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All attendees will be muted and will remain in Listen Only Mode.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.
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Kathy A. Peterson, MD, MSCI
June 25, 2020 at Noon EDT

Visit gi.org/ACGVGR to Register

Week 15: Management of Anti Coagulation for GI Endoscopy
Aasma Shaukat, MD, MPH, FACG
July 2, 2020 at Noon EDT

Disclosures:

Speaker:
Randy Longman, MD, PhD
Consultant: Pfizer
Advisory Board: Ancilia
Research Funding: Boehringer Ingelheim
Clinical Characterization, Pathogenesis, and Treatment of IBD: Associated Spondyloarthritis

Randy Longman, MD, PhD
Director, Jill Roberts Center for IBD
Associate Professor of Medicine and Immunology
Jill Roberts Institute for Research in IBD
Weill Cornell Medicine

Unmet Needs in IBD-Associated Spondyloarthritis

- Despite the frequency of IBD-SpA, clinical diagnostic tools are variably applied and further characterization with validated SpA disease activity indexes are needed.
- Evidence of shared genetic, cellular, and microbial mechanisms underlying both IBD and SpA independently, highlight the potential for a distinct clinicopathologic entity, but pathogenesis is not well understood.
- Existing treatment paradigms focus on management of luminal inflammation, but a better understanding of the underlying pathogenic mechanisms in IBD-SpA are need to pave the way for more targeted and effective therapies.
Learning Objectives

• Understand and define diagnostic criteria for IBD-SpA
  – Clinical criteria
  – Disease activity scores
• Define IBD-SpA as a unique clinicopathologic entity
  – IL-17/IL-23 pathway and effectors
  – Microbiome
• Integrate emerging medical therapy into treatment paradigm

Joint inflammation is common in IBD

• 30-40% of patients with active IBD experience EIMs\(^1,2\)
• Arthritis is the most common EIM reported in IBD, but large variability in prevalence of IBD associated peripheral arthritis (5-44%) and axial inflammation (1-25%) reflect this lack of uniformity in clinical disease characterization\(^3,5,13\)
• Crohn’s disease > UC \(^3,5\)
• In 20% cases, joint inflammation precedes initial diagnosis of intestinal disease \(^6,7\).
• Inflammation of the sacroiliac joints is classically associated with IBD, both peripheral and axial joints can be involved

Under-diagnosis and inadequate assessment limits the ability to track symptom response and impedes delivery and optimization of therapy
Defining Inflammatory Extra-Intestinal Manifestations

- An inflammatory pathology in a patient with inflammatory bowel disease (IBD) that is located outside the gut whose pathogenesis is either
  - Dependent on extension or translocation of immune responses from the intestine
  - An independent inflammatory event perpetuated by IBD or that shares a common environmental or genetic predisposition with IBD
- True extraintestinal manifestations (EIMs), as described above, exclude pathologies (such as associated autoimmune conditions) or complications of IBD and its treatment

*As defined by the European Crohn’s and Colitis Foundation.
CD=Crohn’s disease; EIM=extraintestinal manifestations; IBD=inflammatory bowel disease.

Commonly Affected Organ Systems by EIMs

<table>
<thead>
<tr>
<th>System</th>
<th>EIMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal</td>
<td>Erythema nodosum, Pyoderma gangrenosum, Sweet syndrome, Metastatic CD</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Epidermolysis Bullosa, Erythema nodosum, Pyoderma gangrenosum, Sweet syndrome, Metastatic CD</td>
</tr>
<tr>
<td>Ocular</td>
<td>Epidermolysis Bullosa, Uveitis, Scleritis</td>
</tr>
<tr>
<td>Oral</td>
<td>Oral CD, Orofacial granulomatosis, Metastatic CD</td>
</tr>
</tbody>
</table>

Defining Spondyloarthritis: Disease Subtypes

**Axial SpA**
- In patients with ≥3 months back pain and age of onset <45 years
- Sacroiliitis on imaging
  - Sacroiliitis on imaging AND ≥1 SpA feature
- HLA-B27 positive AND ≥2 other SpA features
  - HLA-B27
  - Erythema nodosum
  - Pyoderma gangrenosum
  - Pruritus
  - Scleritis
  - Elevated CRP

**Peripheral SpA**
- Peripheral Arthritis and/or Enthesitis and/or Dactylitis
- ≥1 SpA feature
- ≥2 other SpA features

Retrospective analysis using ASAS criteria to characterize SpA in IBD cohorts provided estimates of axial SpA (7.7-12.3%) and peripheral SpA (9.7-27.9%)7,8
Diagnosing IBD-Spondyloarthritis

<table>
<thead>
<tr>
<th>Axial IBD-SpA</th>
<th>Peripheral IBD-SpA</th>
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<tbody>
<tr>
<td>Inflammatory back pain* in a patient with IBD AND Sacroiliitis on imaging** OR HLA B-27 antigen positivity</td>
<td>Arthritis and/or dactylitis and/or enthesitis in a patient with IBD AND Exclusion of other specific forms of inflammatory joint disease</td>
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</table>

* Insidious onset, chronic back/buttock pain with morning stiffness lasting ≥ 30 minutes, improvement with activity and nocturnal exacerbation.
** Active inflammation on MRI highly suggestive of sacroiliitis OR definite radiographic sacroiliitis according to modified New York criteria


Defining IBD-SpA Disease Activity: PROs

**Bath Ankylosing Spondylitis DAI (BASDAI):**
0.2 x (fatigue + spinal pain + peripheral + enthesitis) + 0.5 (stiffness + duration)

**Ankylosing Spondylitis DAS (ASDAS):**
0.121 x spinal pain + 0.058 x stiffness duration + 0.11 x PGA + 0.073 x peripheral arthritis + 0.579 x log(CRP+1)
Defining IBD-SpA Disease Activity: Multi-D

44 or 66/68 point joint count

Peripheral SpA Response Criteria (PSPARC40)

Imaging criteria for IBD SpA still need to be defined

Mechanisms Linking Inflammation to EIMs

- Independent inflammatory events may be initiated or perpetuated in the presence of IBD or shared genetic/environmental risk factors
- EIMs may arise from an extension of an immune response from the intestine to extra-intestinal sites

- IL-23 dependent cellular immunity
- Gut as the portal of disease
- Role for the microbiome
Defining the role for IL-23/IL-17 in SpA

Taams, et al. Nature Reviews Rheumatology 2018
Defining the role for IL-23: Independent of IL-17


Gut as the portal for SpA

Ileocolonoscopy in Seronegative Spondyloarthropathy

M. DE YOOS, C. CVUELIER, H. MIELANTS, E. VEYS, F. BARBIER, and A. BEURKERT
Department of Gastroenterology, Pathology, and Rheumatology; State University of Ghent, Ghent, Belgium


Kumar, et al. J Gastroenterol. 2020. PMID 32367294
Defining a role for microbiota in IBD-associated spondyloarthritis (SpA)

Microbial Mechanisms of IBD-SpA

A. Molecular mimicry
B. Microbial translocation
C. Soluble microbial-derived factors
D. Disruption of the gut barrier

Is there an IBD SpA microbiota that promote systemic inflammation?

A potential role for Klebsiella in AS

Sequential studies in ankylosing spondylitis
Association of Klebsiella pneumoniae with active disease

R. W. Ehringer, D. D. Cawdell, P. Cowling, and A. Ehringer

ANKYLOSING SPONDYLITIS, HLA-B27 AND KLEBSIELLA. I. CROSS-REACTIVITY STUDIES WITH RABBIT ANTISERA

J. Welsh, H. Avarian, P. Cowling, A. Ehringer, P. Wooley, and R. Ehringer

AUTOANTIBODIES TO HLA B27 IN THE SERA OF HLA B27 PATIENTS WITH ANKYLOSING SPONDYLITIS AND REITER'S SYNDROME

Molecular Mimicry with Klebsiella Pneumoniae as Potential Mechanism of Autoimmune Disease

By Peter L. Schewimbeck, David T. V. Vu, and Michael B. A. Oldstone

Comparison of the Ammon Acid Sequences of HLA Antibodies and Klebsiella pneumoniae

Antibodies to HLA B27 Individually and in Combination With Other HLA Antigens

<table>
<thead>
<tr>
<th>Serum Amino Acid Sequence</th>
<th>HLA B27 Individuals</th>
<th>Non-HLA Amino Acid Sequence</th>
<th>HLA B27 Individuals</th>
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<tbody>
<tr>
<td>HLA B27</td>
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</table>

American College of Gastroenterology
Defining a role for microbiota in IBD-associated spondyloarthritis (SpA)

The Germfree State Prevents Development of Gut and Joint Inflammatory Disease in HLA-B27 Transgenic Rats
By Joel D. Taucog, James A. Richardson, JoAnne T. Croft, William A. Simmons, Ming Zhou, José Luis Fernández-Suero, Edward Baish, and Robert E. Hammer

Normal Luminal Bacteria, Especially Bacteroides Species, Mediate Chronic Colitis, Gastritis, and Arthritis in HLA-B27/Human R Microglobulin Transgenic Rats
J Clin Invest, 1996

Breban, M et al Ann Rheum Dis 2017

Enterobacteriaceae expansion in peripheral CD-SpA

### Current Medical therapy for IBD-SpA

<table>
<thead>
<tr>
<th>Axial CD-SpA</th>
<th>Peripheral CD-SpA</th>
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<tbody>
<tr>
<td>Short term NSAIDs if IBD in remission*</td>
<td>Short term NSAIDs if CD is in remission*</td>
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<tr>
<td>Anti-TNFα therapy:</td>
<td>local steroid injection for pauciarticular or short-term oral steroid for polyarticular peripheral SpA</td>
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<tr>
<td>Infliximab</td>
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<tr>
<td>Adalimumab</td>
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<tr>
<td>Certolizumab pegol</td>
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<tr>
<td>Sulfasalazine</td>
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<tr>
<td>Methotrexate</td>
<td></td>
</tr>
<tr>
<td>Anti-TNFα therapy: Infliximab, adalimumab, certolizumab pegol</td>
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</tr>
<tr>
<td>No IL12/23 inhibitor therapy is proven beneficial in axial SpA.</td>
<td>Anti IL12/23: Ustekinumab</td>
</tr>
</tbody>
</table>

Kumar, et al. J Gastroenterol. 2020. PMID 32367294

### Medical therapy under development for IBD-SpA

- **Selective JAK-1 inhibitor: Upadacitinib and filgotinib**
  - (successful phase 2 trials in AS, PsA and CD; positive results in phase 3 trial of upadacitinib in PsA. Ongoing phase 3 trial in CD)

- **α4β7 anti-integrin: Vedolizumab**
  - Approved for treatment of moderate-to-severe CD. Based on recent a systematic review, may be effective in preventing onset of arthritis in CD, however, may not be effective in improving co-existing arthritis. Further studies are awaited.

- **Therapies under investigation:**
  - S1P1 receptor modulator – Ozanimod, Etrasimod
  - Anti- TNF like cytokine 1A (anti-TL1A) therapy
  - Fecal microbiota transplant
  - Combination biologic therapy (combining two or more biologics with different mechanism of action)

Kumar, et al. J Gastroenterol. 2020. PMID 32367294
Enhancing the Effective Use of Therapy for IBD-SpA: Sulfasalazine therapy and the microbiome

- SAS is a **pro-drug** released into the distal intestine
- Dose 2-4g daily
- Limited by side effects of GI intolerance and sensitivity to sulfa
- Effective for peripheral arthritis
- Mechanism of impact of the gut microbiome is unclear

Anti-TNFα therapy for IBD-SpA

- Systematic reviews of TNF antagonist therapy support the general efficacy of TNFα blockade (infliximab, adalimumab, certolizumab) in IBD-associated EIMs
- Efficacy of anti-TNFα therapy in AS correlates with the reduction of Th17 cells in the peripheral blood following treatment
- Limited study data is available to characterize the impact of joint disease activity
Anti-α4β7 therapy for IBD-SpA: Increasing systemic inflammatory burden?

Emergence of severe spondyloarthropathy-related enthesal pathology following successful vedolizumab therapy for inflammatory bowel disease


Also, Varks, G et al Ann Rheum Dis 2017

11 patients achieving remission with vedolizumab with HLA-B27 de novo or flare of inactive SpA

Also, Varks, G et al Ann Rheum Dis 2017

Anti-α4β7 therapy for IBD-SpA: Data from larger studies and open questions?


- Joint inflammation improved with bowel disease, but 13% of patients without EIM at baseline developed non-inflammatory arthralgias

GEMINI (Feagen B, et al. JCC 2018)

- Clinical response and clinical remission at W6 and W52 associated with sustained resolution of arthritis/arthralgias
- No association with remission/response and worsening EIM

Open questions:

- Combination therapy (Roblin, et al JCC 2018)
- Data with joint disease activity indexes
Open question: Anti-IL12/23 therapy for IBD-SpA

- IL-17A inhibitor therapy is effective for AS (Baeten D, et al. NEJM 2015), but not effective for Crohn’s with higher rates of adverse events (Hueber W, et al. Gut 2012)


![Abundance of Candida](image)

Optimizing Medical Therapy for IBD-SpA

- Sulfasalazine: Useful in IBD-pSpA, 2-4 g/day as tolerated
- Biologic therapy
  - Anti-TNFα: effective as monotherapy but studies with DAI are needed
  - Anti-α4β7: no clear exacerbation of extra-intestinal inflammatory tone, but dedicated studies are needed with DAI and combination therapy
  - Anti-IL12/23: dedicated studies are needed with DAI
- Emerging therapy
  - Tofacitinib is effective for PsA in Phase 3 trials (Gladman D. NEJM 2017), but 2019 ACR/ASAS guidelines favor TNFi and anti-IL17 therapy over tofacitinib
  - S1P modulators, anti-TL1A, Microbial manipulation
Lecture Objectives: Summary

Define the clinical phenotype:
- ASAS Clinical criteria
- Disease activity scores: BASDAI, ASDAS-CRP, joint evaluation and multi-disciplinary clinic with rheumatology

Define the pathogenesis
- IL-17/IL-23 pathway and cell effectors: Th17, CD8+, Innate lymphoid cells, and Macrophages
- Gut as the portal
- Microbiome: Enterobacteriaceae, R. gnarus; Strain specificity and targeting metabolic effectors

Emerging treatment paradigms
- Role for anti-TNFα, and potential role for anti-IL12/23 therapy, but need for DAI
- Evaluate role for anti-IL17 therapy and anti-α4β7
- Emerging role for JAKI
- Potential role for new agents: S1P modulation, TL1A blockade

Additional References:

Questions?

Randy Longman, MD, PhD

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