

Beyond Corticosteroids: The Case for Targeted Biologics in Lupus Colitis

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Dear Editor,

Lupus colitis, a rare but increasingly recognized gastrointestinal manifestation of systemic lupus erythematosus (SLE), presents a formidable clinical challenge. Characterized by mucosal inflammation and congestion, as depicted endoscopically in Figure 1, protein-losing enteropathy, and, in severe cases, intestinal pseudo-obstruction, it is associated with substantial morbidity.¹ Despite its impact, evidence-based therapeutic protocols remain limited, and most management strategies are extrapolated from the broader SLE literature. We advocate targeted investigation of three biologics with compelling mechanistic rationales: belimumab, voclosporin, and anifrolumab. The supporting evidence is currently mechanistic; direct gastrointestinal clinical trial data are lacking, and we identify this gap as a research priority.

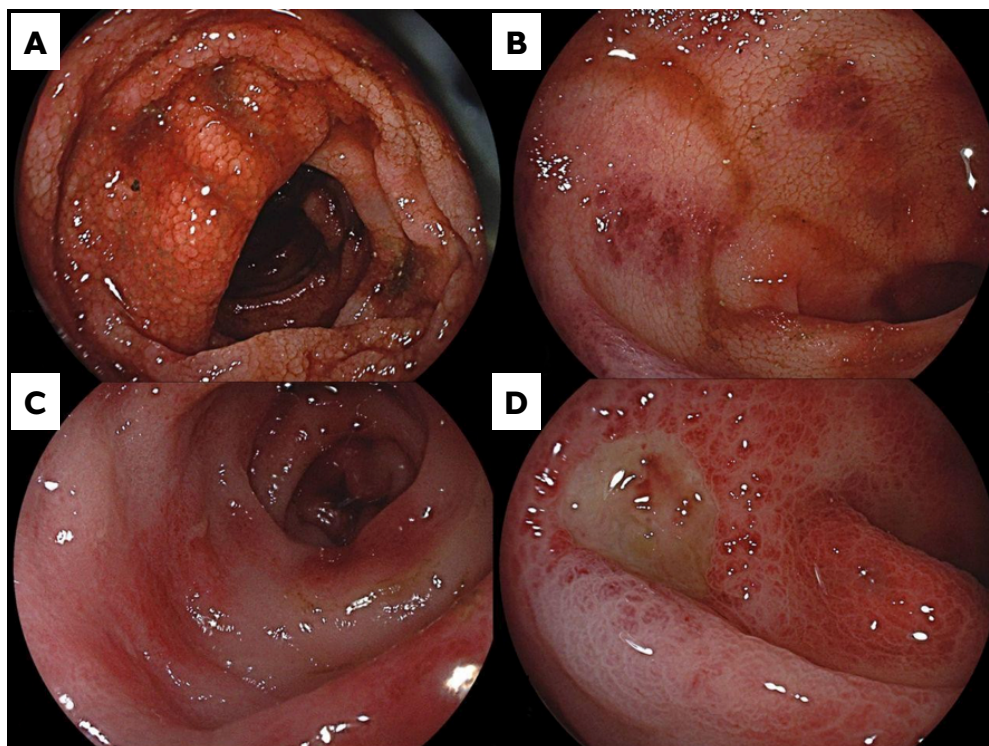


Figure 1. Endoscopic appearance of systemic lupus erythematosus-related colitis, showing congestive and granular mucosa. [1] Adapted from “Fatal Colitis Associated With Active Systemic Lupus Erythematosus Complicated by Cytomegalovirus Superinfection” © 2017, Elisa Gravito-Soares, licensed under CC BY-NC-ND 4.0. Available at: <https://creativecommons.org/licenses/by-nc-nd/4.0/>. Image obtained under a Creative Commons license.

Table 1. Mechanistic rationale and evidence basis for biologic agents in lupus colitis

Biologic	Mechanism	Evidence and Limitations	Proposed Investigation
Belimumab	BLyS inhibitor; reduces autoreactive B-cell survival and pathogenic autoantibody burden	Efficacy established in renal and mucocutaneous SLE. ² Gastrointestinal endpoints are systematically underreported.	Prospective trial with bowel-specific endpoints
Voclosporin	Calcineurin inhibitor; suppresses T-cell activation and downstream cytokine release	Renal efficacy established in the AURORA trials. ^{3,4} No published data on intestinal disease.	Future trials including bowel-specific activity indices
Anifrolumab	Type I IFN receptor antagonist; attenuates IFN-alpha-driven SLE immunopathology	Elevated IFN signatures reported in intestinal SLE. ⁵ Direct colonic evidence is lacking; evidence is limited to a single case report of oral manifestations. ⁶	Mucosal IFN activity studies before and after treatment

Belimumab, a B-lymphocyte stimulator (BLyS) inhibitor approved for active SLE, suppresses autoreactive B-cell survival and reduces the burden of pathogenic autoantibodies. Given that anti-C1q and anti-double-stranded DNA antibodies contribute to complement-mediated intestinal vasculitis in lupus colitis, belimumab's downstream attenuation of humoral autoimmunity is mechanistically persuasive.² Clinical series have demonstrated the efficacy of belimumab in renal and mucocutaneous SLE; however, gastrointestinal endpoints remain systematically underreported.² Dedicated prospective studies of belimumab in patients with active lupus colitis are urgently warranted.

Voclosporin, a next-generation calcineurin inhibitor approved for lupus nephritis, offers enhanced potency and a more predictable pharmacokinetic profile than cyclosporine, without the need for therapeutic drug monitoring.³ Its inhibition of T-cell activation and downstream cytokine release makes it a rational candidate for lupus colitis, in which T-cell-driven mucosal inflammation is a recognized pathogenic contributor. The AURORA trials established its renal efficacy and tolerability.⁴ However, intestinal disease was not an endpoint, and no published data currently address the effect of voclosporin on bowel inflammation. We urge investigators to include bowel-specific disease activity indices in future voclosporin trials.

Anifrolumab, a type I interferon receptor antagonist, represents a third therapeutic avenue. Interferon-alpha dysregulation is central to SLE immunopathology, and elevated interferon gene signatures have been documented in intestinal SLE.⁵ Anifrolumab's approval for moderate-to-severe SLE and its established safety record provide a foundation for gastrointestinal investigation. Published evidence in this domain is currently limited to a single case report involving refractory oral manifestations.⁶ Its applicability to colonic disease is plausible on mechanistic grounds but requires prospective validation, and this limitation must be acknowledged. Studies of mucosal interferon activity before and after anifrolumab treatment would meaningfully advance mechanistic understanding.

Before initiating any biologic therapy for lupus colitis, clinicians must exclude active infection. The case reported by Gravito-Soares et al.¹ illustrates the lethal potential of cytomegalovirus superinfection in the context of immunosuppression. Screening for cytomegalovirus, tuberculosis, hepatitis B, and hepatitis C should be standard practice before biologic initiation; infection risk must also inform treatment sequencing in steroid-refractory and escalation settings.

We call on the gastroenterology and rheumatology communities to

act on three fronts. First, standardized reporting of lupus colitis must incorporate SLEDAI-2K alongside endoscopic and histopathological grading. It should be acknowledged that SLEDAI-2K does not include gastrointestinal subscores; therefore, a complementary bowel-specific activity index, such as a Mayo-adapted or radiologic scoring tool, is necessary to adequately capture the disease burden related to colitis. Second, dedicated registries for biologic use in gastrointestinal SLE should be integrated into existing lupus cohorts. Third, funding bodies must recognize lupus colitis as a distinct, underfunded entity that warrants targeted clinical trial infrastructure.

Patients with lupus colitis experience diagnostic delays, empirical corticosteroid exposure, and escalation to immunosuppressants without evidence to guide treatment sequencing. The biologic era offers real potential, but that potential requires clinical investigation before it can be translated into practice. We urge this journal to champion targeted research and support advocacy for the funding this patient population deserves.

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