

Therapeutic divergence between polymyalgia rheumatica and giant cell arteritis: lessons from IL-17A inhibition

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Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) have traditionally been viewed as closely related conditions within the same inflammatory spectrum (1). They share age of onset, genetic susceptibility, immunosenescence, prominent IL-6-associated systemic inflammation, and substantial clinical overlap. Consequently, much of the pathogenic framework established in GCA, facilitated by access to temporal artery biopsies, has been extrapolated to PMR (1, 2). Yet recent phase 3 trials of secukinumab, a monoclonal antibody that selectively neutralises IL-17A, yielded divergent results in PMR and GCA (3, 4), exposing an instructive paradox: shared immunological architecture does not necessarily imply shared functional and therapeutic dependence on its individual components. In the phase 3 REPLENISH trial, 381 patients with relapsing PMR received secukinumab (300 mg or 150 mg) or placebo with a 24-week prednisone taper. Sustained remission at week 52 occurred in 41.2% and 40.6% *versus* 20.4%, respectively ($p < 0.001$ for both comparisons), with approximately 20–23% lower cumulative glucocorticoid exposure in the secukinumab groups (3). By contrast, the phase 3 GCAPTAIN trial did not meet its primary endpoint in GCA. Among 353 patients analysed, sustained remission at week 52 was 25.6% with secukinumab 300 mg *versus* 16.9% with placebo (absolute difference, 8.7 percentage points; 95% CI, -1.3 to 18.8; $p = 0.09$). No difference was observed with 150 mg (19.4% *vs.* 17.7%) (4). This contrasted with phase 2 TitAIN (n=52), in which the pre-specified Bayesian analysis estimated sustained remission through week 28 at 70% *versus* 20%, whereas observed week-52 rates were 59% *versus* 8% (5). Comparisons between trials require

caution, and any mechanistic inference remains indirect and hypothesis-generating. REPLENISH and GCAPTAIN were independent trials rather than a randomised comparison between diseases, and they differed in populations, disease characteristics, remission definitions, placebo responses, and glucocorticoid regimens (3, 4). TitAIN was also a small proof-of-concept study (5). In GCAPTAIN, secukinumab groups underwent a 26-week prednisone taper, compared with 52 weeks for placebo, potentially making sustained remission harder to achieve with active treatment; however, the result cannot be attributed to taper design alone (4). GCAPTAIN therefore supports a narrower conclusion: selective IL-17A neutralisation did not demonstrate superiority under the conditions tested. Why, then, might neutralising IL-17A produce different therapeutic effects in two closely related diseases?

One possibility involves the interaction with glucocorticoids. In GCA, glucocorticoids rapidly suppress Th17 responses by reducing IL-1 β , IL-6, and IL-23 in blood and arterial tissue, whereas the Th1/IFN- γ axis persists despite glucocorticoid treatment (6). Concomitant glucocorticoids may therefore suppress the pathway subsequently targeted by secukinumab, reducing its incremental therapeutic margin (6). This mechanism, however, cannot by itself explain the contrasting phase 3 results, because secukinumab remained effective when combined with glucocorticoids in PMR. The consequences of IL-17A inhibition are therefore likely to depend on the tissue and inflammatory network in which the pathway operates (7).

GCA is a transmural granulomatous vasculitis embedded within an organised arterial microenvironment containing tissue-resident T cells,

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macrophages, stromal cells, neoangiogenesis, and remodelling programmes (8). In contrast, PMR predominantly involves synovitis, bursitis, and tenosynovitis of periarticular structures (1, 2). Although systemic Th17 responses are expanded in both diseases, local immune composition does not necessarily mirror circulating abnormalities. Immunohistology of PMR subacromial bursa shows predominantly IFN- γ -producing rather than IL-17-producing T cells despite expansion of circulating Th17 cells (2, 9). Recent comparative immunohistology nevertheless found broadly overlapping macrophage and macrophage-related cytokine profiles in PMR subacromial bursa and GCA temporal artery (10). Together, these observations reinforce that tissue abundance does not equal functional relevance; therapeutic divergence may instead reflect pathway position and redundancy within distinct tissue networks. Rather than establishing PMR as intrinsically IL-17A-driven, REPLENISH suggests that IL-17A may occupy a therapeutically consequential, less redundant position within a synovial and periarticular network, rather than the organised vascular niche characteristic of GCA. In isolated PMR, arterial tissue contains IL-2 and macrophage-derived cytokine transcripts, whereas the IFN- γ transcripts characteristic of GCA lesions were not detected (11). By contrast, established GCA lesions contain metabolically adapted CD4⁺CD103⁺ tissue-resident memory T cells within the arterial media, adventitial vasa vasorum, and perivascular lymphoid structures, contributing to vascular autonomy and persistence (12).

In the arterial wall, stromal cells and neointimal myofibroblasts constitutively express IL-17RA and IL-17RC. Within an IFN- γ -conditioned environment, IL-17 signalling promotes IL-6, CCL2, CCL20, GM-CSF, and VEGF production, linking local inflammation to angiogenesis and occlusive neointimal hyperplasia (13). These findings establish pathogenic activity for IL-17A but also place it within a cooperative network. Because IFN- γ conditions vascular myofibroblasts for IL-17 responses, blocking IL-17A may leave

a potent IFN- γ -driven effector arm that can maintain stromal inflammation. This provides a plausible biological basis for the limited efficacy of isolated IL-17A blockade in GCA, whereas the contribution of this vascular stromal axis would be expected to be lower in PMR (1, 2, 9, 13).

Metabolically adapted lesional T cells and broader JAK-STAT-dependent stromal circuits further sustain vascular inflammation (12, 14). In human artery xenografts, CD28 costimulation supports the survival and proliferation of tissue-resident memory T cells through metabolic adaptation. In contrast, JAK-STAT inhibition reduces infiltrating T-cell proliferation, adventitial neoangiogenesis, and CD103⁺ populations (12, 14). These findings support the hypothesis that blocking one downstream cytokine may be insufficient once vascular disease is embedded within resident immune and stromal networks.

Consistent with this network model, GM-CSFR α blockade with mavrilimumab reduced inflammatory-cell infiltration, Th1-related and pro-inflammatory mediators, markers of vascular injury, and neoangiogenesis in *ex vivo* GCA arteries (15). In a 70-patient phase 2 trial using identical 26-week prednisone tapers, mavrilimumab reduced the risk of flare (HR, 0.38; 95% CI, 0.15–0.92; flares, 19% vs. 46%) and increased the rate of sustained remission at week 26 (83% vs. 50%) (16). Together, these findings support GM-CSF-dependent myeloid programmes as therapeutically consequential nodes in GCA, although confirmation in larger trials is required.

Clinical efficacy of IL-6R and JAK inhibition points in the same direction, but should not be interpreted as evidence that broader inhibition is necessarily superior to selective cytokine blockade; differences in populations, endpoints, and glucocorticoid tapers preclude direct efficacy comparisons (17, 18).

An additional, hypothesis-generating clue comes from a single prospective cohort of 57 patients followed for 4.5 years. Elevated arterial IL-17A predicted faster glucocorticoid tapering and fewer relapses; patients with high expression reached prednisone doses be-

low 10 mg/day after a median of 25 *versus* 44 weeks ($p=0.0079$) (19). IL-17A expression did not correlate with RORC or ROR α , and FoxP3⁺IL-17A⁺ cells were identified within vascular lesions and markedly reduced after treatment, suggesting contributions beyond conventional Th17 cells (19). Rather than contradicting Th17 corticosteroid sensitivity, these findings may identify a biological context in which glucocorticoids effectively suppress the pathway, leaving little incremental benefit for secukinumab (6, 19). Cytokine abundance, cellular source, corticosteroid sensitivity, and nonredundant therapeutic dependence should therefore not be considered equivalent biological properties.

The divergent secukinumab trials can therefore be interpreted as functional perturbation experiments in human disease (3, 4). Selectively removing a molecular signal adds a dynamic dimension that static histology cannot provide: shared immune architecture need not confer equal therapeutic dependence. Spatial profiling identified adventitial IgG plasma-cell-rich signatures in sustained glucocorticoid responders, whereas non-responders showed extracellular-matrix remodelling and persistent T-cell activation (20). Such heterogeneity may reduce detectable treatment effects unless the dominant lesional programme stratifies patients. Nevertheless, this remains an integrative hypothesis, not a proven conclusion. No randomised comparison has evaluated IL-17A inhibition across the two diseases; the GCAPtAIN result is compatible with both lower IL-17A dependence in GCA and trial-design constraints, which may coexist. The trials establish neither that PMR is intrinsically IL-17A-dependent nor that IL-17A is irrelevant in GCA.

Future trials should integrate pathway signatures and spatial profiling, stratify new-onset and relapsing disease, and determine whether IL-17A dependence changes as vascular inflammation becomes organised and autonomous. Analogous studies in PMR should connect therapeutic responses to bursal, synovial, and peritendinous biology. Viewed together, the evidence suggests that pathway participation does not

equal pathway dominance. IL-17A may occupy a therapeutically consequential, less redundant position in PMR. In contrast, in established GCA it operates within a vascular ecosystem containing a glucocorticoid-resistant IFN- γ arm, metabolically fit tissue-resident lymphocytes, activated macrophages, stromal cells, and remodelling programmes. The relevant contrast may therefore be less whether IL-17A is present than whether inflammation can persist after its removal.

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