Reconsidering Corticosteroid-First Protocols in Moderate-to-Severe Eosinophilic Granulomatosis with Polyangiitis: A Critical Appraisal of Mepolizumab-Centric Remission Induction Hierarchies

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Abstract. Eosinophilic granulomatosis with polyangiitis (EGPA) has historically been managed through high-dose corticosteroid induction regimens, often supplemented by cyclophosphamide in refractory cases. Emerging immunobiological evidence challenges this paradigm, particularly regarding the primacy of interleukin-5-mediated eosinophilic pathobiology in disease propagation. This study critically appraises therapeutic stratification models in 214 biopsy-confirmed EGPA patients across three tertiary referral centres (2019–2024), comparing corticosteroid-first versus mepolizumab-centric induction protocols. Outcome endpoints included Birmingham Vasculitis Activity Score normalization, glucocorticoid-sparing milestones, and peripheral eosinophil reconstitution kinetics. Mepolizumab-centric protocols demonstrated statistically superior relapse-free survival at 18 months (HR 0.41; 95% CI 0.29–0.57; $p<0.001$) and significantly reduced cumulative corticosteroid exposure. These findings substantiate a fundamental re-evaluation of first-line induction hierarchies in EGPA management guidelines.

Keywords: eosinophilic granulomatosis with polyangiitis, mepolizumab induction therapy, interleukin-5 antagonism, glucocorticoid-sparing strategies, ANCA-associated vasculitis, Birmingham Vasculitis Activity Score, eosinophilic airway inflammation, remission induction hierarchy, systemic immunosuppression protocols

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly designated Churg–Strauss syndrome, represents one of the most immunologically complex small-vessel vasculitides encountered in contemporary clinical practice. Characterized by the triad of late-onset asthma, peripheral blood hypereosinophilia, and granulomatous tissue infiltration, EGPA occupies a unique immunopathological niche at the intersection of type-2 hyperinflammatory dysregulation and antineutrophil cytoplasmic antibody (ANCA)-mediated endothelial injury. Despite its relatively low population-level incidence—estimated at 0.5 to 3.7 cases per million annually—EGPA inflicts a disproportionate burden of end-organ morbidity, with cardiac involvement, peripheral neuropathy, and pulmonary infiltrates representing the principal drivers of long-term disability and mortality in affected cohorts. For the greater part of four decades, systemic corticosteroids have constituted the foundational pillar of remission induction in EGPA, with cyclophosphamide reserved as an adjunctive immunosuppressant for patients presenting with life-threatening manifestations or relapsing-refractory disease trajectories. This therapeutic architecture, largely codified from observational series and expert consensus prior to the era of targeted biologic therapy, has persisted with minimal structural revision despite mounting evidence challenging its immunobiological rationale. The mechanistic basis for corticosteroid primacy rests upon broad-spectrum anti-inflammatory suppression; however, this non-selective mechanism simultaneously abrogates protective immune surveillance, precipitates metabolic sequelae including adrenal insufficiency, osteoporosis, and dysglycemia, and fails to address the upstream IL-5-driven eosinophilopoietic axis that constitutes the dominant pathogenic driver in a substantial proportion of EGPA patients, particularly those who are ANCA-seronegative. The regulatory approval of mepolizumab—a humanized monoclonal antibody targeting interleukin-5—for EGPA in 2017, subsequently reinforced by the MIRRA trial outcomes, introduced a mechanistically precise therapeutic option capable of achieving durable eosinophil suppression without the systemic toxicity profile intrinsic to protracted corticosteroid exposure. Notwithstanding this development, prevailing international guidelines, including those issued by the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR), continue to position mepolizumab as a relapse-prevention or steroid-sparing adjunct rather than a first-line induction agent. This positioning reflects historical inertia, paucity of randomized head-to-head induction trial data, and institutional resistance to paradigm revision within vasculitis subspecialty networks. As the landscape of precision immunology in 2024–2026 increasingly favors endotype-stratified therapeutic hierarchies over one-size-fits-all suppression, the field confronts an urgent need to interrogate whether the corticosteroid-first axiom remains immunologically defensible or whether mepolizumab-centric induction protocols should be elevated to first-line status in biologically eligible EGPA phenotypes. The present analysis contributes to this discourse by systematically evaluating longitudinal clinical outcomes, glucocorticoid burden metrics, and immunological remission biomarkers

across a multicenter EGPA cohort. This paper is structured as follows: Section 2 delineates the patient selection criteria and methodological framework; Section 3 presents comparative outcome data stratified by induction protocol; Section 4 discusses the immunobiological, pharmacoeconomic, and guideline-reform implications of the observed findings; and Section 5 proposes a revised therapeutic stratification algorithm for moderate-to-severe EGPA.

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