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Inflammatory Joint Pain in Inflammatory Bowel Disease (IBD) Patients Treated with Anti-Tumour Necrosis Factor (TNF) Therapy:

Differentiating IBD Arthritis, Paradoxical Arthritis, Anti-TNF-induced Lupus, and Serum-Sickness-Like Reactions

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Key Takeaways
We propose a mechanism based approach assessing bowel activity, timing of drug exposure and auto-antibody profile to manage arthritis in IBD patients treated with anti-TNF therapy.
Paradoxical arthritis, anti-TNF- induced lupus, and serum-sickness-like reaction can occur with anti-TNF therapy; all require a change in targeted therapy.
Managing arthritis in IBD requires multidisciplinary work between gastroenterologist and rheumatologist to optimize treatment of both manifestations.

Introduction

Musculoskeletal complaints remain the most frequent extra-intestinal manifestation (EIM) of inflammatory bowel disease (IBD), affecting up to one-third of patients over their lifetime and representing a major determinant of impaired quality of life.[1,2] Joint symptoms range from transient arthralgia to severe, erosive arthritis and are a leading cause of functional limitation among individuals with Crohn's disease and ulcerative colitis.

The advent of anti-tumour necrosis factor-alpha (anti-TNF-α) therapy revolutionized IBD management. Landmark infliximab trials in the late 1990s demonstrated not only mucosal healing but also marked improvement in arthritic and dermatologic EIMs.[3] Over time, however, long-term experience revealed paradoxical and autoimmune musculoskeletal phenomena—such as new or worsening arthritis in patients with quiescent bowel disease, occasionally accompanied by lupus-like serology or immune-complex reactions.

For clinicians, differentiating classical enteropathic arthritis from paradoxical inflammation, anti-TNF-induced lupus (ATIL), and serum-sickness-like reactions (SSLR) is essential. Misclassification can lead to premature discontinuation of an effective biologic or inappropriate escalation of therapy. This review provides a summary of current knowledge regarding the epidemiology, mechanisms,

Entity	Gut Activity	Onset Timing	Serology	Typical Pattern / Management
IBD Arthritis	Active	Any time	Seronegative	Large joints ± axial — Treat IBD ± DMARDs[1]
Paradoxical	Remission	Months–years	ANA- / RF- / CCP-	RA/PsA-like — Switch class; DMARD ± biologic[4,10]
ATIL	Remission	Months–years	ANA+, dsDNA+, histone-	Lupus rash / serositis — Stop TNF; supportive[7]
SSLR	Remission	7–14 days post-infusion	ATI+, ↓ C3/C4	Fever, rash, polyarthritis — Steroids; avoid culprit[7]

Table 1. Distinguishing Features of Inflammatory Joint Pain in IBD Patients on Anti-TNF Therapy; *courtesy of Vivek Govardhanam, B.Eng, MD, FRCPC and Catherine Ivory, MD, PhD, FRCPC.*

Abbreviations: ANA: antinuclear antibody; **ATI:** anti-TNF antibodies or anti-infliximab antibodies; **ATIL:** anti-TNF-induced lupus; **CCP:** cyclic citrullinated peptide antibody; **DMARDs:** disease-modifying antirheumatic drugs; **dsDNA:** double-stranded DNA; **IBD:** inflammatory bowel disease; **PsA:** psoriatic arthritis; **RA:** rheumatoid arthritis; **RF:** rheumatoid factor; **SSLR:** serum sickness-like reactions; **TNF:** tumour necrosis factor

diagnosis, and evidence-based management of inflammatory joint pain in IBD patients treated with anti-TNF agents.

Epidemiology and Classification

Population-based registries estimate that 20–30 % of IBD patients experience inflammatory joint symptoms.[1,2] Data from the Swiss IBD Cohort and GETAID registries indicate peripheral arthritis occurs in approximately 13–20% of patients, and axial spondyloarthritis affects 5–10%. The risk is greater in Crohn's disease than in ulcerative colitis, particularly among women, and those with extensive or ileocolonic disease.[2] Clinical features and timing of musculoskeletal symptoms can help differentiate the type of arthritis, and guide subsequent management (**Table 1**).

IBD-associated arthritis can be grouped into three clinical patterns[1]:

1. **Type 1 peripheral arthritis**—acute, asymmetric, oligoarticular <5 joints, predominantly knees and ankles, paralleling intestinal flares.
2. **Type 2 peripheral arthritis**—chronic, symmetrical, polyarticular, involving small joints (hands, wrists), independent of bowel activity.
3. **Axial involvement**—sacroiliitis or ankylosing spondylitis, often associated with HLA-B27 positivity and persisting irrespective of gut inflammation.

Paradoxical arthritis, defined as new inflammatory joint disease during sustained gut remission on anti-TNF therapy, occurs in ~2–10% of treated patients.[4,5] It has been reported with all TNF blockers, most frequently infliximab and adalimumab, and often coexists with paradoxical psoriasis.[5,6]

Anti-TNF–induced lupus (ATIL) develops in <1% of exposed patients.[6,7] The syndrome arises months to years after therapy initiation and is characterized by ANA and anti-double-strand DNA (dsDNA) positivity with mild systemic features.

Serum-sickness–like reaction (SSLR) occurs acutely—typically 7–14 days post-infusion—reflecting immune-complex deposition and complement activation. Its overall incidence is <2%, but risk increases markedly after drug holidays.[8]

Pathophysiology of Joint Manifestations in IBD

IBD-Associated Arthritis — the Gut–Joint Axis

The "gut–joint axis" concept integrates intestinal and articular inflammation through overlapping cytokine networks (TNF-α, interleukin [IL]-23, IL-17) and shared genetic risk alleles (HLA-B27, ERAP1, IL23R).[9] Bacterial antigens such as *Klebsiella pneumoniae* and adherent *E. coli* may translocate across a permeable mucosal barrier, activating Th17-dominant responses that migrate to synovial tissue. Consequently, type 1 arthritis

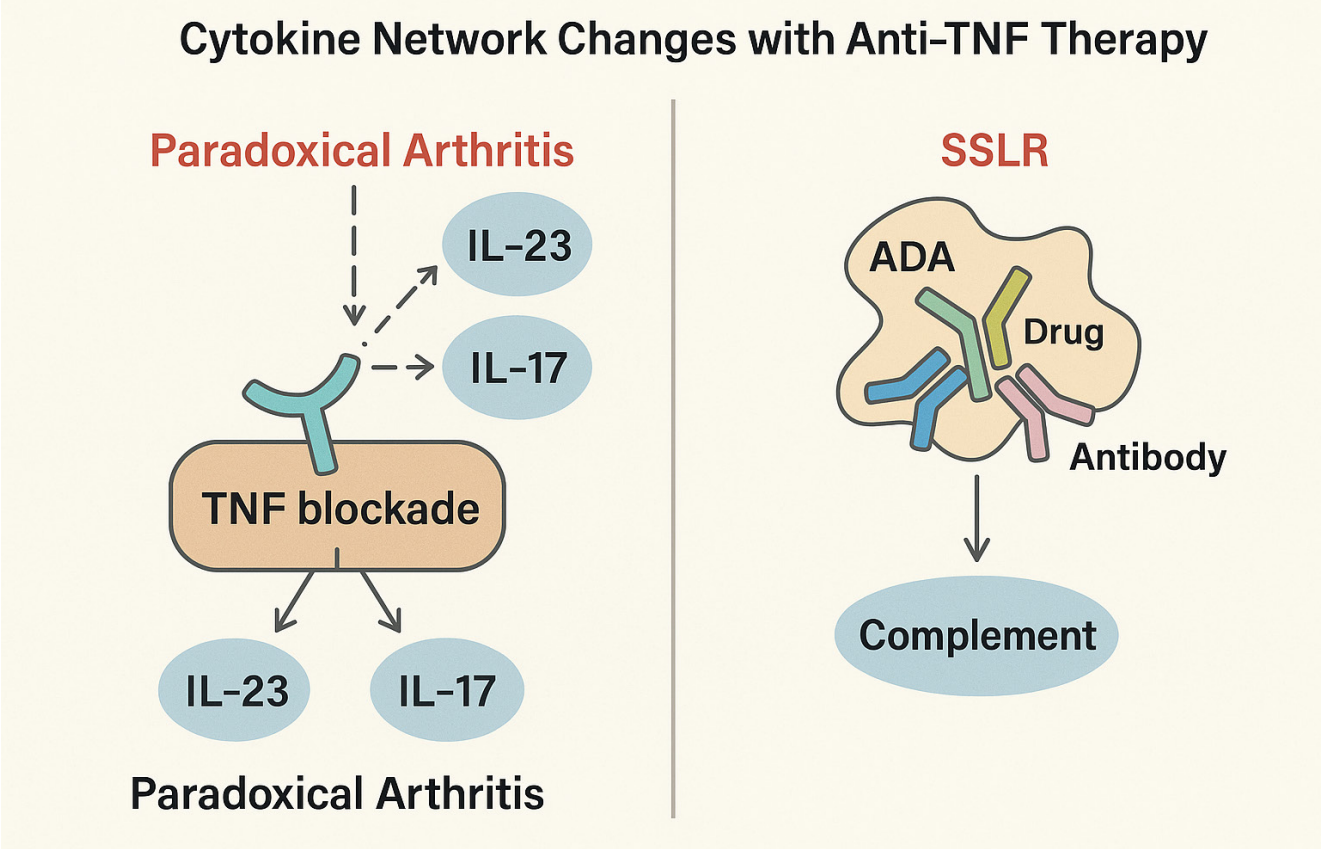

Figure 1. Cytokine network schematic showing tumour necrosis factor (TNF) blockade–induced interleukin (IL)-23/IL-17 and interferon-α up-regulation driving paradoxical arthritis, contrasted with anti-drug antibody (ADA)-mediated immune-complex activation in serum-sickness-like-reaction (SSLR)[6-8,10]; *courtesy of Vivek Govardhanam, B.Eng, MD, FRCPC and Catherine Ivory, MD, PhD, FRCPC.*

mirrors intestinal activity, whereas type 2 and axial disease follow more autonomous courses.

Paradoxical Arthritis under Anti-TNF Therapy

In paradoxical arthritis, TNF blockade disrupts immune equilibrium. Suppression of TNF driven negative feedback leads to compensatory up-regulation of type I interferons and activation of the IL-23/IL-17 axis.[6,9] Histopathologic studies reveal psoriatic-like synovial infiltrates enriched with CD3+, CD20+, and CD68+ cells along with elevated IL-23 expression despite therapeutic drug levels.[10] Importantly, anti-drug antibodies (ADAs) are usually absent, distinguishing this cytokine-rerouting phenomenon from immunogenic "loss of response" (**Figure 1**).

Anti-TNF–Induced Lupus (ATIL)

ATIL arises from autoantibody induction and loss of immune tolerance. Up to 75% of patients on anti-TNF therapy develop new antinuclear antibodies (ANA) and 20–30% develop anti-dsDNA, though only a minority develop drug-induced lupus.[6,7] Unlike classic drug-induced lupus, where anti-histone antibodies predominate, ATIL typically exhibits high-titer ANA (≥1: 320) and dsDNA positivity.[7] Complement activation and immune-complex deposition may contribute to rash, arthritis, and serositis, while severe renal or neurologic involvement remains rare. Among patients with ATIL, cutaneous manifestations are common, reported in approximately 60–70% of cases, but the rash is not uniformly a classic malar rash.[6,7] More frequently, patients develop photosensitive or maculopapular lupus-like eruptions, with malar rash representing only a subset of presentations. Symptoms typically resolve within 2–3 months following discontinuation of therapy.

Serum-Sickness–Like Reaction (SSLR)

SSLR is a type III hypersensitivity reaction. When infliximab is administered intermittently

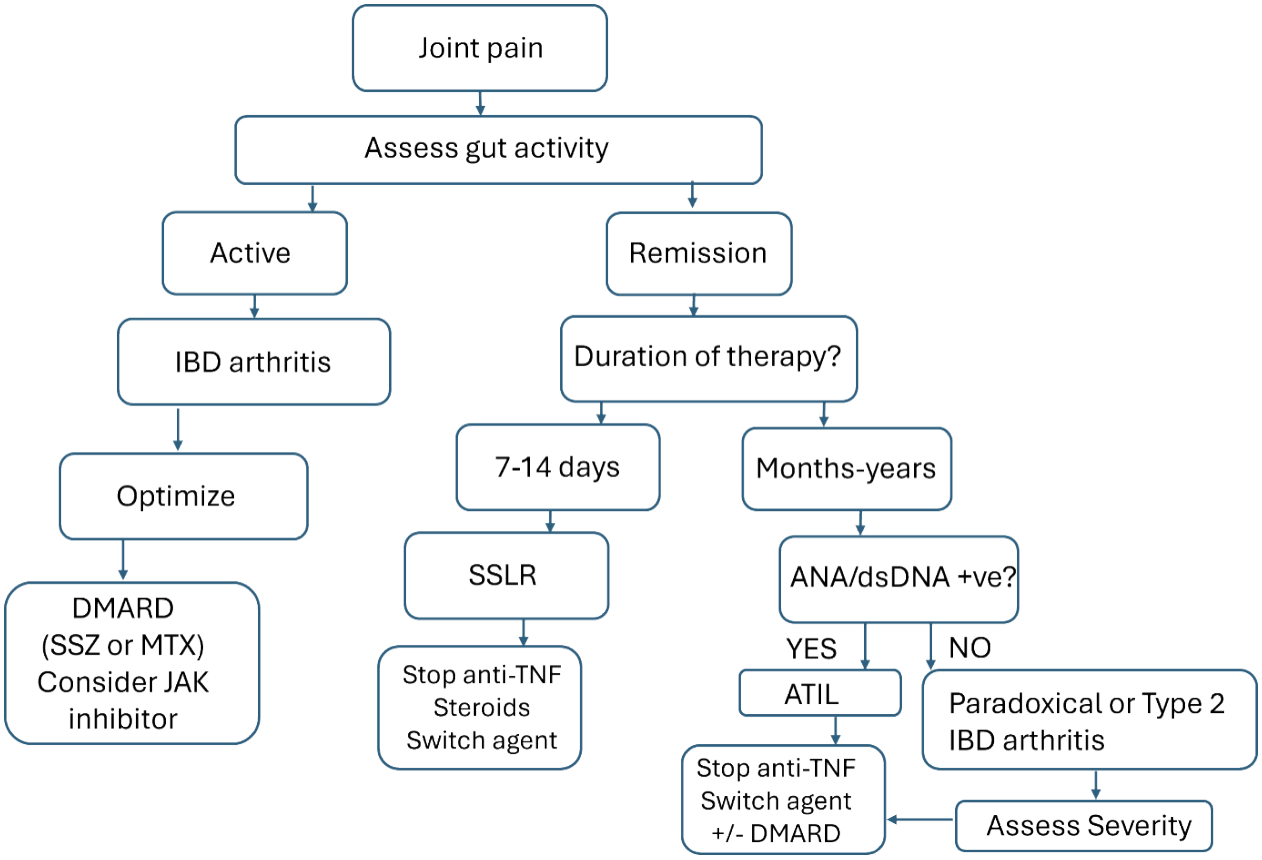

Figure 2. Algorithm for evaluating new arthritis in an anti- tumour necrosis factor (TNF)–treated IBD patient; *courtesy of Vivek Govardhanam, B.Eng, MD, FRCPC and Catherine Ivory, MD, PhD, FRCPC.*

Abbreviations: ANA: antinuclear antibodies; **ATIL:** Anti-TNF- induced lupus; **DMARD:** disease-modifying-anti-rheumatic drugs; **dsDNA:** anti-double-stranded DNA antibodies; **IBD:** inflammatory bowel disease; **JAK:** Janus Kinase inhibitor; **MTX:** methotrexate; **SSLR:** serum-sickness-like-reaction; **SSZ:** sulfasalazine.

or after a long interruption, circulating ADAs form complexes with drug antigen, precipitating complement activation (↓ C3/C4) and cytokine release (**Figure 1**). IgG1-containing immune complexes deposit in small vessels and synovia, causing fever, urticarial or morbilliform rash, and polyarthritis.[8] The reaction subsides rapidly with corticosteroid therapy once the drug is discontinued.

Diagnostic Approach

A systematic evaluation of bowel activity, symptom chronology, serology, and imaging is essential (**Figure 2**).

1. **Assess intestinal activity:** Active gut disease indicates IBD-related arthritis; new arthritis with mucosal remission suggests paradoxical or autoimmune etiology.[1,4]
2. **Timing:**
   - Acute onset (7–14 days post-infusion) → SSLR.[8]
   - Chronic onset (months–years) → paradoxical arthritis or ATIL.[6,7]
3. **Serology:**
   - ANA +/dsDNA + → ATIL.[7]
   - anti-TNF antibodies or anti-infliximab antibodies (ATI) +/low complement → SSLR.[8]
   - ANA −/rheumatoid factor (RF) −/ cyclic citrullinated peptide antibody (CCP) → Paradoxical arthritis.[4,10]

4. **Drug levels:**
   - Therapeutic trough with inflammation → paradoxical disease.
   - Low trough/high ADA → immunogenicity or SSLR.[8]
5. **Imaging:** Musculoskeletal ultrasound detects early synovitis and enthesitis; MRI of sacroiliac joints identifies bone-marrow edema in axial disease.[11,12]
6. **Arthrocentesis:** Exclude sepsis or crystalline arthritis in monoarticular presentations.[13]

General Considerations

Joint pain may not always indicate inflammatory disease. Assessing joint symptoms for active synovitis via ultrasound assessment or MRI can help distinguish osteoarthritis from concomitant fibromyalgia.[11,12] It is important to identify inflammatory arthritis, as it may necessitate adjustments in immunosuppressive therapy. Patients with psoriatic arthritis have an increased risk of gout,[13] which is also inflammatory but does not require changes to IBD therapy. In cases of acute monoarthritis, arthrocentesis is imperative to rule out septic arthritis, particularly in immunocompromised individuals.[14]

Management Strategies

IBD-Associated Arthritis

The primary goal is restoration of bowel remission, which often improves joint symptoms in type 1 IBD-associated arthritis.[1,2] For persistent peripheral arthritis, add sulfasalazine (2–3 g/day) or methotrexate (15–25 mg/week) as steroid-sparing DMARDs.[15] Anti-TNF therapy remains the first-line treatment for axial spondyloarthritis.[1] Short courses of COX-2-selective NSAIDs can be used safely in patients with quiescent bowel disease.[16] Corticosteroids may serve as bridge therapy during induction or when transitioning between biologics.

Paradoxical Arthritis

Disease severity often dictates management[4,10]:

- **Mild:** Add a DMARD (methotrexate or sulfasalazine).
- **Moderate–severe:** Discontinue the TNF inhibitor and switch to a different therapy.
  - **Ustekinumab (IL-12/23 blockade)** has shown improvement in articular symptoms in case series and registry data.[10]
  - **Vedolizumab**, though gut-selective, may allow joint inflammation to subside after TNF withdrawal.
- **Additional advanced therapies** such as JAK inhibitors, S1P receptor modulators and IL-23 inhibitors may be considered in selected cases, though data remain limited.
- **TNF-to-TNF switching** is seldom effective because paradoxical inflammation is considered a class-wide phenomenon.[5]

Anti-TNF–Induced Lupus (ATIL)

Immediate drug cessation is essential.[7] Symptomatic treatment may include NSAIDs, hydroxychloroquine, or low-dose corticosteroids. Lupus manifestations resolve within 6–12 weeks. If ongoing biologic therapy is required, consider switching to an alternate biologic therapy with a different mechanism of action; re-challenging with another TNF agent carries a small but measurable recurrence risk.[7]

Serum-Sickness–Like Reaction (SSLR)

Initiate systemic corticosteroids (0.5–1 mg/kg/day prednisone equivalent) and supportive care.[8] Symptoms typically abate within 48–72 hours. The offending drug should be permanently discontinued and documented as an allergy. For subsequent treatment, consider fully human antibodies (e.g., adalimumab, golimumab) or a non-TNF biologic.[8,17]

Emerging Therapies

JAK inhibitors (tofacitinib, upadacitinib, filgotinib) block multiple cytokine pathways downstream of TNF and IL-23 signalling. Phase 3 trials in ulcerative colitis and real-world data demonstrate their efficacy in managing concomitant arthropathy.[17,18] JAK inhibitors also carry on-label indications for rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, thus addressing both bowel and joint inflammation in most cases. Their oral administration and systemic activity make them particularly attractive for patients with overlapping gut and joint inflammation, although careful

monitoring for infection and thromboembolic risk is required.

Conclusion

Inflammatory joint pain in IBD patients treated with anti-TNF therapy spans a continuum from classical bowel-driven arthritis to paradoxical and autoimmune syndromes. Recognizing the temporal relationship to drug exposure, bowel activity, and antibody profile is critical for appropriate management.

A mechanism-based approach, including treating gut inflammation for enteropathic arthritis, targeting alternative cytokine pathways for paradoxical disease, and discontinuing TNF blockade for ATIL or SSLR, achieves optimal outcomes while preserving intestinal remission. Multidisciplinary coordination among gastroenterology, rheumatology, and dermatology should be the standard for managing these complex immune intersections.

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