GI Case Presentations

Novel Approaches to Old Problems

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April 20, 2013

Objective

- To present clinical cases that illustrate how gastroenterology and hepatology practice have evolved over the last five years

Disclosures

- Abbvie
- Aptalis
- Gilead
- Janssen
- Merck
- Roche

Patient # 1

- 57-year old Asian male referred for ascites
- HPI:
  - 2009 – HBV cirrhosis, EGD no varices, platelet count 125
  - 2012 – another EGD - +HP, no varices
  - 2013 (Feb) – epidural abscess – spine surgery
  - 2013 (March) – to ER with one week of ascites
- PMHx: DM, HTN
- Meds: Furosemide 40 mg OD, diltiazem, Fe
- Family history: No HBV, cirrhosis or hepatoma
- Social history: Non-smoker, no ETOH use

Patient # 1: Continued

- Labs:
  - Platelet 94, Cr 95,
  - ALT 14, AST 132, ALP 176
  - INR 1.3, albumin 19, bilirubin 23
  - U/S: ascites, splenomegaly, inhomogeneous liver
  - HBeAg negative, eAb positive
  - HBVDNA – Feb 2012 – 1 x 10 ^ 6 IU/mL; March 2013 – 1 x 10^7 IU/mL
  - MELD score 11

Patient # 1: Next steps?

- Would this patient benefit from fibrosis testing?
- Would he benefit from antiviral therapy?
- Should he be referred for liver transplant?
- What else should be done in the meantime?

Management of chronic hepatitis B: Canadian Association for the Study of the Liver consensus guidelines

Carla S Coffin MD MSc, FRCPC[1], Scott K Fung MD FRCPC[2], Mang M Ma MD FRCPC[3]

CS Coffin, SK Fung, MM Ma. Management of chronic hepatitis B: Canadian Association for the Study of the Liver consensus guidelines. Can J Gastroenterol 2012;26(12):917-938.

La prise en charge de l'hépatite B chronique : les lignes directrices consensuelles de l'Association canadienne pour l'étude du foie

Hep B Facts

- 360 million chronic carriers
- 6% of immigrants
- Non-Canadian born 12X as likely to be HepB+
- Majority are infected at birth or in childhood
  - Vertical transmission or through bodily fluids
  - 90% of infected infants and 25-50% of infected children become chronic carriers
- Only B.C. has universal vaccination policy

Hep B: Natural History

- 20-25% develop cirrhosis
- 5% risk of hepatoma
- Acute liver failure with immunosuppression
  - Anti-TNF agents, rituximab, chemotherapy
- Extrahepatic manifestations
- 0.5%-0.8% of chronic carriers clear HBsAg/yr

Hep B: Five Phases

Phases	HepBsAg	HBeAg	Anti-Hbe	ALT pattern	HBV DNA
Immune Tolerant	+	+	-	Normal	$>2x10^4$ to 2 x 10^8 IU/mL
Immune Clearance	+	+	-	Normal or elevated	$>2x10^4$ to 2 x 10^8 IU/mL
Inactive Disease	+	-	+	Normal	< 200 IU/mL
HepBeAg neg chronic hepatitis	+	-	+	Normal or elevated	Not detected to >2 x 10^8 IU/mL
Resolution of infection	-	-	+	Normal	Undetectable

Hep B: Progression of Fibrosis

Phases	HepBsAg	HBeAg	Anti-Hbe	ALT pattern	HBV DNA
Immune Tolerant	+	+	-	Normal	$>2x10^4$ to 2 x 10^8 IU/mL
Immune Clearance	+	+	-	Normal or elevated	$>2x10^4$ to 2 x 10^8 IU/mL
Inactive Disease	+	-	+	Normal	< 200 IU/mL
HepBeAg neg chronic hepatitis	+	-	+	Normal or elevated	Not detected to >2 x 10^8 IU/mL
Resolution of infection	-	-	+	Normal	Undetectable

Hep B: Goals of Antiviral Rx

- Prevent advanced fibrosis/hepatoma
  - Immune clearance phase
    - Hep B eAg+, HBV DNA > 20,000
  - HBeAg neg chronic hepatitis
    - Hep B eAg-, HBV DNA > 2,000
    - (threshold may soon be lower)
  - Identify patients with persistently abnormal ALT or who already have significant fibrosis **(F2 or higher)**
  - **In Hep B, high viral load and cirrhosis independent risk factors for development of hepatoma**

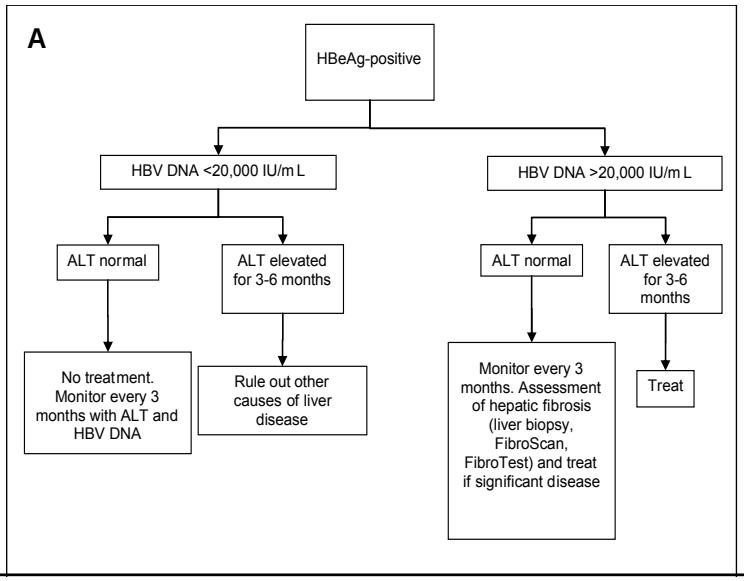
Hep B: Normal Liver Enzymes

- ALT < 19 for females, < 30 for males
- Upper limit of normal for most labs represent abnormally high ALT
  - Active viral hepatitis, alcohol use or fatty liver
- Higher mortality in patients with ALT in upper limit of normal for most lab references

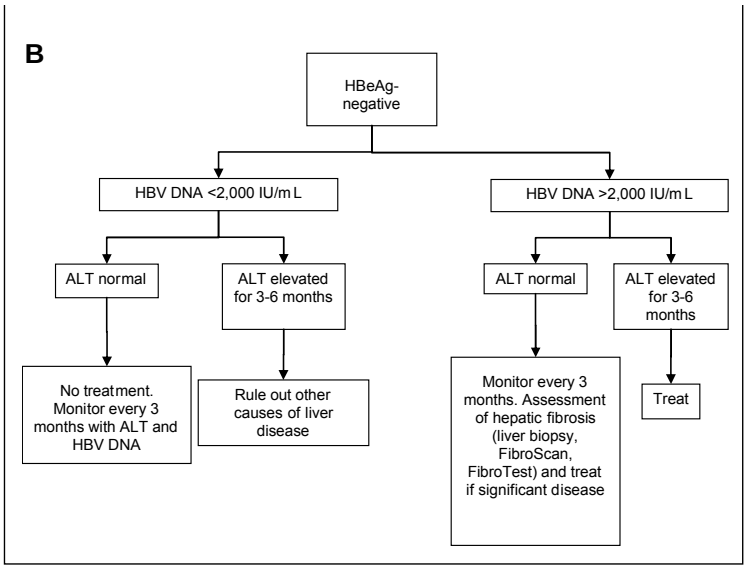
Hep B: Role of Fibrosis Testing

- Routine tests that suggest cirrhosis
  - AST > ALT
  - Platelet < 150
  - Ultrasound - splenomegaly
- **Non-invasive testing**
  - **For patients with high viral loads and persistently normal ALT**
  - **Fibroscan (transient elastography)**
    - **Cut-off of 7.1 Kpa >90% NPV for significant fibrosis, cirrhosis**
  - **Fibrotest**
    - **Bilirubin, GGT, alpha-2 macroglobulin, apo-lipoprotein a1, haptoglobin**
- Liver biopsy
  - Generally reserved for patients where diagnosis is unclear or non-invasive testing equivocal

HBeAg+ Treatment Algorithm



HBeAg- Treatment Algorithm



Hep B: Goals of Antiviral Rx 2

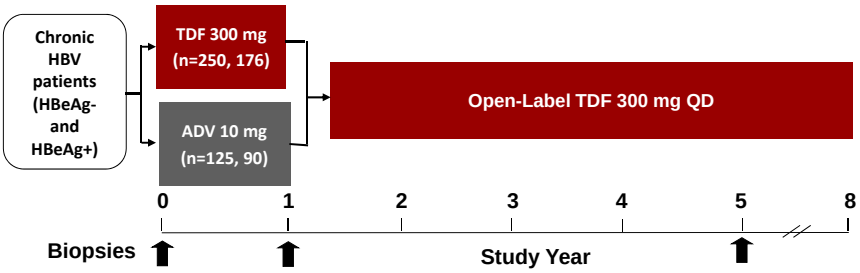
- **If already cirrhotic**
  - **Treat if HBV DNA ≥ 2000 IU/mL**
  - **Observe or treat if HBV DNA < 2000 IU/mL**
- Treat if extrahepatic manifestations present
- Prevent immunosuppression-related HBV reactivation
  - Ideally start one month before until 12 months after immunosuppression is completed
- Prevent vertical transmission in pregnant women
  - At week 28 if HBV DNA > 2 x 10^6 IU/mL
  - Continued until four weeks post partum
  - Should not breastfeed during antiviral therapy

HBV Treatment Choices

- Standard interferon and pegylated interferon
  - High ALT, high viral load, non-cirrhotic, non-pregnant, extrahepatic manifestations, mainly eAg+ patients
  - Expensive, not covered by government plans but finite duration of therapy
- Antiviral therapy
  - High genetic barrier to resistance
    - **Tenofovir (FDA category B and no reports of resistance)**
    - **Entecavir (except in lamivudine resistance)**
  - Low genetic barrier to resistance
    - Lamivudine
    - Telbivudine (FDA category B)
  - ? Tenofovir and Emtricitabine in decompensated cirrhosis
  - Studies needed to determine if/when can discontinue therapy

Two Pivotal Studies: 102 (HBeAg-) and 103 (HBeAg+)

- Phase 3, randomized, double-blind trials
- All patients received open-label TDF after Year 1 for a total study duration of 8 years*
- Liver biopsies obtained at baseline, Year 1, and Year 5 (non-mandatory)

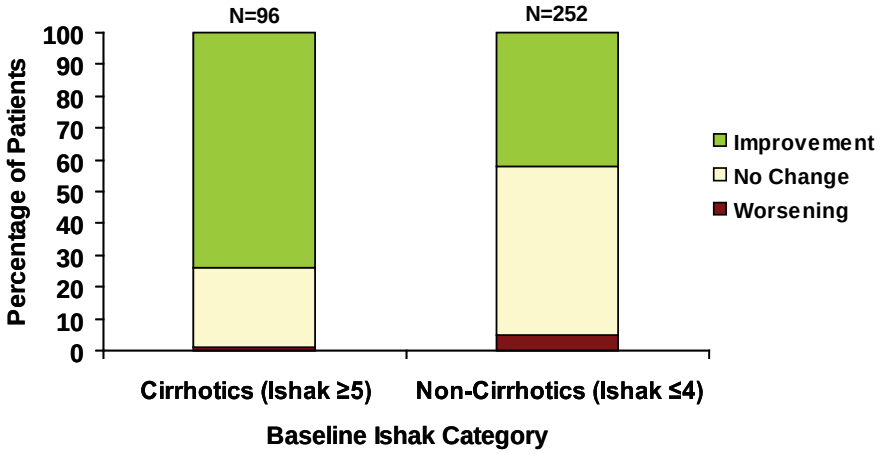


* TDF = tenofovir disoproxil fumarate (Viread®)

FTC could be added for confirmed viremia on/after Week 72
Emtricitabine (FTC) is not licensed for use to treat CHB

Gane E, *et al*. APASL 2012; Oral #PS06-05.

Liver Fibrosis Regressed Significantly over 5 Years of Treatment with Viread® *



Improvement defined as a decrease in Ishak fibrosis score of ≥ 1; Worsening defined as increase in score of ≥ 1

Buti M, et al. EASL 2012; Poster #501.

* Viread® = tenofovir disoproxil fumarate (TDF)

Back to Case # 1: 57 yo M - HBV-related cirrhotic ascites

- Liver decompensation triggered by recent surgery
- No role for fibrosis testing – he has obvious cirrhosis
  - ALT actually normal – 14 U/L even with HBV DNA at 7 logs!
- Standard ascites management
  - Sodium restriction, diuretics, paracentesis if needed
- Started tenofovir 300 mg po OD
  - Close monitoring of Cr as diabetic and on diuretics
- MELD score > 10 and ascites - transplant assessment
- Hepatoma surveillance – U/S q6 months
- Variceal surveillance – EGD yearly

Hepatitis B Take Home Points

- Think of vaccination in all patients who are not infected or immune
- Normal ALT <19 for females, < 30 for males
- Fibrosis testing in appropriate cases
- Treat if F2 or persistently elevated ALT, cirrhotic
- Treat with antiviral with high genetic barrier for resistance – benefits re: fibrosis regression
- Future studies to determine if/when therapy can be discontinued

Patient # 2

- 49 year old female referred for HCV infection
- PMHx: Bipolar disorder, hypothyroidism, spinal stenosis, cholecystectomy
- Meds: OxyIR 5 mg prn, Oxyneo 80 mg OD
- HPI: Elevated AST and ALT on routine physical
- Soc Hx: No significant ETOH, blood transfusion as a baby for Rh incompatibility, no IVDU

Patient # 2: Continued

- O/E: Ht 5'6", Wt 222 lbs, BMI 35
  - No jaundice, no signs of chronic liver disease
- Labs: platelet 215, bili 6, AST 39, ALT 54, INR 1, albumin 40, HIV/HBV negative
- Ultrasound: Hepatomegaly 17.4 cm, prominent spleen 12 cm, no ascites
- Gastroscopy April 2012 for dyspepsia – no varices mentioned

Patient # 2: Next steps

- What other investigations are needed?
  - ?Blood work
  - ?Fibrosis testing
  - ?Gastroscopy
- Should she be referred for treatment?
- If so, which regimen?
- Any other concerns?

SPECIAL ARTICLE

An update on the management of chronic hepatitis C: Consensus guidelines from the Canadian Association for the Study of the Liver

Robert P Myers MD MSc[1], Alnoor Ramji MD[2], Marc Bilodeau MD[3], Stephen Wong MD MHSc[4], Jordan J Feld MD MPH[5]

RP Myers, A Ramji, M Bilodeau, S Wong, JJ Feld. An update on the management of chronic hepatitis C: Consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol 2012;26(6):359-375.

Mise à jour sur la prise en charge de l'hépatite C chronique : des lignes directrices consensuelles de l'Association canadienne pour l'étude du foie

Hepatitis C Facts

- 0.8% of Canadians infected with Hepatitis C
- 60% are IVDU, 20% infected immigrants, 11% from contaminated blood
- Prevalence peaked but increasing incidence of decompensated cirrhosis/hepatoma
- 80% of acute infection become chronic
- 30% of chronically infected have a severe progressive course of disease

Hepatitis C diagnosis

- ALT unreliable as can fluctuate
- Screen with Hep C antibody
- Diagnosis confirmed by detectable HCV RNA
  - Genotype
  - Viral load

HCV Treatment Goal

- Sustained virologic response
  - Complete elimination of virus – "cure"
  - Undetectable HCV RNA 12-24 weeks after rx
  - Better quality of life, resolution of extrahepatic manifestations, improvement in liver histology, decrease in liver-related morbidity and mortality
- SVR does not represent immunity to HCV, reinfection can occur

Traditional Treatment

- Pegylated interferon and ribavirin
  - Genotypes 1, 4, 5 and 6 – treat for 48 weeks if have early treatment response at week 12
    - SVR 40-50% only
  - Genotypes 2 and 3 – treat for 24 weeks – SVR > 80%
- Side effects: Pancytopenia, depression, irritability, mania, fatigue, myalgias, exacerbation of autoimmune disease, retinal hemorrhages
- **Pregnancy is the only absolute contraindication**

New Rx for HCV: Direct acting antiviral agents (DAA's)

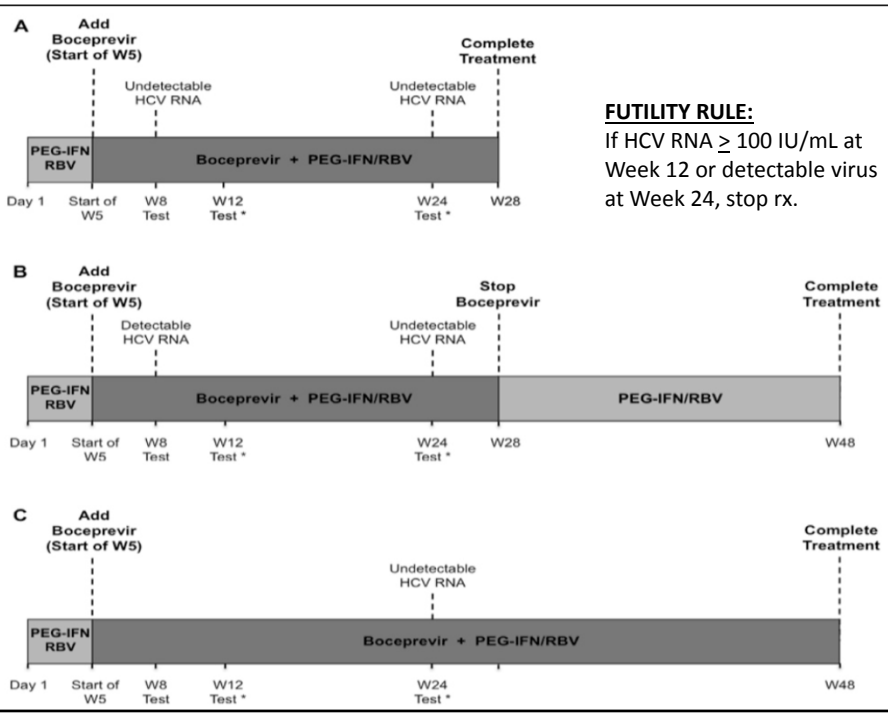
- Target NS3/4A serine protease inhibitor
- Improvement in viral kinetics (ie. Greater initial drop in HCV RNA) likely enables immune system to clear the virus especially for patients with decreased interferon sensitivity
- Two agents approved over past year
  - Bocepravir + PEG-IFN/Ribavirin
  - Telapravir + PEG-IFN/Ribavirin
- Only for Genotype 1 HCV
  - Non-cirrhotics – SVR 66% vs. 38% with dual rx
  - Cirrhotics – SVR 42% vs. 31% with dual rx

New Rx for HCV: Direct acting antiviral agents (DAA's)

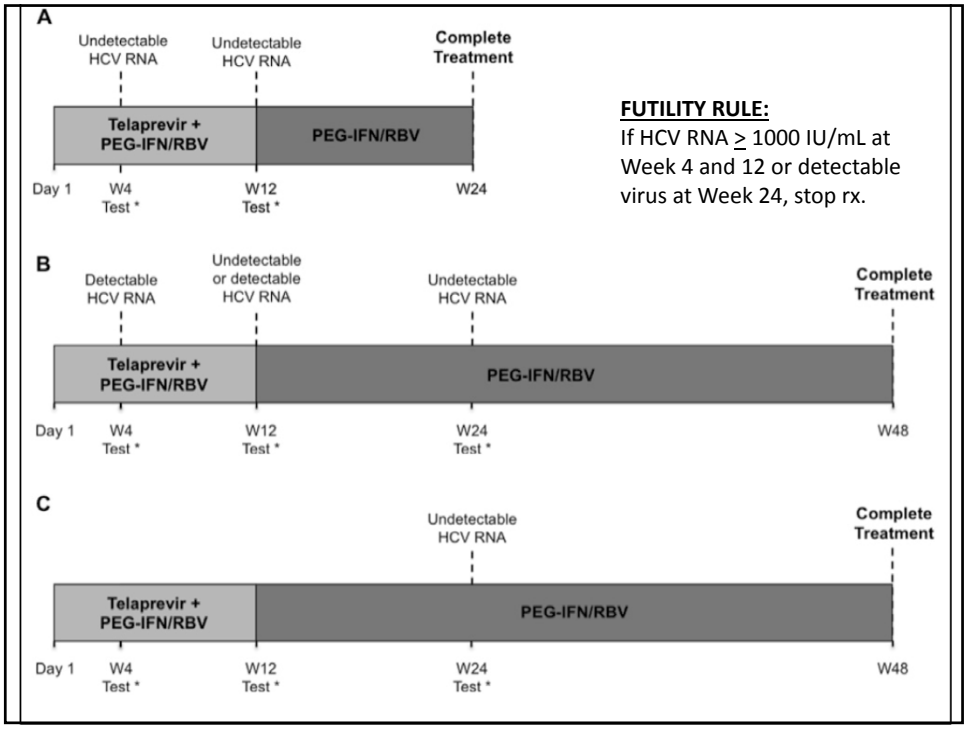
- Higher rates of side effects but potentially shorter duration of therapy in non-cirrhotics
- Need closer monitoring for cytopenias, greater risk of adverse effects for patients with platelet counts < 100
- Telapravir – rash, Steven Johnsons' Syndrome
- ++ Drug interactions
- Very costly

Fibrosis Testing in HCV

- To determine duration of treatment especially with regimens that include protease inhibitors
  - Cirrhotics need longer duration of rx but at higher risk of treatment side effects
- In patients who have minimal fibrosis, may choose to wait for interferon-free regimens
- If established cirrhosis, need ongoing hepatoma surveillance regardless of treatment response



FUTILITY RULE:
If HCV RNA ≥ 100 IU/mL at Week 12 or detectable virus at Week 24, stop rx.



IL28B Gene Testing in HCV

- Located on chromosome 19
- In Genotype 1 HCV – 80% SVR if CC genotype vs. 40% SVR if CT or TT
- If rapid virologic response (Neg HCVRNA at week 4 on dual therapy)
  - 86 to 97% SVR with 48 weeks of therapy
  - If HCV RNA < 400,000, may consider 24 weeks of rx
  - In theory would not need PI-based therapy but would need rapid viral load results at week 4

Back to Patient # 2

- HCVRNA – Genotype 1 - 1.47 E+6 IU/mL
- Fibroscan – Stage 4 fibrosis, early cirrhosis
- Repeat EGD Jan 2013 – small varices
- Psychiatry assessment – safe to start
- IL28B testing unlikely to change management
- Started on PEG-IFN/ribavirin/bocepravir triple therapy – expected SVR rate 42%
- Will need ongoing hepatoma surveillance

Hep C Take Home Points

- New agents available for HCV Genotype 1 infection
- Pregnancy is the only absolute contraindication to HCV therapy
- Fibrosis testing is useful to assess for urgency of treatment
- Interferon-free regimens may become available in the future

Patient # 3

- 66 year old male from Afghanistan
- RFR: EUS/FNA of pancreatic body mass
- HPI:
  - 1 year hx - anorexia, fevers, night sweats, 10 lb wt loss
  - Extensive ID workup in June 2012
  - BW: Anemia, elevated ALP, CRP, ESR but negative blood cultures, TB skin test, brucellosis, ecchinococcal, strongyloides, amoebiasis, HIV serology
  - CXR – pleural thickening
  - Negative gastroscopy/colonoscopy, Normal 2D echo

Patient # 3

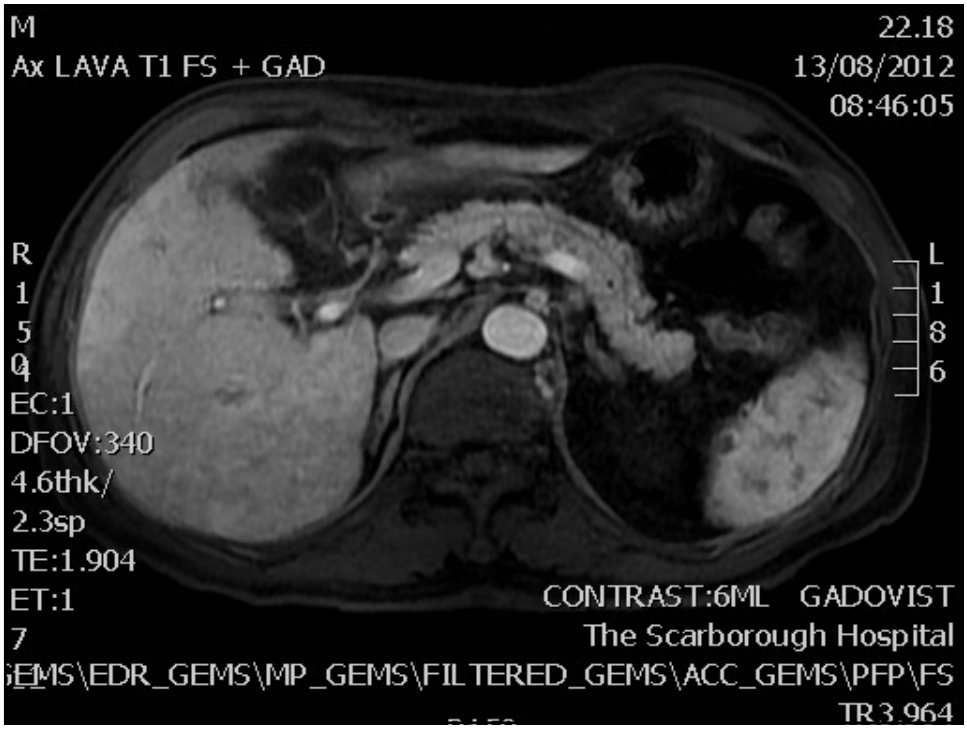
- HPI (continued)
  - CT chest/abdo/pelvis
    - Subcarinal, tracheobronchial, precarinal nodes up to 13 mm in size, slightly larger than 2008
    - Pleural based density left mid-lung 9.3 mm x 13.1 mm in size
    - Mass in body of pancreas 17.6 mm x 25 mm
    - Abdominal lymph nodes up to 15.5 mm
  - DDx: Pancreatic CA vs. Lymphoma
  - CT guided biopsy of pancreas and mid-chest pleural based mass suggested by radiologist

Patient # 3

- PMHx: Right nephrectomy for nephrolithiasis
- Meds: None
- NKDA
- Social history: From Afghanistan, travel back and forth since 1999, non-smoker, no ETOH use, married, 1 son
- Family history: Negative for GI malignancy
- ROS: Arthralgias but no h/a, cough, diarrhea, rash or neuro symptoms

Patient # 3

- Physical exam:
  - Thin (lost 50 lbs since onset of illness), unwell, but in no distress
  - No jaundice or lymphadenopathy
  - Abdomen soft, non-tender, no palpable masses, no leg edema
- MRI/MRCP:
  - 1.2 x 2.8 cm lesion arising from the junction between body and tail. There appeared to be traversing vessels through this lesion. Solid lesion is not favoured. ? Cystic lesion vs. Renal cell carcinoma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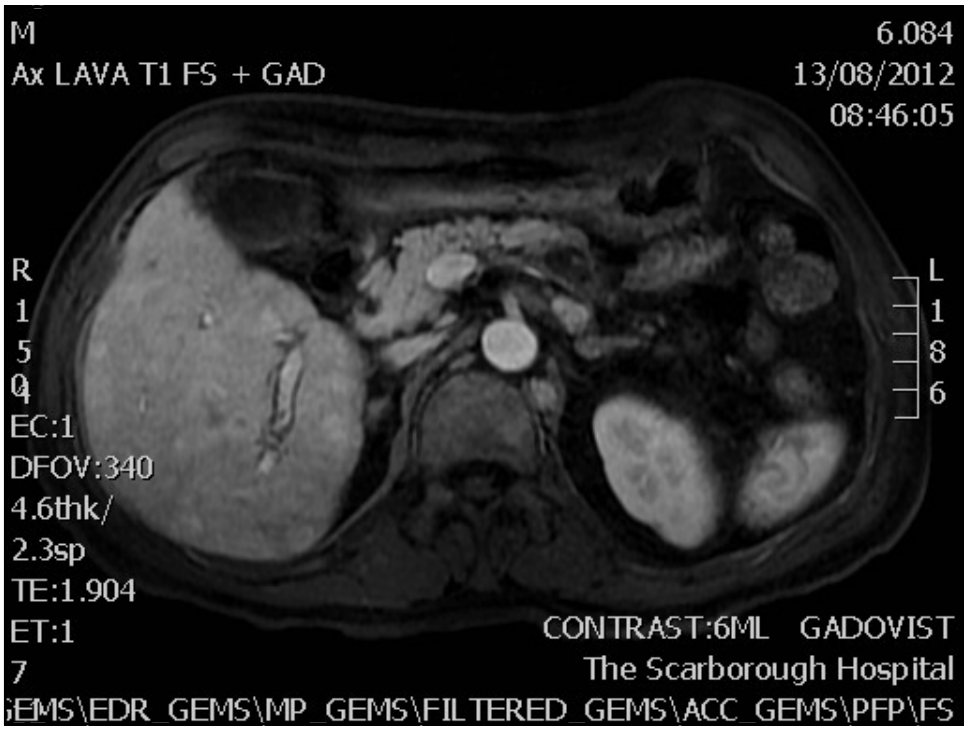
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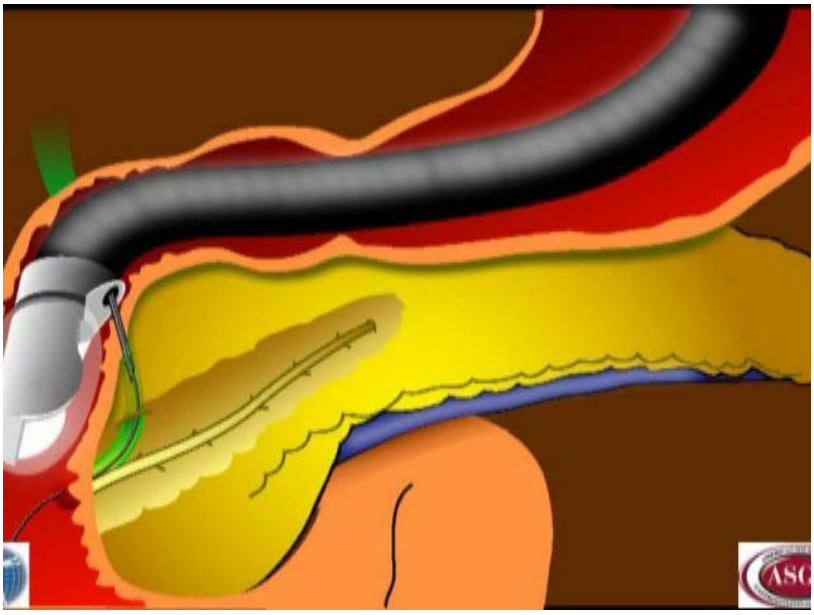
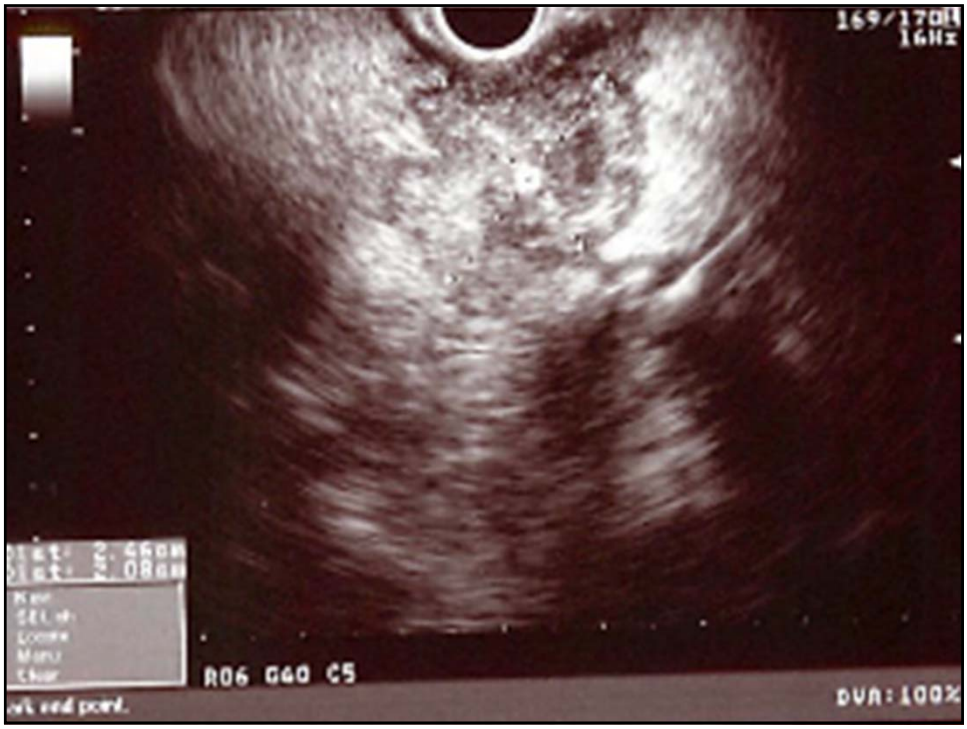


Patient # 3: EUS Findings

- Vague hypoechoic area in pancreatic body
  - 2.46 cm x 2.08 cm in size, second lesion 1.97 cm x 1.17 cm in size very close to splenic vein
  - Celiac nodes up to 1 cm in size
  - Biopsy through the stomach with with 22 gauge needle – sent for cytology, TB and fungal culture
- BW sent same day
  - Hgb 84, normal WBC/platelet, amylase 50, bili/AST/ALT normal, ALP 250
  - CA 19-9 < 1
  - ANA normal, IgG4 1.93 (ULN 0.864)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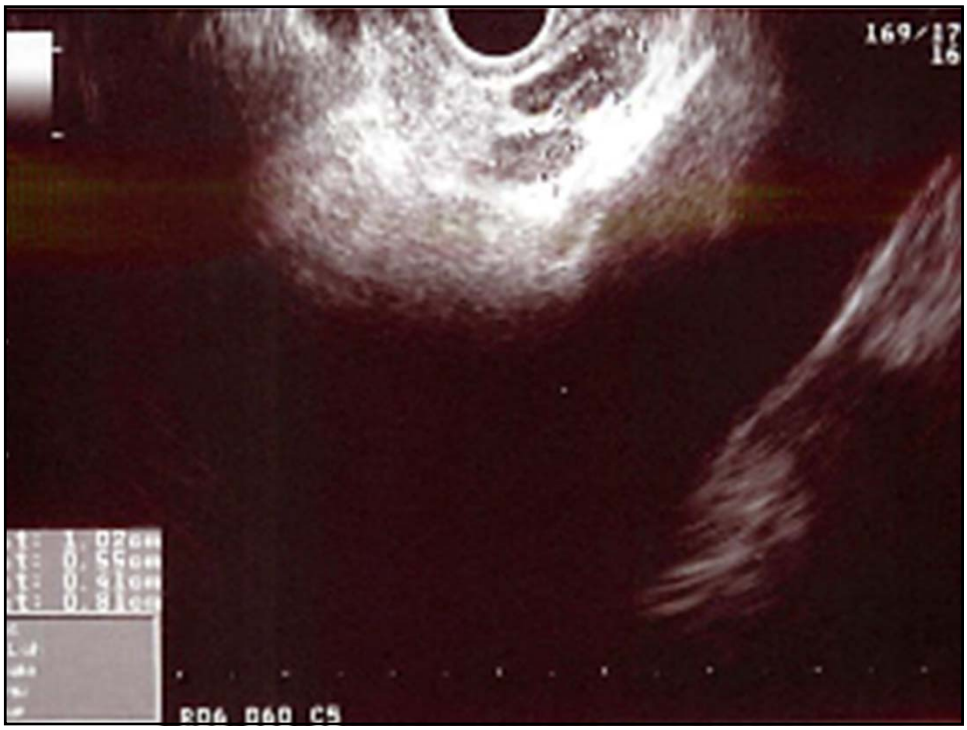
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Patient # 3: Cytology Results

- Abundant blood with scant cellularity.
- Atypical cells suspicious for malignancy.
- Acid-fast stain negative.

- Patient seen for follow-up Oct 10, 2013.
- I wondered about autoimmune pancreatitis due to high IgG4.
- Re-referred to ID due to persistent fevers, HIV test ordered.
- No pulmonary symptoms, scheduled for repeat EUS Oct 11th but EUS cancelled due to new results.

Patient # 3: Final Diagnosis

- Pancreatic TB culture results:
  - Mycobacterium Tuberculosis complex
- Repeat CXR Normal
- Started on INH, pyrazinamide, rifampin, ethambutol, pyridoxine
- Repeat CT abdomen 6 months later showed resolution of pancreatic abnormalities

Pancreatic Tuberculosis

- Rare condition even in endemic countries
- Pancreas protected due to presence of pancreatic enzymes which interfere with seeding of MTb
- Most likely mechanism of spread is lymphohematogenous dissemination from occult focus in the lungs

Pancreatic TB (Continued)

- Symptoms include pain (81%), weight loss (55%), fever (36%), recurrent vomiting (19%), jaundice (17%)
- High ESR, CRP, +TB skin test in 2/3 cases
- Other presentations include obstructive jaundice, pancreatic abscess, secondary diabetes, massive GI bleed, acute or chronic pancreatitis, portal or splenic vein thrombosis

Pancreatic TB (Continued)

- Most patients diagnosed at laparotomy
- Image-guided percutaneous FNA for TB – 50% success rate
- EUS-FNA 80-95% success rate in pancreatic or peripancreatic masses
- First case reported using EUS-FNA was in 2005.
- If EUS-FNA negative
  - Laparoscopy – AFB stain 20-40% yield, culture 77%.
  - Caseating granuloma in 75-100% of cases.
- PCR rapidly available but unable to test for sensitivities

JOP. J Pancreas (Online) 2005; 6(6):598-602.

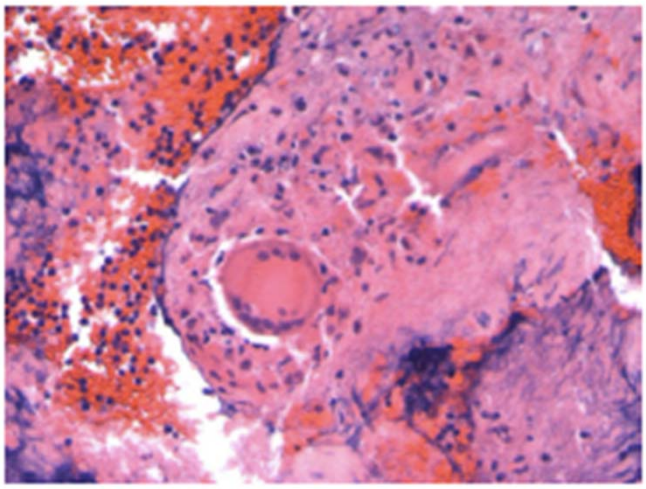


Figure 2. Photomicrograph (H&E stain x200) of celiac axis lymph node cytology showing epitheloid granuloma.

Patient # 4

- 32-year old female, married, no children
- RFR: Chronic constipation
- HPI:
  - 15 years of constipation
  - Colonoscopy x 2 in 5 years – told normal
  - Bowel movements q1-2 weeks, ++ bloating, pellet-like stools despite fiber, bisacodyl, PEG solutions
  - Frequent visits to ER, walk-in clinics, intermittent enemas
- PMHx: Menorrhagia
- Meds: Recently started Fe tablets
- NKDA
- Family hx: No colon cancer

Patient # 4

- Next steps
  - ? Blood work
  - ? Repeat colonoscopy
  - ? Other imaging, motility studies
  - ? Laxatives vs. other therapy

Chronic Constipation

American College of Gastroenterology (ACG)

"Unsatisfactory defecation characterized by infrequent stools, difficult stool passage, or both."

- Difficult stool passage includes straining, a sense of difficulty in passing stool, incomplete evacuation, hard/lumpy stools, prolonged time to stool, or need for manual maneuvers to pass stool

NORMAL BOWEL HABIT
"THE PASSAGE OF ≥ 3 SPONTANEOUS COMPLETE BOWEL MOVEMENTS PER WEEK"

Causes of Constipation

Lifestyle
- inactivity
- low fibre/fluid intake
- ignoring urge to defecate

Medications:
- analgesics, narcotics, anticholinergics, antidepressants, antihistamines…

Endocrine/metabolic
- hypothyroidism
- hypercalcemia
- diabetes

Neurological/CNS
- Parkinson's
- MS

GI structural
- Crohn's, CRC,

Anorectal
- Hirshprung's, anal fissure

Tack *et al*. Neurogastroenterol Motil. 2011 Aug;23(8):697-710

Subtypes of Functional Constipation

SLOW TRANSIT

" I never get the urge to go….
I get progressively bloated
& distended.."

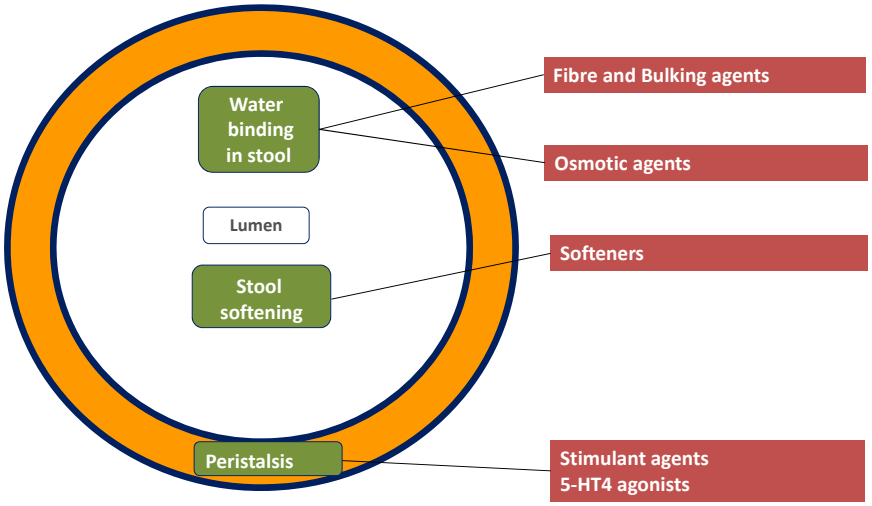
OUTLET DYSFUNCTION

"I always get the urge to go, I strain and strain but very little happens…"

Tests to consider:

- Marker/transit test
- Anorectal manometry
- Defecography

Treatment for Constipation



Tack & Müller-Lissner. *Clin Gastroenterol Hepatol* 2009;7:502

Quality of evidence

Treatment modality	Quality of evidence	Recommended dosage
Physical activity	Low	–
Psyllium	Moderate	6–12 g daily
Sodium ducosate	Low	100–200 mg twice daily
Lactulose	Moderate	15–30 mL daily
PEG (electrolyte enriched)	High	250–500 mL daily
PEG 3350 (electrolyte free)	High	17 g daily
Senna	Low	Vary
Bisacodyl/SPS	Moderate	10 mg daily as needed
Probiotics	Low/very low	Vary
Prucalopride	High	2 mg daily

Liu, L.W. Can J Gastroenterol 2011; Vol 25(B): 26B

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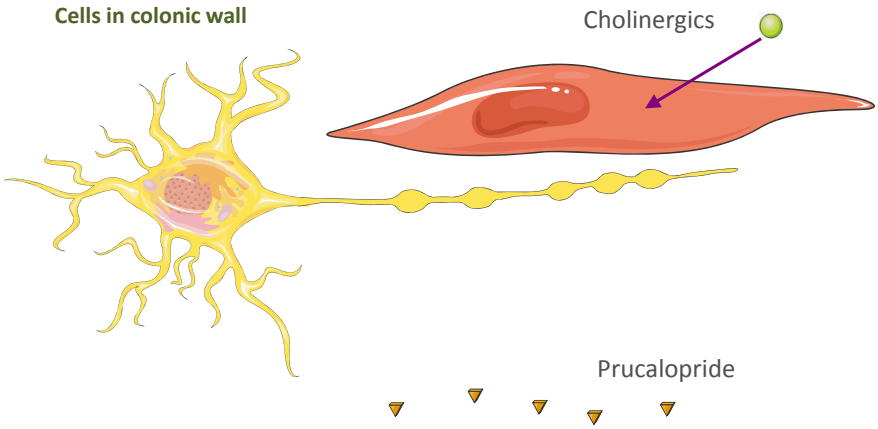
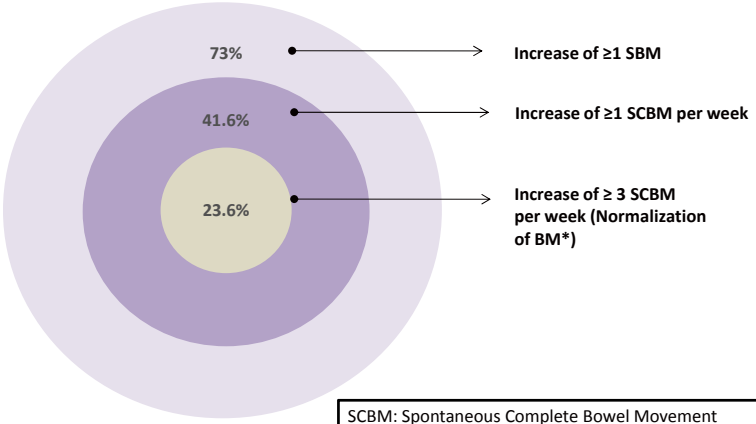
Mode of action of Prucalopride



Resolor® - *prucalopride, Differential Pharmacology,* Jan Schuurkes, Joris De Maeyer.

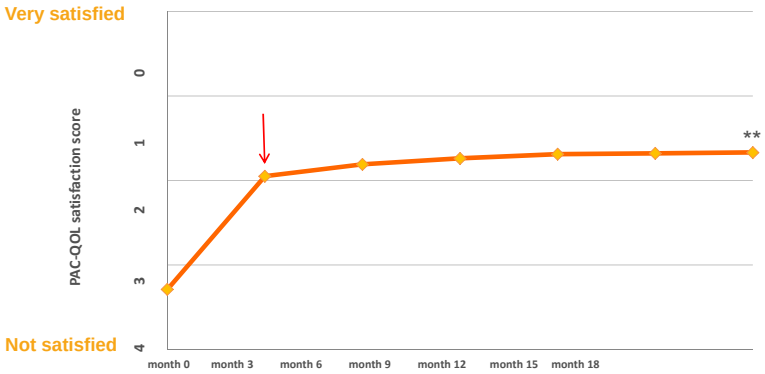
Clinical Benefit - Prucalopride 2 mg OD



SCBM: Spontaneous Complete Bowel Movement
SBM: Spontaneous Bowel Movement
BM: Bowel Movement

Stanghellini1 V et al, Abstract OP 185, 18th UNITED EUROPEAN GASTROENTEROLOGY WEEK, 23-27 October 2010, Barcelona, Spain

Improved Patient Satisfaction maintained up to 18 months with Prucalopride



**** p < 0.001 vs. double-blind baseline (paired t-test)**

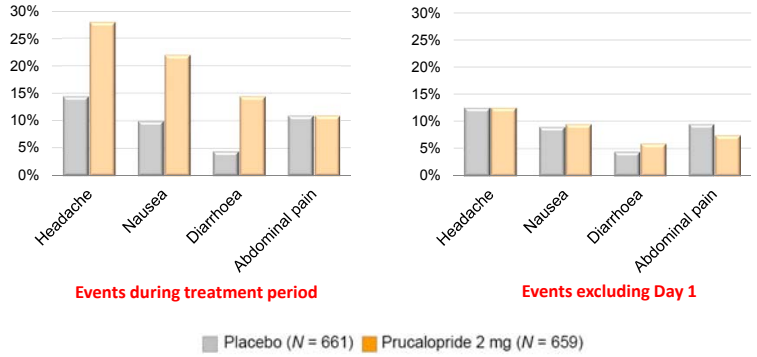
Month 0 reflects satisfaction score at baseline before the entry into the randomized controlled study.

M. Camilleri et al. Aliment Pharmacol Ther 2010; 32: 1113–1123

Favorable safety and tolerability profile

Most frequent drug-related adverse events* (%), pooled data from three pivotal phase III studies (12-weeks treatment period)

*Defined as adverse events occurring in ≥5% patients in any prucalopride treatment group



Tack JF et al. DDW 2008; T1322

Prucalopride

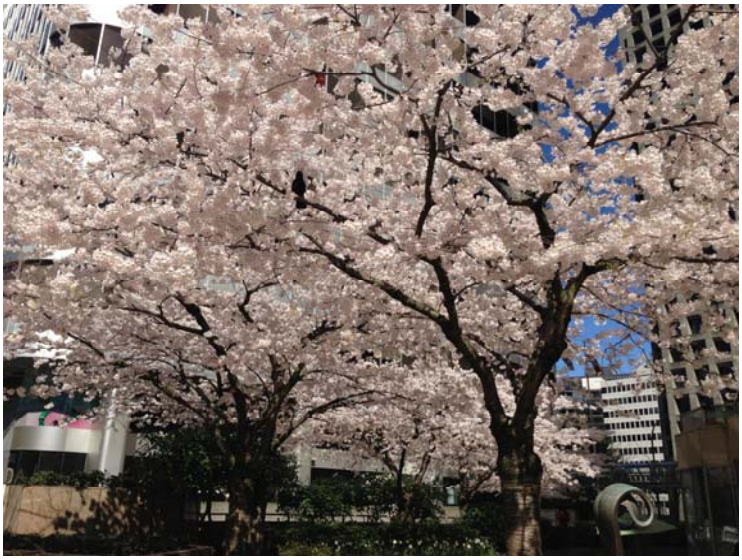
- **Indicated for the treatment of chronic constipation in adult female patients in whom laxatives failed to provide adequate relief. Trials ongoing regarding other patient groups (males, pediatric).**
- **Effective in 2/3 of patients. Quick response.**
- **Safe in elderly.**
- **No demonstrated cardiotoxicity with recommended dose.**
- **No significant drug/drug interactions (SSRIs, warfarin, digoxin, alcohol, BCP)**
- **Adult dose 2 mg OD**
  Elderly and severe renal/hepatic impairment 1mg OD
  No dose adjustment needed for mild-moderate renal impairement.

Back to Patient # 4

- Blood work – normal CBC, TSH, serum calcium level
- AXR - ++ stool throughout colon
- Lower endoscopy not repeated
- Started prucalopride 2 mg po OD, warned re: unknown teratogenic effects and need to stop the drug if trying to conceive
- Headache x 2 days but well-tolerated otherwise
- Returned for follow-up at 3 months, reported good symptom relief after 2 months but constipated again after stopping the drug on her own

Chronic Constipation Take Home Points

- Identify patients with slow-transit constipation who would benefit from prucalopride
- 2/3 of patients responded well in clinical studies with minimal adverse effects
- Unlike previous prokinetics, good cardiac safety profile at recommended dose



THANK YOU FOR LISTENING!