virulent infection that is affecting the community generally… We think this is a new therapy for this infection…and in a few years should advance to be available…25.3% of people will get a recurrence, and we dropped it to 6.9% (p=0.0004)."

There was also a reduction in new hospitalizations from 20% to 9% and a trend to a reduction in severe diarrhea. Adverse events were actually higher with placebo than the antibody.

Dr. Israel Lowy of Medarex said, "We hypothesized that fully-human monoclonal antibodies might provide a protective umbrella and allow the gut to rebalance and prevent recurrence."

➢ **NPS PHARMACEUTICALS' teduglutide, a GLP-2 analog for short bowel syndrome** – showed some positive results in a small post hoc analysis. Dr. Palle Jeppesen of Denmark presented the results of a 72-hour balance substudy of a larger Phase III 24-week efficacy study that failed. Unfortunately, there was a lot of incomplete data, so he could only provide results on 14 patients. He concluded, "With this drug, you can decrease the diarrhea at Weeks 8 and 24."

➢ **OPTIMER PHARMACEUTICALS' OPT-80** – no new data. Data on OPT-80 vs. vancomycin in *C. diff* were presented at DDW as a late breaker, but this was not new data.

➢ **Proton pump inhibitors and hip fractures** – causality still not clear. Dr. Douglas Corley of Kaiser Permanente presented the results of a nested case control study looking at 33,752 cases and 130,471 controls. He found that patients with a hip fracture were 30% more likely than controls to have taken at least a two-year supply of a PPI and 18% more likely to have taken a 2-year supply of an H2 blocker. Patients taking <1 pill/day had a 12% fracture risk increase. The greatest relative increase in risk for PPI use >2 years was in patients age 50-59, but the largest number of fractures was in 80- to 89-year-old patients.

Kaiser is working with the FDA on this, and the data are being shared with the FDA, which is reviewing the issue of PPIs and fractures. Dr. Corley said, "Are these medications causing this? Unfortunately, epidemiological studies have difficulty with confounding…I think the finding that there was not a dose response raises a question about whether it is causal, but the fact that there is a decrease (in fractures) after the PPI is discontinued (argues the other way)…I think the main finding that there is at least some association is constant."

What advice should doctors give patients? Dr. Corley said, "What to advise patients…is very tricky…In general, what I recommend is that these are very effective agents, and there are not a lot of alternatives. For people with a lot of heartburn resolved by PPIs, the question is what else can they do? H2 blockers are not necessarily effective…The main thing is to be sure you have an indication for being on a PPI, and use the lowest effective dose…If you are at risk for osteoporosis, you should discuss with your primary care doctor to make sure you are on appropriate therapy for that…I don't recommend (a PPI) for most people with risk factors for osteoporosis (e.g., renal disease, glucocorticoids) or risk factors for falls (e.g., dementia, anxiolytics, etc.)."

Asked if PPIs are over-used, Dr. Michael Shaheel of the University of North Carolina School of Medicine said, "The answer is an unequivocal yes. PPIs are over-used. Anyone with an ache between the chin and the knee is likely to walk about with a PPI prescription. Some is appropriate, and some is inappropriate. Once they are on, they are often times on forever. So it is not unusual to see someone who gets started, and no one takes them off five years later…The safety profile of the drugs (PPIs) is good…And these are highly effective marketing machines (companies). You can't turn on the TV without seeing someone advertising a PPI…and that plays into it, too."

➢ **UCB's Cimzia (certolizumab).** New data from the 539-patient, multicenter, Phase IIIb WELCOME study found that Cimzia can be effective for moderate-to-severe Crohn's disease patients who failed Remicade, with a duration of response up to Week 26. After a 6 week induction period, 62% of Cimzia patients achieved a response, and 39% achieved remission. By Week 2, 33% of patients had responded to Cimzia, and by Week 4, 44% had responded.

➢ **VERTEX's telaprevir** – data were updated, but nothing new was presented. Dr. Adrian Bisceglie of St. Louis University School of Medicine reviewed the PROVE-3 trial results of telaprevir in hepatitis C that were presented at the European Association for the Study of the Liver (EASL), concluding, "I personally believe this is a very important finding that presents a new paradigm for how we will treat non-responders in the future."

Asked if patients are being warehoused or delaying treatment to wait for either telaprevir or ***Merck/Schering-Plough's boceprevir***, Dr. Shaheel said, "I personally am not warehousing patients…Until the new treatment is available, I think people with biopsies with significant liver disease should be treated now. Our current treatments are not bad, but it is important to inform patients about new treatments coming and the possibility of waiting, and I do that. The more severe the liver disease, the more I am directing patients to being treated now…The less severe, the more I think there is an option to potentially delay treatment." Dr. Brent Tetri of St. Louis University said, "It depends on the patient. Some want to start therapy right away, and if a trial is available, we do that. It is up to the patient…No one needs to wait. We don't know what the results of the studies will be. The studies are exciting, but we don't know the side effect profile (yet)… About half our patients are waiting. Folks who have had HCV (hepatitis C virus) for decades, for them to wait six months is not an issue."

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