State of the Art 2019: Cases in IBD

@ibddoctor

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Case 1: Ben, CD

- Ben: ileocolonic CD since age 15
- Initially Pentasa x 2y – surgery
  - ileocecectomy 2009
- Aza x 3y, flared 2012
- Now on combo IFX/Aza x 7y
  - 5 mg/kg q8w & 100 mg qd, CRP 2 mg/L
- Slowly worsening over last 2y
  - More pain, CRP 24 mg/L, rare bleeding

Case 1: Ben, CD

- IFX level checked – 2.2, no ABA
- Dose increase to 10 mg/kg q6
  - Trough level up to 13.4
- WBC 7.1, MCV 85
  - Aza dose increase to 150 mg qd
- Bleeding stops, CRP down to 14
- Still having abdominal pain ~ 3 times/week

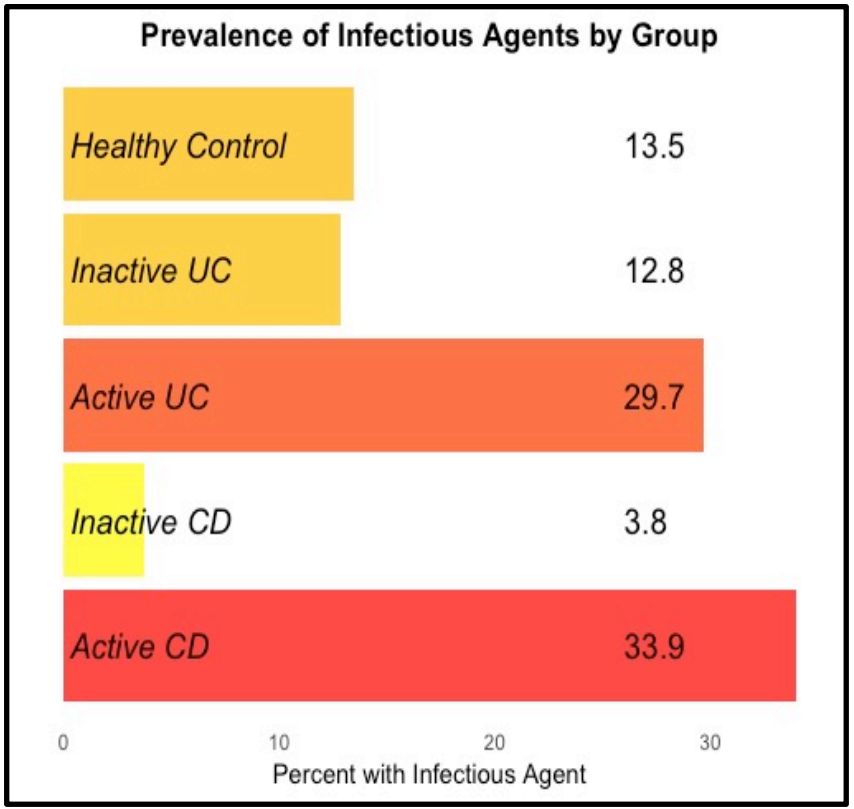
Case 1: Ben, CD

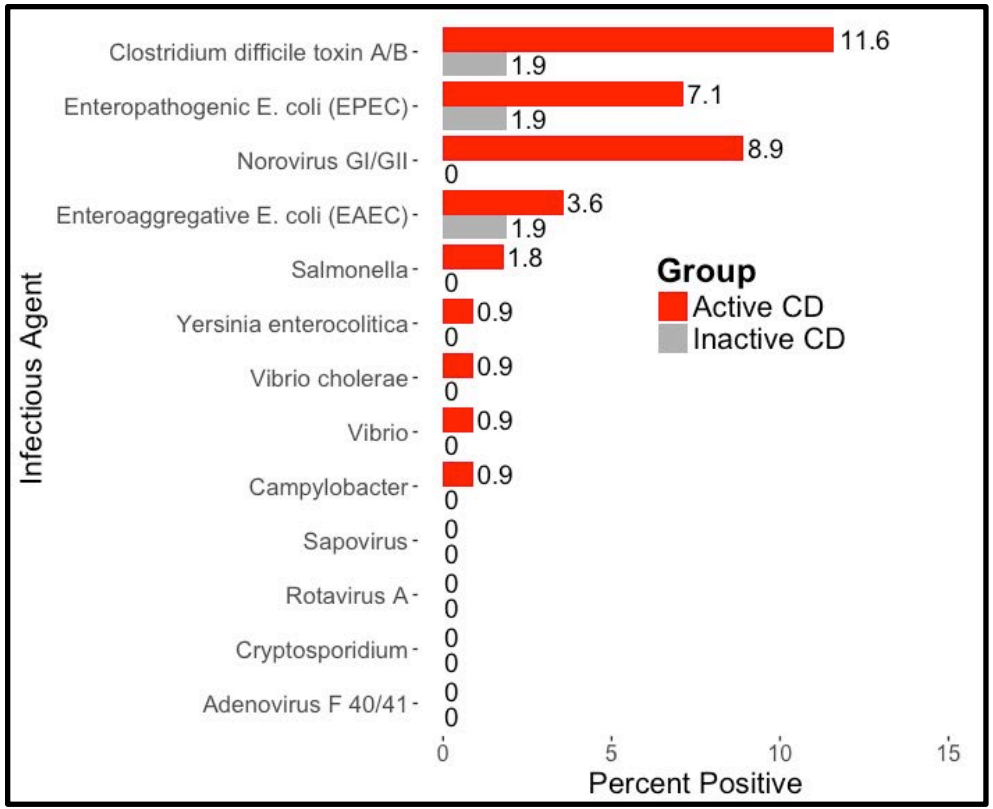
- Ben has increased bloating, distension
- Tested with glucose HBT
- Positive test – methane > 26 ppm
  - Improves with Rifaximin 550 mg bid x 1 week
  - Sees nutritionist for low FODMAP diet
  - Bloating, distension improve

Case 1: Ben, CD

- In late spring, Ben has rapid onset of watery diarrhea, 8x/day
- C diff toxin negative, CRP 16
- Calls office, asks for prednisone
  - No blood
  - GI PCR test comes back + for ***norovirus***
  - Outpatient IV fluids, recovers

Infectious Agents During Flares in IBD





Limsrivilai, Higgins, et al. DDW 2018

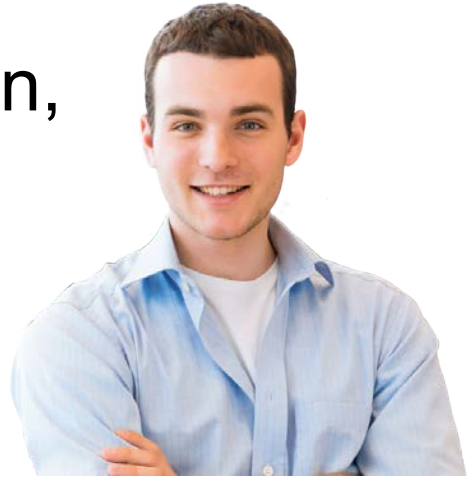
Case 1: Ben, CD

- In August 2018 Ben admitted for pain, no bowel movements x 3 d
- CTE identifies obstruction
  - 7 cm stricture in neo-TI, 20 cm of upstream enhancement, comb sign +
  - CRP 29
  - No infection
  - IV steroids – improves, able to eat, home in 3 days

Case 1: Ben, CD

- Outpatient follow-up visit
- CRP at 8, tapering prednisone
- Pain episodes start to return
- Back to ~ 3x/week at 5mg daily.
- Discuss endoscopic dilation, but too long (>5cm) for high success per literature.
- Enrolls in biomarker research study
- Adherent to Aza and IFX, bump IFX to q4wk

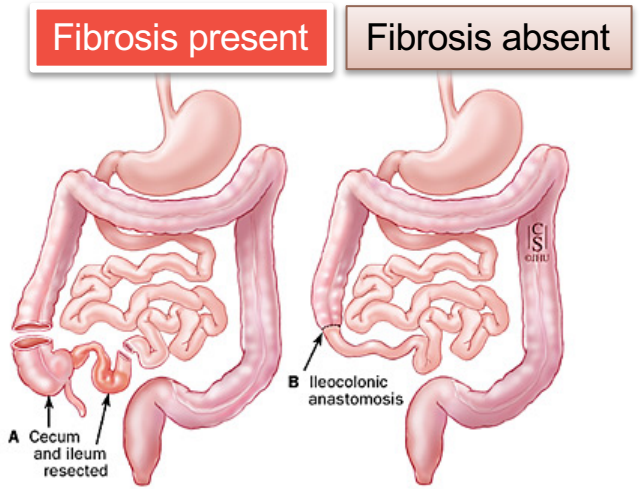
Case 1: Ben, CD



- In January 2019 Ben admitted for pain, no BMs x 36h
- CTE confirms obstruction
  - 11 cm stricture in neo-TI
  - No infection
  - CRP 9 mg/L, IFX level 19.1
  - IV steroids – improves slowly, home in 5 days
- Research lab update – serum ECM1 elevated

ECM1 Serum Biomarker

- Proteomics research
- Serum at diagnosis



- Validated in RISK Cohort
- Serum ECM1 protein has HR 5.33 for future stricturing
  - Multivariate analysis also significant:
    - ASCA IgA↑, CBir1↑

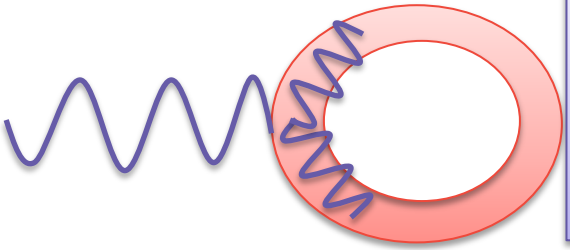
Stidham, Higgins, et al. AJG 2019; 114: 777-785

Case 1: Ben, CD

- Research ultrasound
  - Average of 5 sites in stricture: shear wave velocity 4.8 m/s
    - Very stiff terminal ileum
  - Discuss risks of
    - Perforation, abscess, urgent surgery
  - Discuss change in Rx:
    - Stick with TNF vs. change class vs. elective resection

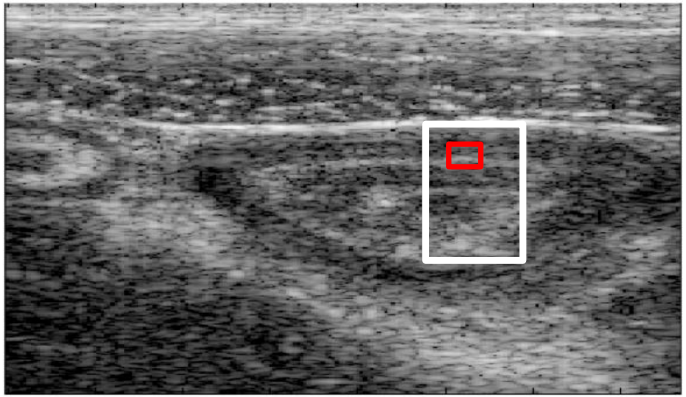
Shear Wave Velocity Ultrasound

Ultrasound Pulse

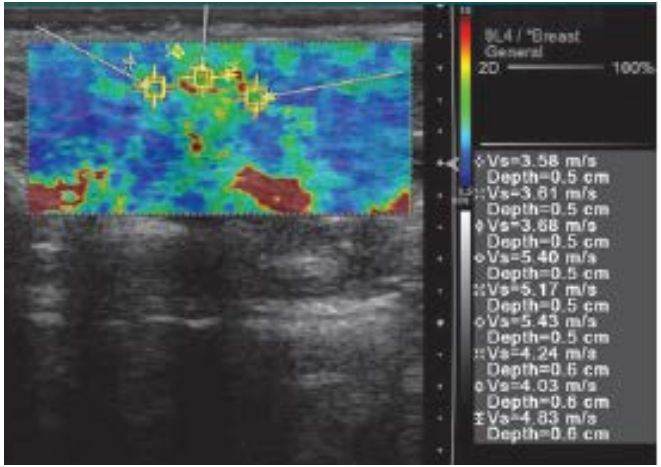


The pulse initiates a shear wave In the tissue

Shear wave velocity ~ tissue stiffness



Measure velocity in bowel wall



Case 1: Ben, CD

- Chooses elective laparoscopic resection
- Does well, out of hospital in 4d
- Slow recovery
  - Feels better rapidly
  - Gradually gets stamina back
  - Runs a 5K at 6 months postop
  - FCP at 3m, 6m both <20

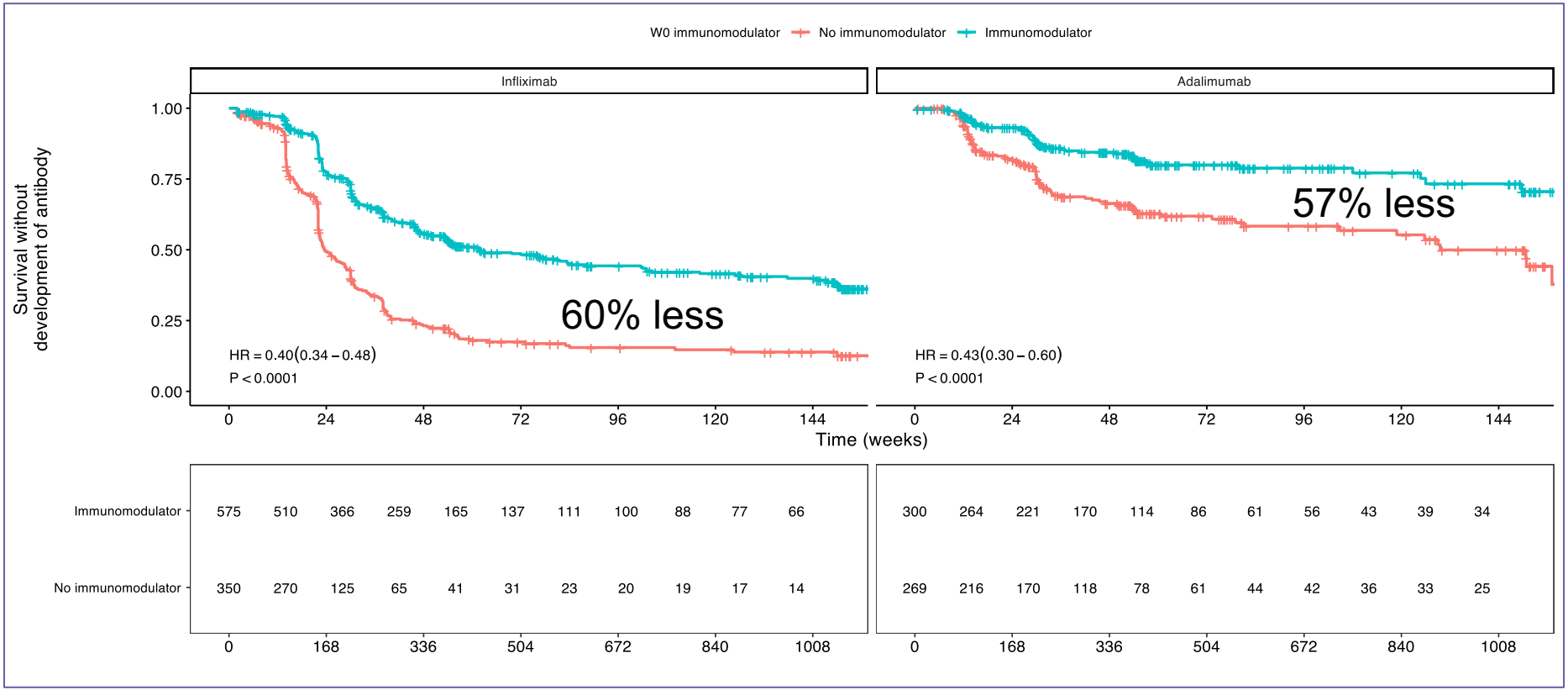
Case 1: Ben, CD

- FCP at 9m postop is 158
- Scope reveals 3 ulcers on anastomosis, open and easily passed, but recurrent i3 ulceration in neoTI.
- CRP 7, asymptomatic
- Risk stratification
  - Nonsmoker, no Hx penetrating complications
  - One prior surgery. Did well on anti-TNF for years.

Case 1: Ben, CD

- Ben starts Humira/Aza
- Does well, FCP back to <20
- F/U scope in 6m with i0
- Slight ulceration remains at anastomosis.
- Anti-IL12/23 as backup plan
- How long on combo with Aza? PANTS data

PANTS: Combo Rx and αBiologic Antibodies



Custom figure courtesy of Nick Kennedy

Case 1 Take Home Points from Ben

- 33% of IBD flares are associated with infections
- Many patients with CD strictures have near-miss obstructions leading up to surgery
- Elective >> urgent surgery for penetrating complications
- Stricture research tools are approaching clinical utility
- Prospective cohort data
  - combo for longer (>= 3y), at least for anti-TNFs

Case 2: Alissa, Perianal CD

- Alissa is diagnosed at age 19 with ileal and rectal CD
- Presents with perianal tags and a fissure, CRP 12 mg/L
- Responds symptomatically to Ada monotherapy, then develops posterior perianal fistula at 4 o’clock

Case 2: Alissa, Perianal CD

- Initially just mild purulent drainage, then develops a painful abscess.
- Comes into ER, gets urgent drainage, Cipro/flagyl, then seton one week later as outpt
- CRP 5 after Abx and seton, ADA level 4.
- Scope – ileum much improved, rectum only low patchy inflammation, <10 aphthous ulcers

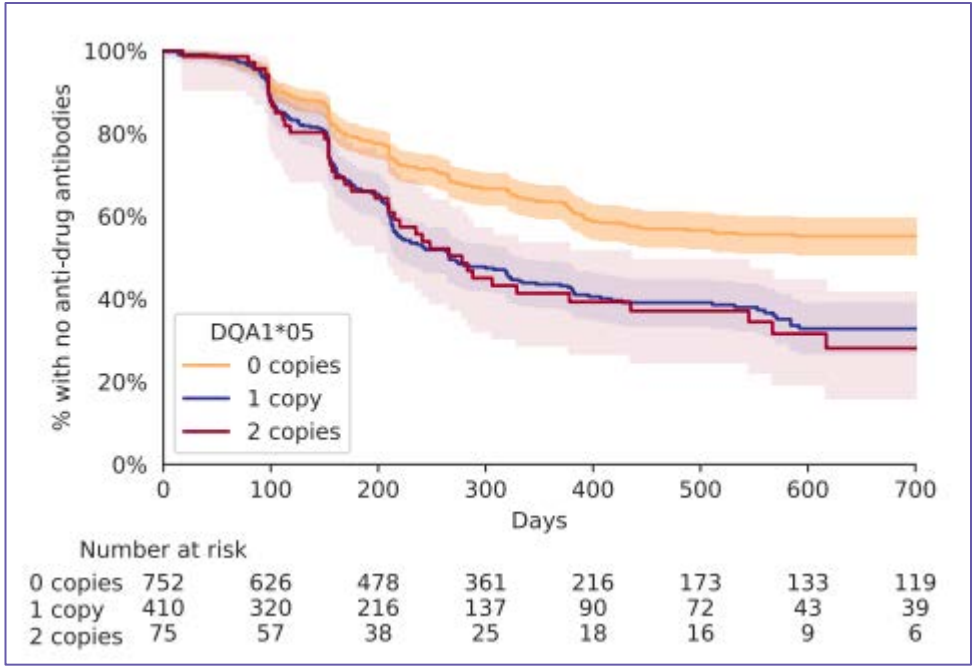
Case 2: Alissa, Perianal CD

- Increase dose to weekly, add Aza 100 mg
- ADA level increases to 8.8,
  low level antibodies
- Fistula improves, less drainage.
- After 3 months, seton “falls out”
- Does well on weekly ADA for 9 months
- Then abscess recurs.

Case 2: Alissa, Perianal CD

- Another cycle of drainage, Abx, seton
- ADA level now 1.9, ABA 147
- Switch to IFX plus Aza.
  - Monitor IFX level at week 14 trough: 32.1
  - WBC 4.3, MCV 96
  - Iron sat 4%, ferritin 12. Hgb 7.3 with fatigue.
    - Transfused with 2 U PRBC. Blood bank notes HLA-DQA1*05
  - CRP improves to 2.

PANTS HLA Data



HLA DQA1*05 doubles the risk of forming antibodies to IFX or ADA.

Data from a prospective cohort study (PANTS) in the UK of
~ 1200 patients starting anti-TNF

Lancet Gastroenterol Hepatol. 2019 May;4(5):341-353.

Case 2: Alissa, Perianal CD

- Does well for 2 years, seton out after 6m
- Then small abscess that she treats with sitzbath and drains at home.
  - Same location
- Fistula has returned. CRP 11, IFX level 6.
  - She reports she stopped filling Aza ~ 8m ago.
- Abx, seton, IFX to 10 mg/kg q6w

Case 2: Alissa, Perianal CD

- 6m later, 2 new fistula openings.
- IFX level now 2.3, ABA titer 320
- Scope – rectal mucosa erythematous, friable, 15-20 low rectal aphthous ulcers
- Setons in new fistulas
- Propose change to Ustekinumab

Case 2: Alissa, Perianal CD

- Ustekinumab data for fistulizing CD

Study or subgroup	Drug therapy Events (Fistula response)	Total	Placebo Events (Fistula response)	Total	Weight	Risk ratio M-H, fixed, 95% CI
1.1.3 TNF-alpha antagonists						
Hanauer 2006(CLASSIC-1)	6	26	2	6	5.3%	0.69 [0.18, 2.62]
Present 1999	39	63	8	31	17.6%	2.40 [1.28, 4.49]
Sandborn 2004	33	60	9	26	20.6%	1.59 [0.89, 2.83]
Sandborn 2007	3	20	5	25	7.3%	0.75 [0.20, 2.77]
Sandborn 2007(PRECISE-1)	14	46	19	61	26.8%	0.98 [0.55, 1.74]
Sands 2004(ACCENT-2)	9	43	7	44	11.3%	1.32 [0.54, 3.22]
Schreiber 2011(PRECISE-2)	11	28	7	30	11.1%	1.68 [0.76, 3.73]
Subtotal (95% CI)		**286**		**223**	**100.0%**	**1.44 [1.09, 1.90]**
1.1.4 Ustekinumab						
Feagan 2016(IM-UNITI)	12	15	5	11	21.1%	1.76 [0.88, 3.53]
Sandborn 2012(CERTIFI-M)	9	24	6	30	19.5%	1.88 [0.78, 4.53]
Sands 2017	39	161	12	77	59.4%	1.55 [0.86, 2.80]
Subtotal (95% CI)		**200**		**118**	**100.0%**	**1.66 [1.10, 2.51]**
Total events	60		23			

Heterogeneity: Chi² = 0.15, df = 2 (*P* = .93); I² = 0%

Test for overall effect: Z = 2.41 (*P* = .02)

Risk ratio M-H, fixed, 95% CI

Comparable to, Possibly slightly better than αTNF

CGH 2018; 16: 1879-1892

Case 2: Alissa, Perianal CD

- Patients who make ABA to one biologic are more likely to make ABA to future biologics.
- Start Uste with co-therapy with Aza
  - Protect the biologic!
  - Emphasize adherence
  - Adjust Aza dose to achieve WBC ~ 4.5, MCV > 95

Case 2: Alissa, Perianal CD

- Fistulas stop draining
- Follow-up scope at week 16 w/o ulcers
- Setons in place
- No abscesses
- She reluctantly concedes that this is success
- But she is tired of setons and fistulas
- She wants stem cell therapy.

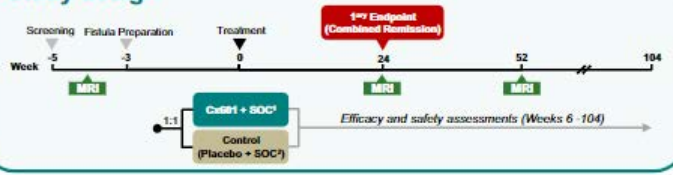
Case 2: Alissa, Perianal CD

ADMIRE CD Study: Cx601 for Complex Perianal Fistulas in Crohn's disease

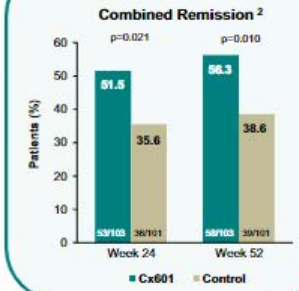
Treatment

Cx601 is a suspension of allogeneic expanded adipose-derived stem cells (eASC) injected locally, and has been shown to be efficacious and well tolerated in Crohn's disease patients with treatment-refractory complex perianal fistulas

Study design



Efficacy



1. Standard of care; 2. mITT population (modified intention to treat)

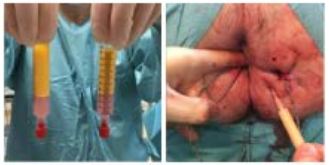
Gastroenterology

Efficacy of Injection of Freshly Collected Autologous Adipose Tissue Into Perianal Fistulas (PF) in Patients With Crohn's Disease(CD)

21 CD Patients w/ PF
- 13 transsphincteric
- 7 anovaginal
- 1 intersphincteric

Repeated injections
Two injections: 9 pt.
Three injections: 4 pt.

Injection(s) with autologous adipose tissue →



Results 6 months after
- Overall response in 76%
  - Fistula healing in 57%
  - Ceased secretion in 14%
  - Reduced secretion in 5%

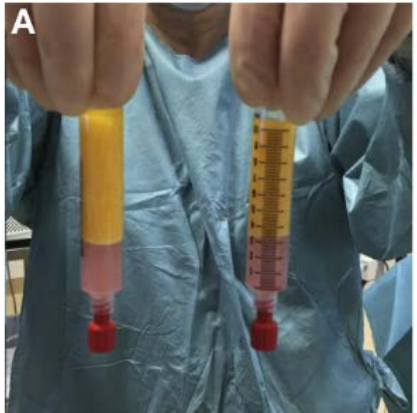
Complications
Abscess (*n*=2), postoperative urinary retention (*n*=1), proctalgia (*n*=4), bleeding (*n*=1)

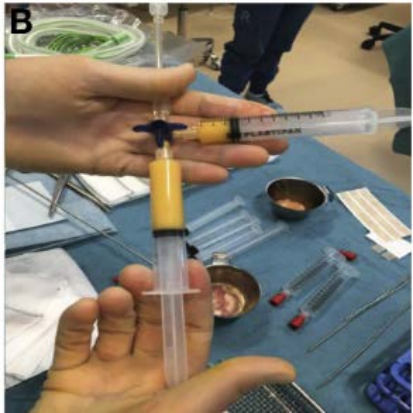
Gastroenterology

Gastro 2018;154: 1334-1342
Gastro 2019; 156: 2208-2216

Case 2: Alissa, Perianal CD

- She is determined to close fistulas
- In Madrid, gets liposuction/stem cells
  - She considers liposuction a bonus. ☺
- One side heals completely
- Returns 4m later for 2nd treatment
- Now all fistulas closed.



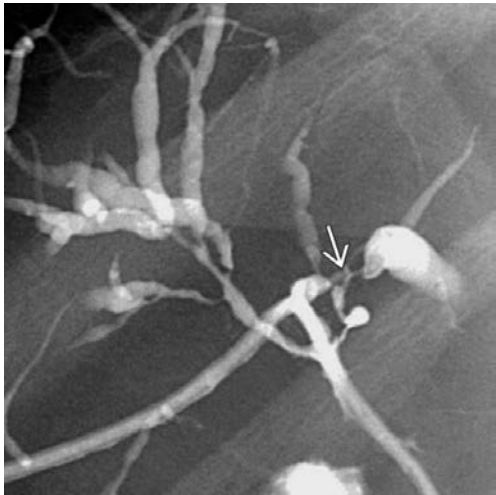


Case 2: Take Home Points from Alissa

- Some patients (HLA DQA1*05) are especially prone to make ABA
- Having made Ab to one biologic – you are more likely to make ABA to future biologics
- Early evidence for Uste in fistulizing CD is good
- Stem cell therapies for fistulas are already available in Europe.

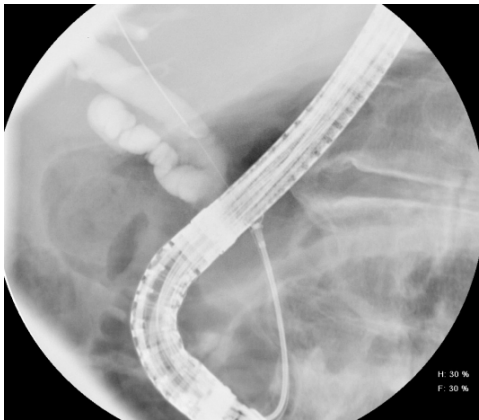
Case 3: Emily, UC with PSC

- Emily presented with fevers and RUQ pain age 24, workup revealed cholangitis
- Responded to antibiotics, but diagnosed with unsuspected PSC.
- Follow up colonoscopy found mild-moderate L sided colitis. Some history of diarrhea x 2 y, rare blood. Treated with 5-ASA daily



Case 3: Emily, UC with PSC

- UC did well, but PSC progressed.
- Rising Alk phos to 500-1000 would indicate recurrent obstruction
- ERCP with sludge removal would help for 8-12m
- Several episodes of cholangitis
- Worsening liver function over 7 years
- Progressed to OLT

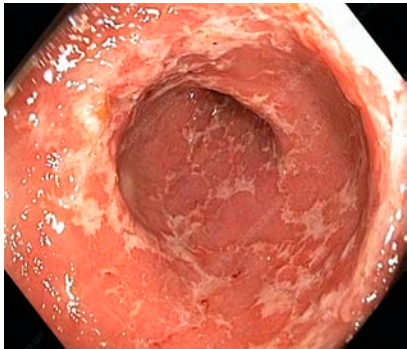


Case 3: Emily, UC post OLT

- After an episode of early rejection, did well with OKT, then transplant regimen
- Tacrolimus, mycophenolate, and 5 mg of prednisone maintained OLT well.
- Diarrhea slowly worsened to 8 BM/d, traces of blood. FCP 517
  - Mycophenolate vs. infection suspected
  - GI PCR and C diff testing negative

Case 3: Emily, UC post OLT

- Scope for diarrhea found pancolitis
- Consistent with chronic UC, not due to mycophenolate
- Surprising to see UC worsen on strong immunosuppressive regimen for OLT?



Case 3: Emily, UC post OLT

- Associated with Tacro OLT regimens
  - Worsening UC in 50%
  - Even *new* UC in ~ 25%
  - More often in Tacro, Cyclo > Aza regimens
  - Cumulative risk for IBD 54% at 10y post OLT
  - Risk factors:
    - Use of Tacro (HR 2.6)
    - CMV+ donor/ CMV – recipient (HR 4.4)
    - 5-ASA use protective (HR 0.2)

Gut, 1998; 43: 639-644.
Am J Transplant 2006; 6:1422-29.

Case 3: Emily, UC post OLT

- Where to go next?
- OLT doing well. Regimen working.
- 5-ASA partially effective, 5BM, FCP 380
- How about anti-TNF?
  - Anti-TNF effective, but high rate of infections in combination with OLT regimens
  - Cryptosporidium, C. difficile, pneumonia
  - EBV+ PTLD reported

APT, 2012; 36: 569-574.
Am J Transplant 2006; 6:1422-29.

Case 3: Emily, UC post OLT

- Gut-specific options
  - Budesonide
    - MMX > Entocort
  - Vedolizumab effective & safe for colonic IBD
- Where possible, stay out of OLT lane
- Could consider change to older Aza regimen
  - May not help much once UC worsened

Gut 2014; 63: 433-41.
Liver Transpl 2017; 23: 968-971.

Case 3: Emily, UC post OLT

- Starts on Budesonide MMX 9 mg daily
- Improves. FCP to 143, blood stops
- Insurance insists on change to Entocort
  - Slowly worsens to 5 BM/d, blood, FCP 456
  - Infection testing negative
  - Flex sig – active ulceration, no CMV, HSV
- Entyvio approved but MMX budesonide not covered, because insurance.

Case 3: Emily, UC post OLT

- Improves on Entyvio plus Entocort.
- Blood, mucus, and urgency resolve
- FCP to <16
- Able to taper Entocort to 3 mg daily

Case 3: Take Home Points from Emily

- Patients without IBD before OLT are 54% likely to develop IBD
- This is increased on modern Tacro IS.
- IFX is effective, but additive IS: more infxn/PTLD
- 5-ASA can help
- Budesonide (MMX>Entocort) can help
- Vedolizumab effective and safe in OLT.

Case 4: Bill, Severe UC

- 36 y/o Bill starts seeing blood in stool
- 2014 sees GI, gets scope, Dx UC
  - 35 cm extent, moderately active
- Starts 5-ASA (oral + enema), improves
- Tapers to oral 4.8 g/d, flares
- First course of prednisone x 8 weeks

Case 4: Bill, Severe UC

- Does well, tapers off prednisone
- Maintained on 5-ASA oral Rx
- Flare 3y later – initially pain, fever, and watery diarrhea, then turned bloody
- *Clostridium difficile* EIA toxin and PCR +
- Treated with vancomycin x 14 days
  - Improves

Case 4: Bill, Severe UC

- Worsens about 2 weeks after vanco
- 5-6 BM daily, trace blood
- *C diff* PCR still positive, toxin negative
  - Carrier? Or recurrence?
- Longer 2nd course of vancomycin x 8 weeks, plus prednisone 40 mg taper over 8 weeks
  - Improves

Case 4: Bill, Severe UC

- 2018 flares, tapers pred by 2.5 mg/wk
- WBC down to 4.2, FCP 327
- Blood again at 5 mg prednisone
  - C diff testing negative
- Flex sig - moderately active to > 50 cm
  - Extent has increased.
- Adds IFX at 5 mg/kg
  - Better– stools formed, blood and mucus gone.

Case 4: Bill, Severe UC

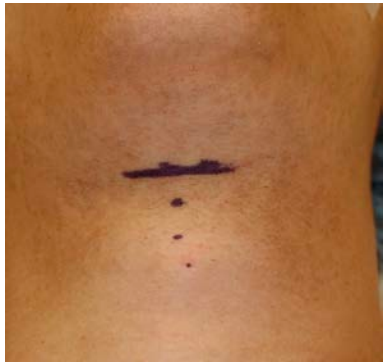
- 2019: Week 14 trough IFX 4.3, FCP 492, blood now daily
- Colonoscopy – now pancolitis, appears more active. GI PCR negative
- Change to 10 mg/kg q 6 weeks, Aza to 200 mg
- Add prednisone 40 mg with 8 week taper

Case 4: Bill, Severe UC

- May 2019: hospitalized for flare at 20 mg oral prednisone, on high dose IFX, Aza. FCP 923, CRP 38, Alb 2.9
  - Last dose IFX 1 week ago
- Reports compliance with Rx, but 8-12 BM daily with 30 second urgency and blood
- *C diff* and GI PCR testing negative

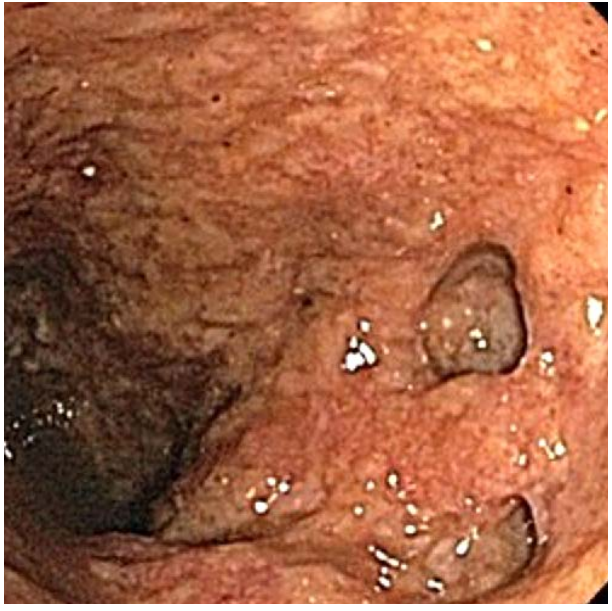
Case 4: Bill, Severe UC

- 38 y/o with refractory pancolitis
  - Failing IFX/Aza combo + OP prednisone
  - Recent IFX dosing, so Cyclo not an option
  - Vedo too slow, Uste not approved for UC
- Meets with surgeons, marked for ostomy
- He is not thrilled
- Wants other options



Case 4: Bill, Severe UC

- Flex sig – severe, deep ulcers
- Biopsies negative for CMV, HSV, other causes
- What next?



Tofacitinib Option

Clinical Gastroenterology and Hepatology 2019;17:988–990

RESEARCH CORRESPONDENCE

Efficacy of Induction Therapy With High-Intensity Tofacitinib in 4 Patients With Acute Severe Ulcerative Colitis

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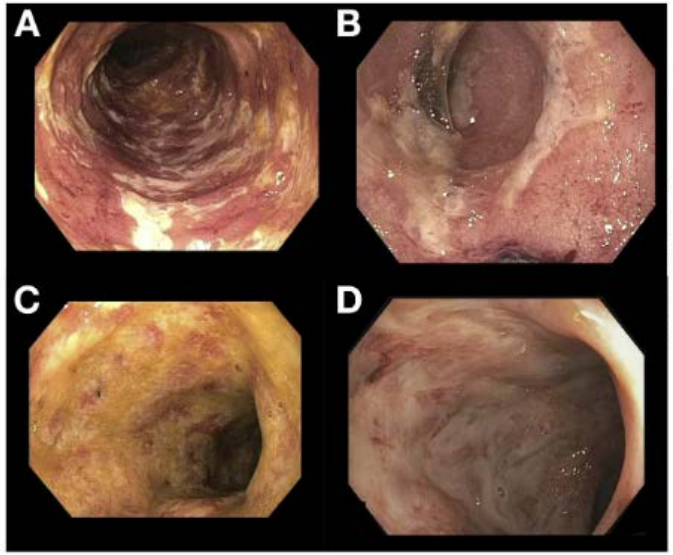
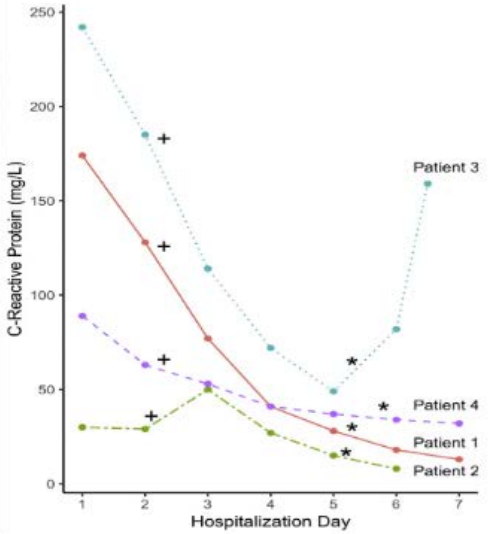




Case Series:
Tofacitinib 10 mg tid plus
IV solumedrol rescued
3 of 4 high risk ASUC patients.

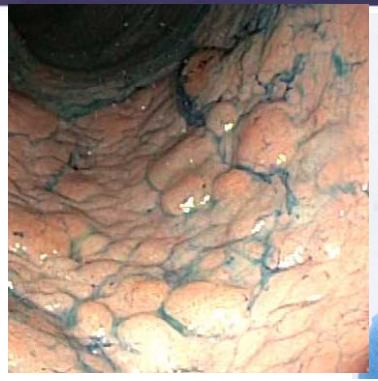
Case 4: Bill, Severe UC

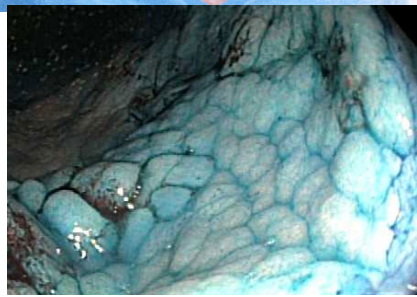
- Started on IV solumedrol 15 mg q6h
- Plus tofacitinib 10 mg tid
- CRP falls rapidly – 4 after 9th dose
- FCP pending
- Symptoms much improved, 2 BM daily, no more mucus or blood on 5th day
- Tapers to tofacitinib 10 mg bid, prednisone 40mg

Case 4: Bill, Severe UC

- Tapers off prednisone
- Gets approval for tofacitinib 10 mg bid
- Feels better than since before UC Dx
- Now almost 8 years since Dx.
- Follow up scope/1st surveillance scope 6m post hospitalization

Case 4: Bill, Severe UC

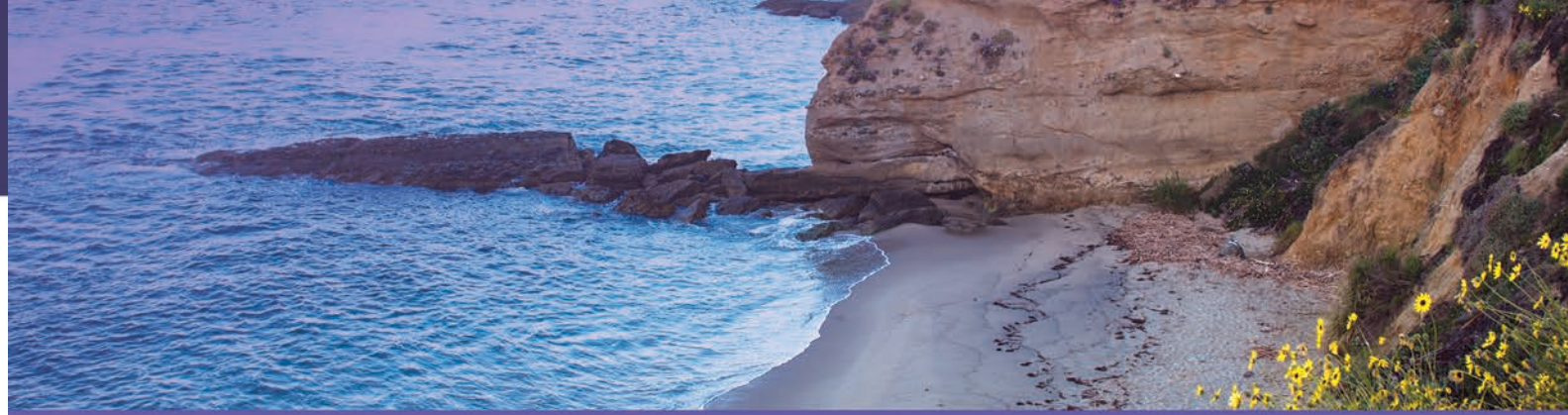




- Mucosa healed, but lumpy.
- Some worrisome lesions
- Switch to chromoendoscopy
  - Lesions now look ***very*** worrisome
  - Large, multifocal areas of HGD in R, TV, L
- Goes to elective colectomy
  - Stops tofacitinib 1 week prior
  - Does well, stage 1 CRC confined to colon, nodes (-)

Case 4: Bill, Severe UC

- *C diff* can change UC trajectory
- Chronic active inflammation – can develop CRC before 8 years
- Be ready to use chromo in bad cases
  - Switch if schedule allows
  - Reschedule if not
- Better to save the person than the colon



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