Enteropathic Arthritis

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Disclosures

- Site PI on UCB NR-Ax-SpA trial
- Site PI on Abbvie AS trial

Outline

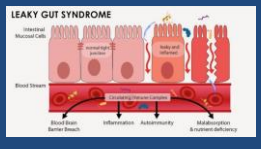
- SpA and Colitis
- IBD and Arthritis
- Other intestinal processes associated with arthritis
  - Whipple's Disease
  - Intestinal Bypass Arthritis
  - Celiac Disease

Definition

- Arthropathies associated with disease of large and small intestines:
  - Inflammatory bowel disease
    - Crohn's disease
    - Ulcerative colitis
  - Infectious enteritis (reactive arthritis)
  - Whipple's disease
  - Intestinal bypass surgery
  - Celiac disease

Pathogenesis

- Perturbation of gut barrier?
  - Leaky gut syndrome?
  - Permits antigen (microbiome? diet?) to cross 'unprocessed' and be presented to the immune system, leading to a host response
- Genetic predisposition with environmental trigger?
  - Clear genetic associations
    - HLA B27, CARD 15, others
  - The microbiome?
- Circulating microbial components
  - Cannot culture
  - PCR of synovial fluid?



How Often do Patients with SpA Have Intestinal Inflammation?

Type of SpA	Macroscopic	Microscopic
Enteropathic ReA	30-46%	64-89%
Urogenital ReA	Rare	19%
AS	29-49%	25-62%
PsA	26%	Unknown
Undifferentiated SpA	24-38%	24-72%

Peng S. WRAMC 2/2009

Relation Between Arthritis and Colitis Histology

- Reactive Arthritis
  - Acute lesions
- Undifferentiated arthritis
  - Chronic > acute lesions
- AS
  - Chronic >>acute lesions
- Arthritis remission = normal gut histology
- Joint flares = gut inflammation

De Vos et al. Gastroenterol. 1996;110:1696.
Mielants et al. J Rheumatol. 1995;22:2279.

Spondyloarthopathic Ileitis and Crohn's Disease

- Subclinical vs. preclinical Crohn's disease
- Study of 123 patients with SpA who underwent ileocolonoscopy
- Baseline and repeat at 2-9 years
  - Normal 32%
  - Acute lesions 23 %
  - Chronic lesions 45%
- 6% developed CD

Rudwaleit M and Baeten D. Best Pract Res Clin Rheumatol. 2006;20:451-471

Risk factors for GI disease in patients with SpA

- Chronic inflammation at greatest risk
- Persistently high C-reactive protein
- Radiographic sacroiliitis in the absence of HLA-B27

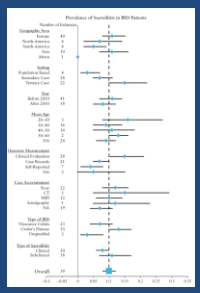
How often do patients with IBD have arthritis?

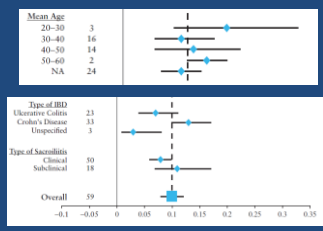
The Prevalence and Incidence of Axial and Peripheral Spondyloarthritis in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis

Maren C. Karreman,[a,b] Jolanda J. Luime,[a] Johanna M. W. Hazes,[a] Angelique E. A. M. Weel[a,b]

J Crohns Colitis. 2017 May 1;11(5):631-642.

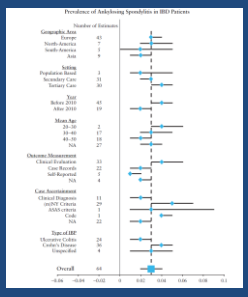
Sacroiliitis (imaging) in IBD Patients

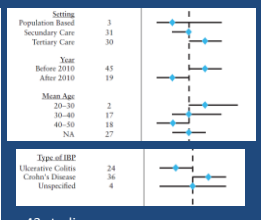




- 41 studies
- Overall risk about 10%
- CD: 13%; AS: 7%

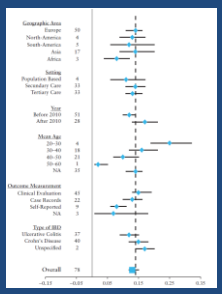
AS in IBD Patients

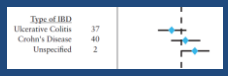




- 43 studies
- Overall about 3%
- CD: 4%; AS 2%
- NR-Ax-SpA not included; may explain different in pre 2010/post 2010 findings

Peripheral Arthritis in IBD Patient





- 52 studies
- Overall rate about 13%
- Unspecified: 17%; CD 15%; UC 12%
- Enthesitis: 8 studies, ranging from 1 to 54%
- Dactylitis: 6 studies, ranging from 0 to 5%

IBD and Arthritis Prevalence: Key Points

- Overall worse in younger patients
- Prevalence for AS in IBD is low (3%) but imaging shows sacroiliitis more frequently (10%)
- Peripheral arthritis is more common (13%); individual studies have shown much higher rates
- Dactylitis is rare
- Enthesitis prevalence is unclear

Risk Factors for Arthritis in IBD

- Large bowel disease
- Other extraintestinal manifestations
  - E nodosum
  - Stomatitis
  - Uveitis
  - P gangrenosum

IBD and Peripheral Arthritis

- Arthritis is the most common extra-intestinal manifestation of IBD
- Can occur before bowel symptoms and at any time in the disease course
- Most frequent with extensive UC and CD;
  - Abscesses
  - Perianal disease
  - Erythema Nodosum
  - Pyoderma Gangrenosum

IBD and Peripheral Arthritis

- Male=Female
- Occurs at any age
- Relationship between flares and severity of bowel disease (UC)
- In UC, surgical resection of diseased segment **may** stops the arthritis
- In CD, surgical resection does not help arthritis

Differential Diagnosis

- In patients with known IBD:
  - AVN
  - Septic arthritis
    - Including SI joints, in patients with fistulas
    - May be polymicrobial
    - New onset monoarthritis in an IBD patient is septic until proven otherwise
  - HPOA
- DDx when joint pains and GI sx presenting together
  - IBD
  - ReA
    - Enterics (except E. coli)
    - Pseudomembranous colitis
  - Whipples
  - Behcets
  - Celiac
  - Intestinal bypass arthritis
  - Parasitic infection

Classification of IBDAA

- Peripheral arthritis:
  - Type I
    - Pauciarticular (5 or fewer joints)
  - Type II
    - Polyarticular
- Axial Arthritis (Type III):
  - Sacroiliitis/Spondylitis

Type I IBDAA

- Affects about 5% of patients with IBD
- 5 or less joints; Most often affects the knee
- Usually self limiting, non-erosive
- Strongly associated with all extra-intestinal manifestations of IBD
- Equal incidence between males and females
- Peak age of onset 25-44
  - Incidence is 3.6% in UC and 6% in Crohn's
  - Often parallels the intestinal activity; role for surgery in UC?
  - Associated with HLA-DRB1*0103, HLA-B27 and HLA-B*35

Holden w, et al. Rheumatic Disease Clinics of North America 2003;29:513-530.
Orchard TR,et al. Gut 1998;42:387-391

Type II (Polyarticular) Peripheral Arthritis

- Incidence:
  - 2.5% in UC and 4% in Crohn's
- Polyarticular arthritis:
  - 5 or more joints
  - Most common: MCP's
  - May be migratory
  - Usually non-erosive
- No HLA-B27 association
  - Associated with HLA-B*44
- Exacerbations/remissions

Type II (Polyarticular) Peripheral Arthritis

- Chronic course independent of activity of the IBD
- Duration: persists for months to years
- Associated with uveitis but not with other extraintestinal manifestations

Peripheral Arthritis

- Peripheral arthritis associated with IBD is seronegative
- Typically non-deforming and nonerosive
  - Erosive disease affecting the hips, elbows, MCP joints, MTP joint and erosive polyarthritis has been described
    - Concomitant 2nd disease?
- In MCP and MTP's, arthropathy differs from RA as it is predominately asymmetric

Axial (Type 3) Arthritis

- Ulcerative colitis 2-6%, Crohn's 5-22%
- Presents as either:
  - Spondylitis:
    - 1-26% of IBD pts
    - May occur with type I arthritis
  - Sacroiliitis:
    - Asymptomatic
      - About 10%
    - Ankylosing spondylitis-like
      - 3%

Axial (Type 3) Arthritis

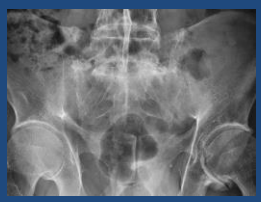
- Male: female ratio 2:1
- Occurs at any age
- Axial involvement and IBD course are usually independent
- **Usually precede onset of IBD by many years**
- Genetic associations
  - CARD15 and HLA-B27
- Inflammatory back pain
  - Lumbar straightening, dorsal kyphosis, limited chest expansion

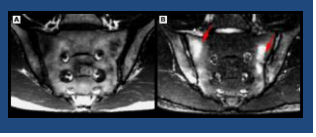
IBDAA Synovium

- Synovial fluid: WBC 1500 – 50,000
  - PMN predominate
- Synovial membrane biopsy:
  - Mild chronic inflammation indistinguishable from RA
  - Proliferation of synovial lining cells, increased vascularity, infiltration of mononuclear cells

IBDAA – SI Joint Imaging

- Indistinguishable from AS
  - Bilateral sacroiliac erosions
  - "Pseudowidening" of the SI joint
  - Fusion with complete obliteration of SI joint
  - MRI is most sensitive/specific for sacroiliitis





IBDAA – Radiology (besides the SI joints)

- Spine:
  - Shiny corners or Romanus lesions
  - Syndesmophytes
    - Symmetric, delicate appearing, marginal (AS-like)
- Peripheral joints:
  - Soft tissue swelling, juxta-articular osteoporosis, mild periositis, effusion
  - Usually without erosions/destructions
- Enthesitis:
  - Faint periosteal reaction at bony prominence

NSAIDs and IBD

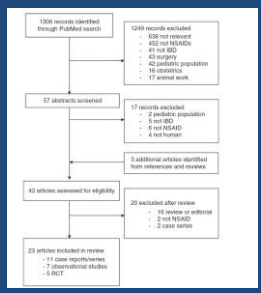
- Classic teaching is that NSAIDs exacerbate IBD; what is the data, however?

Nonsteroidal anti-inflammatory drugs and exacerbations of inflammatory bowel disease

CHARLOTTE L. KVASNOVSKY[1], USMAN AUJLA[2] & INGVAR BJARNASON[1]

Scandinavian Journal of Gastroenterology. 2015; 50: 255–263

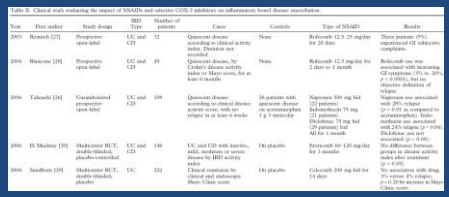
Meta-Analysis and Review



Observational Data

- 7 studies; generally small, single center
- Varying quality
- Appears to be an association between NSAID use and hospitalization for IBD
- Not clear if patients given NSAIDs were in IBD remission at the time NSAIDs were given
- Were NSAIDs given for inflammatory arthritis that may have indicated active IBD?

RCT Data



- 4/5 studies assessed COX-2 inhibitors; no increased risk of IBD flare/relapse
- One study with NSAIDs given to IBD in remission – 20% relapse rate, but was generally mild and transient
  - Naproxen: 28%
  - Indomethacin: 24%
  - Diclofenac: Not associated with an increase in risk

IBD Treatment and Arthritis

Table 1. Therapy of arthritis associated with inflammatory bowel disease (IBD).

Axial involvement and active IBD	Axial involvement and IBD in remission	Peripheral involvement and IBD	Peripheral involvement and IBD in remission
Physical activity	Physical activity	Local (type 1) or systemic (type 2) steroids	Local (type 1) or systemic (type 2) steroids
TNF-α inhibitors Coxibs???	NSAIDs/COXIBs TNF-α inhibitors	Sulfasalazine TNF-α inhibitors MTX???	NSAIDs/COXIBs Sulfasalazine TNF-α inhibitors

COXIBs, selective inhibitors of COX-2; IBD, inflammatory bowel disease; NSAIDs, nonsteroidal anti-inflammatory drugs; TNF, tumour necrosis factor.

Table 2. When to start treatment with TNF-α inhibitors.

Axial involvement	Persistently high disease activity (BASDAI >4)
	Failure at least two NSAIDs
Peripheral involvement	Failure of local or systemic steroids
	Failure of DMARDs
Enthesitis/dactylitis	In severe case or after failure of traditional therapy.
Poor prognostic factor risk	High CRP/ESR bone edema at MRI
Active inflammatory bowel disease	Moderate or severe form in case of fail to respond at least one DMARDs
Inflammatory bowel disease complicated by abdominal abscess or stricture	Abdominal surgery before starting TNF-α inhibitors

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; NSAIDS, nonsteroidal anti-inflammatory drug; TNF, tumour necrosis factor.

What about other IBD treatments / SpA treatments?

- Steroids
- Anti-Integrin Therapies (Vedolizumab and Natalizumab)
- Ustekinumab
- Secukinumab

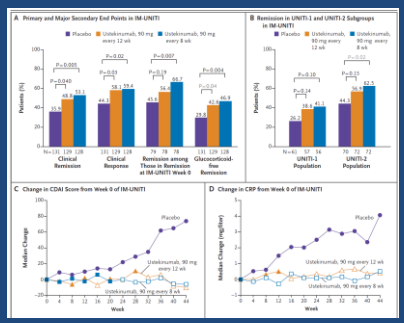
Ustekinumab in IBD

Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease

B.G. Feagan, W.J. Sandborn, C. Gasink, D. Jacobstein, Y. Lang, J.R. Friedman, M.A. Blank, J. Johanns, L.-L. Gao, Y. Miao, O.J. Adedokun, B.E. Sands, S.B. Hanauer, S. Vermeire, S. Targan, S. Ghosh, W.J. de Villiers, J.-F. Colombel, Z. Tulassay, U. Seidler, B.A. Salzberg, P. Desreumaux, S.D. Lee, E.V. Loftus, Jr., L.A. Dieleman, S. Katz, and P. Rutgeerts, for the UNITI–IM-UNITI Study Group*

N Engl J Med 2016;375:1946-60.

Ustekinumab is Effective in CD



Secukinumab for CD

Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial

Wolfgang Hueber,[1] Bruce E Sands,[2] Steve Lewitzky,[3] Marc Vandemeulebroecke,[4] Walter Reinisch,[5] Peter D R Higgins,[6] Jan Wehkamp,[7] Brian G Feagan,[8] Michael D Yao,[9] Marek Karczewski,[10] Jacek Karczewski,[10] Nicole Pezous,[4] Stephen Bek,[3] Gerard Bruin,[1] Bjoern Mellgard,[1] Claudia Berger,[1] Marco Londei,[11] Arthur P Bertelsen,[1] Gervais Tougas,[3] Simon P L Travis,[12] for the Secukinumab in Crohn's Disease Study Group

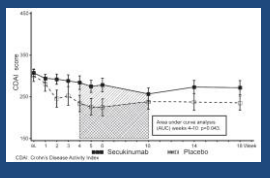
Table 2 Primary end point (Bayesian analysis including historical controls)

CDAI change from baseline to week 6

Treatment	n	Mean (SD)	95% Credible interval*
Secukinumab twice 10 mg/kg	39	−29.2 (14.0)	−56.9 to −1.4
Placebo	20	−63.1 (13.9)	−90.4 to −35.9
ΔCDAI (AIN457 vs placebo)		33.9 (19.7)	−4.9 to 72.9

*Probability that secukinumab reduces CDAI more than placebo >4.4%.
Probability that secukinumab reduces CDAI by >50 points more than placebo <0.1%.
Probability that secukinumab reduces CDAI by >40 points more than placebo >99.9%.
†Bayesian statistics report probabilities and credible intervals, unlike frequentist statistics that report p values and CIs.
CDAI, Crohn's Disease Activity Index.

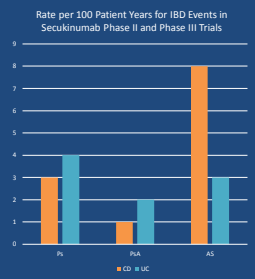
"Inhibition of IL-17A by secukinumab was ineffective in this trial of patients with moderate to severe Crohn's disease. Compared with placebo, secukinumab had a smaller effect and patients on secukinumab showed higher rates of adverse events."



Gut 2012;**61**:1693–1700. doi:10.1136/gutjnl-2011-301668

Is Secukinumab Use Dangerous in Patients with Spondyloarthritis?

- Pooled data
  - Ten Ps (N=3430), two PsA (N=974), two AS trials (N=591)
- 12 total CD cases – 6 in hx of CD
- 9 total UC cases – 4 in hx of UC
- Rate similar to expected background rates



Whipple's Disease

- Rare multisystem systemic disease
  - Infection caused by Tropheryma Whippelii
  - Predominance in the small bowl
- Male to female ratio of 9:1
- Mean age 55 (range 20-82)
- Symptoms:
  - Diarrhea, weight loss, fever and arthritis
  - LAD, hyperpigmentation, serositis, CNS

Whipple's Disease

- Lab abnormalities:
  - Anemia, hypoalbuminemia, low serum carotene and iron
  - Increased stool fat
- Biopsy:
  - Villi become distended with foamy and PAS + macrophages
  - Rod-shaped free bacilli in the lamina propria
- PCR of tissue or blood

Whipple's Disease

- Peripheral arthritis
  - Polyarticular and symmetric
    - 67% as their only symptoms
    - Migratory and episodic
  - Precedes GI symptoms by 5 years
  - Arthritis flares not related to GI symptoms
  - Erosions rare
- Axial arthritis
  - Incidence controversial; reported 8-20%
  - Relation to HLA-B27 unclear

Intestinal bypass arthritis

- Jejunocolic and jejunoileal bypass surgeries
- Inflammatory joints in 6-52%
- Usually within 3 years of surgery
- Females > males
- No HLA association
- Arthritis:
  - Peripheral symmetric, polyarticular,
    - Knees, wrists, MCP's and MTP's
- Vesiculopustular skin rash
  - Occurs in over ½ of patients with arthritis

Intestinal bypass arthritis

- Pathogenesis:
  - Bacterial overgrowth in blind loop
  - Mucosal changes allow increased absorption of bacterial antigens
  - Formulation and circulation of immune complexes
  - Immune complexes demonstrated in synovium, synovial fluid and skin lesions

Intestinal bypass arthritis

- Therapy
  - NSAIDs → Can cause dehiscence though!
  - Antibiotics
  - Corticosteroids
    - Effective for both the arthritis and dermatitis
- Surgical revision
  - Total revision is curative

Celiac Disease

- Gluten-sensitive enteropathy
  - **Not gluten sensitivity**
- Small bowel develops villous flattening and atrophy leading to malabsorption
- Symptoms:
  - Diarrhea and weight loss
    - 50% of adult patients do not have diarrhea
  - Malaise, weight loss and low serum folate
  - Steatorrhea, distension, flatulence, greasy stools
- Associated disorders:
  - Dermatitis herpetiformis, hyposplenism, arthritis and autoimmune disorders

Celiac Arthritis

- Arthropathy:
  - Peripheral 37%
  - Axial 29%
  - Combined 25%
- Most common pattern is a polyarticular, symmetrical arthritis affecting large joints
  - Non-erosive and non-deforming
  - Knees, hips and shoulders
- High frequency of HLA-B8 and DR3
- May precede GI symptoms

Farrell R and Kelly C. N Engl J Med 2002;346:180-188

Questions?