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REVIEW

The Impact of IL-17A Inhibition in Rheumatic and Musculoskeletal Diseases: Current Insights and Future Prospects

Sofia Ramiro · Georg Schett · Helena Marzo-Ortega · Wolfgang A. Schmidt

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ABSTRACT

Interleukin-17A (IL-17A) plays a pivotal role in many rheumatic immune-mediated inflammatory diseases. Targeting the IL-17 pathway has transformed the way psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) are managed, with a number of IL-17A inhibitors now available for treating rheumatic and musculoskeletal diseases. This narrative review will describe the opportunities presented by novel imaging techniques in understanding the metabolic and mechanical changes that characterize the pathogenesis of PsA and axSpA. It will look at the current consensus definitions of early disease in PsA and axSpA, present evidence for the benefit of early treatment, and highlight the gaps in current knowledge. Finally, it will describe novel treatment targets to address the unmet needs in giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) and discuss the potential role of IL-17A inhibition in treating GCA and PMR.

Keywords: Axial spondyloarthritis; Early treatment; Early diagnosis; Giant cell arteritis; IL-17A; IL-17A inhibition; Polymyalgia rheumatica; Psoriasis; Psoriatic arthritis; Rheumatic and musculoskeletal diseases

S. Ramiro (✉)
Leiden University Medical Center, Leiden and Zuyderland Medical Center, Heerlen, The Netherlands
e-mail: sofiaramiro@gmail.com

G. Schett
Department of Medicine 3 - Rheumatology and Immunology, Friedrich-Alexander-Universität Erlangen-Nürnberg and Uniklinikum Erlangen, Erlangen, Germany

H. Marzo-Ortega
NIHR Leeds Biomedical Research Centre, The Leeds Teaching Hospital NHS Trust and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK

W. A. Schmidt
Immanuel Krankenhaus Berlin, Berlin-Buch, Germany

Key Summary Points

Treatments targeting the interleukin (IL)-23/IL-17 axis have already transformed the way psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) are managed.

There are promising new imaging techniques to monitor metabolic and mechanical changes in psoriatic disease that may aid the early identification and potential prevention of PsA when combined with early management strategies.

In patients with axSpA, new guidance on defining early disease will allow a better understanding of how early treatment may support the management of axSpA.

Several treatment targets have been or are being explored in giant cell arteritis and polymyalgia rheumatica, with an IL-17A inhibitor, secukinumab, in late-stage development for both of these diseases.

INTRODUCTION

The interleukin-17 (IL-17) family is a group of pro-inflammatory cytokines that play a key role in coordinating innate and adaptive immune responses and maintaining barrier integrity [1–3]. Six members have been identified, labeled alphabetically from IL-17A to IL-17F (IL-17E is also known as IL-25), with IL-17A being the most studied member of the family [4]. IL-17 cytokines promote infiltration of immune cells into the joints and plaques of patients with psoriatic skin lesions [5–7]; they also promote mesenchymal stem cell proliferation and new bone formation at entheseal sites [6].

Disruption of IL-17 homeostasis has been linked to the development and progression of several rheumatic and musculoskeletal diseases (RMDs) [2, 3]. In particular, IL-17A plays a pivotal role in many rheumatic immune-mediated inflammatory diseases [2]. It activates downstream signaling pathways via Act1, ultimately promoting epithelial cell proliferation and survival [1].

As a result, IL-17A has become a treatment target for a number of rheumatic immune-mediated inflammatory diseases [1]. Here, we review how an increased understanding of the IL-17 pathway has advanced the treatment of RMDs. We describe the opportunities presented by novel imaging techniques in understanding the pathogenesis and treatment of psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA). Consensus definitions of early disease in PsA and axSpA are reviewed, evidence for the benefit of early treatment is examined, and gaps in current knowledge are highlighted. Finally, we explore unmet needs and the potential role of IL-17A inhibition in giant cell arteritis (GCA) and polymyalgia rheumatica (PMR).

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

SUMMARY OF APPROVALS IN IL-23/IL-17 AXIS INHIBITORS

Since their discovery over 30 years ago [1, 8], a deeper understanding of the IL-23/IL-17 axis has transformed how PsA and axSpA are managed, providing an increasing number of treatment options for these diseases [1]. Specific targets for the IL-23/IL-17 axis include inhibiting two distinct subunits of IL-23, inhibiting IL-17A directly on its own, and joint inhibition of IL-17A and IL-17F. A timeline of first approvals by either the United States Food and Drug Administration or European Medicines Agency is shown in Fig. 1.

Aside from these, additional IL-17A inhibitors for the treatment of rheumatic immune-mediated inflammatory diseases are in development, including izokibep (novel, small molecule IL-17A inhibitor [previously ABY-035]) and dual IL-17A and F inhibitor, sonelokimab [33, 34].

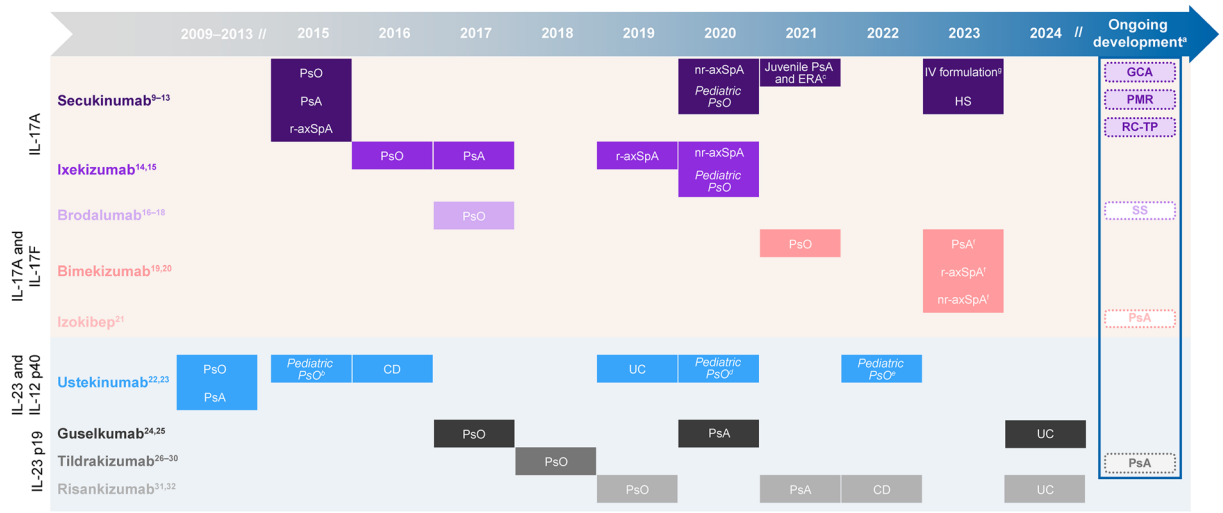

Fig. 1 Summary of approvals and ongoing phase 3 clinical development of IL-17 and IL-23 inhibitors. First approval date (EMA or FDA). Pediatric is defined as ≥ 6–18 years of age, unless otherwise stated. [a]Phase 3 studies in RMDs registered on ClinicalTrials.gov by February 9, 2024; [b] ≥ 12 years; [c]FDA only; [d]ERA ≥ 4 years and PsA ≥ 2 years; [e] ≥ 6– < 12 years; [f]EMA only; [g]FDA approval of IV formulation secukinumab for the treatment of adults with PsA, AS, and nr-axSpA. *AS* ankylosing spondylitis, *axSpA* axial spondyloarthritis, *CD* Crohn's disease, *EMA* European Medicines Agency, *ERA* enthesitis-related arthritis, *FDA* United States Food and Drug Administration, *GCA* giant cell arteritis, *HS* hidradenitis suppurativa, *IL* interleukin, *IV* intravenous, *nr-axSpA* non-radiographic axial spondyloarthritis, *PMR* polymyalgia rheumatica, *PsA* psoriatic arthritis, *PsO* psoriasis, *r-axSpA* radiographic axial spondyloarthritis, *RC-TP* rotator cuff tendinopathy, *RMD* rheumatic and musculoskeletal disease, *SS* systemic sclerosis, *UC* ulcerative colitis

NOVEL IMAGING TECHNIQUES IN EXPLORING THE PATHOGENESIS OF PSORIATIC DISEASE

Early Detection of Radiographic Damage in IL-17A-Associated Diseases

In autoimmune diseases that are closely associated with imbalances in IL-17 levels, earlier detection and intervention can be critical for effective management [1, 35] through playing a key role in reducing disease burden, preventing structural damage, and improving quality of life (QoL). By the time of diagnosis, many patients already have established disease [36, 37]. Some patients already have radiographic damage at diagnosis, affecting 22–31% with PsA and 12–16% with axSpA [38–42]. Genetic markers and high-risk factors may help to identify patients before there is evidence of inflammatory damage [36, 37]. In PsA, the presence of psoriasis (PsO) in the group at risk may facilitate this area of research, for example, by identifying biomarkers predictive of higher likelihood of progression [37]. Novel imaging techniques can aid in understanding the pathogenesis of PsA and axSpA and assist in the clinical management of these conditions; three of these will be explored here.

High-Resolution Peripheral Quantitative Computed Tomography

Enthesitis is a significant and recurrent symptom in musculoskeletal disease [6]. Discrete traumatic injury can trigger inflammation and acro-osteolysis, leading to new bone formation at entheseal sites in patients with PsO. This is known as deep Koebner phenomenon [43, 44]. Data have shown that patients with PsO and a deep Koebner phenomenon progress quickly and consistently to PsA, whereas patients without the

phenomenon remain free of musculoskeletal disease [43]. The phenomenon was also observed in a subset of patients without clinical PsA, suggesting that the process in the joints starts long before patients consult a healthcare professional about their symptoms [43]. In a different study, patients with PsO who did not show any clinical signs of PsA had impaired hand function mirroring that of patients with rheumatoid arthritis and PsA compared with healthy controls [45].

Using high-resolution micro-computed tomography, osteophytic lesions caused by deep Koebner responses were identified in metacarpophalangeal joints in patients with PsA [46]. Bone formation was not affected by the antirheumatic treatment strategies of methotrexate or tumor necrosis factor (TNF) inhibitors [46]. However, high-resolution peripheral quantitative computed tomography (HR-pQCT) has shown that patients using biological disease-modifying antirheumatic drugs (bDMARDs), such as IL-17A inhibitors, have improved bone microstructure compared with patients with PsA not receiving bDMARD treatment [47]. These results suggest that HR-pQCT could potentially be used in the early detection of structural lesions at entheseal sites of patients with psoriatic disease, which could lead to earlier treatment and, therefore, improved patient outcomes.

Multispectral Optoacoustic Tomography

Multispectral optoacoustic tomography (MSOT) uses a near-infrared laser to excite tissues and detect the emitted acoustic energy. This allows for a non-invasive measurement of target tissue based on absorbance at multiple wavelengths [48, 49]. MSOT can be used to measure several parameters simultaneously, such as collagen content, lipid content, and tissue hemoglobin levels—all hallmarks of reconstruction of entheseal structure in psoriatic disease and, thus, targets for early detection of PsA [48, 50].

As detected by MSOT, entheses of patients with PsO, both with and without PsA, exhibit similar unique metabolic patterns of oxygenated hemoglobin, oxygen saturation, and lower collagen levels that are not found in healthy individuals [50], suggesting that tissue remodeling may be occurring in the preclinical phase of the disease. Enhanced vasculature, leukocyte infiltration, and nerve growth in entheseal structures during the development of PsA lead to changes in the metabolic environment, such as enhanced oxygen and hemoglobin content, as well as changes in the collagen architecture of the enthesis [51]. This suggests a rebuilding of entheseal structures in PsA and SpA, increasing sensitization to pain and enhancing susceptibility to inflammation [51].

These findings using MSOT provide evidence for an intrinsic change of the metabolic structures in the musculoskeletal system in PsO and PsA [50]. Measuring these parameters could provide context for the extent of vascularization and inflammation at entheseal sites [50].

Fibroblast Activation Protein Positron Emission Tomography

Elevated expression of the fibroblast activation protein (FAP) leads to extracellular matrix digestion and remodeling, angiogenesis, and immunosuppression [52]. FAP shows low expression in most organs and, thus, could be used as a target for diagnosis and treatment of FAP-related diseases [52, 53].

Radiolabeled FAP inhibitors have shown promise as tracers for diagnostic imaging and possibly targeted therapy in rheumatoid arthritis [52]. Positron emission tomography/computed tomography (PET/CT) imaging with the tracer ^{68}Ga-FAPI-04, which specifically binds to FAP expressed by activated mesenchymal cells, was performed in patients with inflammatory joint disease, including rheumatoid arthritis, PsA, axSpA, and controls without arthritis [54]. In this study, mesenchymal cell activation was observed in patients with arthritis, but not in non-arthritic controls [54]. Patients treated with TNF and IL-17A inhibitors showed reduction and often complete abolition of the FAP signal after cytokine blockage, providing evidence that mesenchymal activation is reversible during resolution of inflammation. This suggests that resident fibroblasts may change their

functional pattern and acquire a more pro-resolving phenotype, known as CD200$^+$ [54]. Levels of these CD200$^+$ fibroblasts increased as the inflammation resolved, and they appeared to orchestrate this process directly. IL-17A inhibitors significantly induced CD200$^+$ fibroblasts and largely decreased FAP-tracer uptake, with TNF inhibitors demonstrating milder effects [54].

These results suggest that fibroblast activation is high in active arthritis and decreases after IL-17A inhibition. Therefore, resolution of inflammation could potentially be identified by monitoring the mesenchymal tissue response in patients with PsA and SpA through FAP tracer uptake of CD200$^+$ fibroblasts [54]. As patients with PsO already demonstrate mesenchymal activation before manifestation of PsA, radiolabeled FAP inhibitors may be a useful tool in early detection.

NEW EVIDENCE FOR DEFINING AND TREATING EARLY PSA AND AXSPA

According to the current European Alliance of Associations for Rheumatology (EULAR) recommendations, treatment of PsA and axSpA should aim for remission, if possible, or low disease activity otherwise [55, 56]. Although exact definitions of remission in either condition are still subject to debate [55, 56], in PsA this may be quantified with a Disease Activity for Psoriatic Arthritis (DAPSA) score of ≤ 4 [35], whereas in axSpA, an Axial Spondyloarthritis Disease Activity Score (ASDAS) indicating inactive disease (< 1.3) is a recognized measure [55]. Targets for low disease activity may be defined using minimal disease activity (MDA) for PsA and ASDAS for axSpA [55–57].

Impact of Early Diagnosis and Treatment of PsA

In PsA, data show that delayed diagnosis is associated with poorer long-term outcomes. In one study, a 6-month delay from symptom onset to first rheumatologist visit contributed to the development of peripheral joint erosion and worsening of long-term physical function compared with those without the delay [58]. However, the diagnostic delay in PsA has shortened over time, largely due to the wider implementation of early arthritis clinics [59]. Recent data suggest that patients with PsA diagnosed within 1 year from symptom onset are more likely to achieve DAPSA remission, with a shorter time to diagnosis associated with greater likelihood of achieving MDA and DAPSA remission over time [35]. Additionally, achieving MDA within a year of diagnosis suggests better long-term outcomes, with one study showing that patients with PsA who did not reach MDA in the first year after diagnosis had worse health-related QoL and a substantial disease burden that persisted over years despite intensified treatment with bDMARDs [60].

A study in patients with PsA treated shortly after diagnosis (average disease duration 0.5 years compared with 6–7 years in typical phase 3 studies) showed that many patients with early PsA achieved remission at 8 weeks, with remission achieved in nearly double the number of patients treated with golimumab and methotrexate compared with those treated with placebo and methotrexate [61]. A pooled analysis looking at treatment response according to disease duration demonstrated that secukinumab led to improved clinical outcomes and QoL in patients with PsA regardless of time since diagnosis, demonstrating efficacy also at the early stages of disease [62]. The effects of early treatment initiation have not only been seen with biologics but also in patients treated with conventional synthetic DMARDs [63]. Additionally, early intervention with bDMARDs in patients with PsO has the potential to mitigate the risk of developing PsA [64].

A consensus definition of early PsA has been provided by EULAR for patients with PsO [65]; although this provides much-needed guidance to support early diagnosis and treatment of PsA, detection of progression to early stage PsA remains a challenge for patients with long-term PsO.

Impact of Early Diagnosis and Treatment of axSpA

For patients with axSpA, diagnosis and treatment before irreversible changes occur are important goals in the management of the disease [55, 66]. Here, as in PsA, early diagnosis and treatment may also lead to improved longer-term outcomes, and recent advances, especially the use of magnetic resonance imaging, have made early disease detection easier [67]. However, until recently, there was no consensus on how to classify early axSpA [67], and the lack of a standardized definition has led to substantial heterogeneity and arbitrary definitions being used across studies [68]. Following the 2023 Assessment of SpondyloArthritis international Society (ASAS) consensus definition of early axSpA as 'patients with a diagnosis of axSpA with duration of axial symptoms of ≤ 2 years', 'regardless of the presence/absence of radiographic damage', where 'axial symptoms should include spinal/buttock pain or morning stiffness and should be considered by a rheumatologist as related to axSpA' [67], it is hoped a more uniform approach may be beneficial in future research.

Until the publication of the 2023 ASAS consensus definition, there was no generally agreed upon definition of early axSpA, so studies were not adequately designed to address the question of early treatment benefits. Previous data, such as a post hoc analysis of the MEASURE program, showed that age, rather than time since diagnosis was a significant predictor of treatment outcomes in patients with radiographic (r)-axSpA, with age being a proxy of symptom duration [69]. This conclusion may reflect the heterogeneity of the axSpA patient journey, for example, at what point in their disease from the time of symptom onset patients seek medical advice. In addition, it reflects inherent differences within healthcare systems, rather than being an accurate measure of the stage of the disease.

In patients with non-radiographic (nr)-axSpA, the PREVENT study showed that the IL-17A inhibitor secukinumab improved ASAS partial remission and ASDAS ID over a 2-year period, but these patients still had a baseline mean duration of symptoms of around 8.5 years [70].

A small number of studies have looked at symptoms that are short in duration in patients with axSpA. In patients with a mean duration of back pain < 2 years, treatment with infliximab led to a sustained remission in 24% of patients with nr-axSpA at 6-year follow-up [38, 71]. This finding was mirrored in the INFAST study, where patients had a mean symptom duration of < 3 years; 62% of patients with axSpA achieved partial remission at week 28 that was sustained in ≥ 40% of patients beyond 1 year regardless of the treatment that they were taking [72, 73]. However, although early diagnosis and treatment may improve chances of achieving remission and maintaining good disease control, a direct comparison between treatment in early and established disease has not been made. A systematic literature review of 27 studies addressing the impact of symptom/disease duration or the presence of radiographic damage on treatment response concluded that when early axSpA was defined by a symptom duration of < 5 years, early treatment possibly resulted in better outcomes in patients with nr-axSpA, but not r-axSpA. No differences were noted between groups when early axSpA was defined based on disease duration or radiographic damage [74]. However, a recent meta-analysis of 11 randomized controlled trials of approved bDMARDs and targeted synthetic DMARDs in patients with axSpA concluded that there were no differences in short-term outcomes between treatment in early and established disease [75]. The concept of a window of opportunity in axSpA and how this concept is defined is still a subject of debate [76].

Evidence for early intervention in PsA and axSpA is mounting, with more research needed. The EULAR and ASAS definitions for early PsA and axSpA may help with future studies. For now, although uncertainty around the concept of a window of opportunity remains, treatment should be based on currently available evidence as summarized in up-to-date treatment recommendations [35, 55, 56].

UNMET NEEDS AND POTENTIAL ROLE OF IL-17A INHIBITION IN THE MANAGEMENT OF GCA AND PMR

GCA and PMR are closely related inflammatory diseases that may present together or separately [77–79]. Both diseases are two to threefold more common in women than men, with the highest incidence found in people of northern European descent and age of disease onset typically ≥ 50 years [77–79]. Although a diagnosis of GCA focuses on cranial symptoms, including headache, jaw claudication, visual disturbance, and temporal artery abnormalities [77], PMR diagnosis is based on low-grade fever, weight loss, shoulder girdle and back pain, and acute phase reactants; however, these signs and symptoms may also overlap with GCA [77, 80]. Intriguingly, imaging studies in PMR suggest extracapsular inflammation in peripheral joints is a more prominent feature than joint synovitis. These findings of extracapsular inflammation are typically seen in seronegative arthropathies, including spondyloarthritis [81].

An emerging concept in this field is that GCA and PMR are, in fact, a spectrum of diseases, comprising different subsets requiring different imaging techniques for diagnosis and subsequent management [77]. In one study of patients with GCA, > 50% also displayed symptoms of PMR [82], and of patients diagnosed with GCA in the Berlin-Buch Fast Track Clinic, 48% of patients had cranial type arteritis, 21% had extracranial GCA, and 32% had mixed-type GCA [79]. In patients with ischemic GCA, specialized fast-track clinics may be beneficial in preventing permanent vision loss [83–86].

In patients with PMR, the prevalence of subclinical GCA was found to be 15–23% when performing ultrasound of temporal and axillary arteries in those without clinical GCA symptoms [79, 87, 88]. Patients with PMR and subclinical or 'silent' GCA had an approximately fourfold higher rate of relapse compared with patients with isolated PMR [89]. In clinical practice, it is important to differentiate between patients with PMR and those with 'silent' GCA, as one may hypothesize that the latter may benefit from being treated as having GCA; further research is needed to manage this group.

When we look at the current management of PMR, the majority of patients are managed within a primary care setting [90]. Only 25% of new patients were referred by primary care practitioners to a rheumatologist for diagnosis [90]; of these, 50% were returned to the general practitioner for treatment. A total of 39% of rheumatologists evaluated patients with suspected PMR within 2 weeks of referral, with 50% of patients with newly diagnosed PMR starting treatment before rheumatologic evaluation [90]. Generally, patients who were referred early for suspected PMR had faster PMR diagnosis and lower hospitalization rates, and initiated glucocorticoids at a lower dose, emphasizing the importance of early referral and management [91].

An international task force for the treatment of PMR recommends that individuals with suspected or recently diagnosed PMR should be considered for specialist evaluation, with rapid access strategies implemented for those with severe symptoms [92, 93]. Individuals with suspected PMR referred via rapid access should only commence glucocorticoid therapy following evaluation by a specialist. Patients diagnosed from specialist care who have a good initial response to glucocorticoids and a low risk of glucocorticoid-related adverse events can generally be managed within primary care [92].

Table 1 Examples of dose-reduction schemes for GCA and PMR [94, 96, 125]

	GCA – higher starting dose [96]	GCA – lower starting dose [96]	GCA with ischemic complication [94, 96]	GCA – tocilizumab [125]	PMR – higher starting dose [96]	PMR – lower starting dose [96]
Starting dose	60 mg/day	40 mg/day	250–1000 mg/day iv	60 mg/day	25 mg/day	15 mg/day
Duration	for 2 weeks	for 1 week	for 3 days	for 1 week	for 1 week	for 1 week
Reduction per week (between 10 and 60 mg/day)	50–40–30–20–17.5–15–12.5–10 mg/day	35–30–25–20–17.5–15–12.5–10 mg/day	60–60–50–40–30–20–17.5–15–12.5–10 mg/day	50–40–35–30–25–20–15–12.5–12.5–10 mg/day	22.5–20–17.5–15–12.5–10 mg/day	14–13–12–11–10 mg/day
Further reduction (from ≤ 10 mg/day and lower)	1 mg/month	1 mg/month	1 mg/month	10 to 7 mg/day: every week, 6 to 0 mg/day: every 2 weeks	1 mg/month	1 mg/month

GCA giant cell arteritis, *iv* intravenously, *PMR* polymyalgia rheumatica

Treatment

For patients with GCA, a high glucocorticoid starting dose of 40–60 mg/day (prednisone equivalent) is recommended [94]. When the disease is controlled, glucocorticoid therapy should be tapered to 15–20 mg/day within 2–3 months and to ≤ 5 mg/day after 1 year [94].

For patients with PMR, joint EULAR/American College of Rheumatology (EULAR/ACR) recommendations include a minimum starting dose of 12.5–25 mg/day oral prednisolone equivalent for most patients, with subsequent gradual reduction provided remission is maintained [95, 96]. Examples of dose-reduction schemes are provided in Table 1.

A rapid access method for contacting the rheumatologist should be provided in case of symptoms that indicate relapse [93]. Data suggest that around 40% of patients with PMR experience ≥ 1 relapse within the first year of treatment [97], whereas half of patients with GCA relapse in the first year following diagnosis [98]. Although rapid initiation of glucocorticoids is important and necessary to induce remission and prevent ischemic complications, glucocorticoid-related adverse events and high relapse rates are major challenges, which highlight the need for glucocorticoid-sparing therapies [94, 97–99]. Methotrexate is often used as a glucocorticoid-sparing therapy; however, data supporting its efficacy in the management of GCA are sparse [100]. Ongoing studies comparing methotrexate with tocilizumab or placebo will hopefully provide more information in the future [101, 102]. Several novel treatment targets for GCA and PMR have been identified, including IL-6R, granulocyte–macrophage colony-stimulating factor, Janus kinase (JAK), and IL-17A, with new therapies on the horizon (Box 1) [11–13, 103–106].

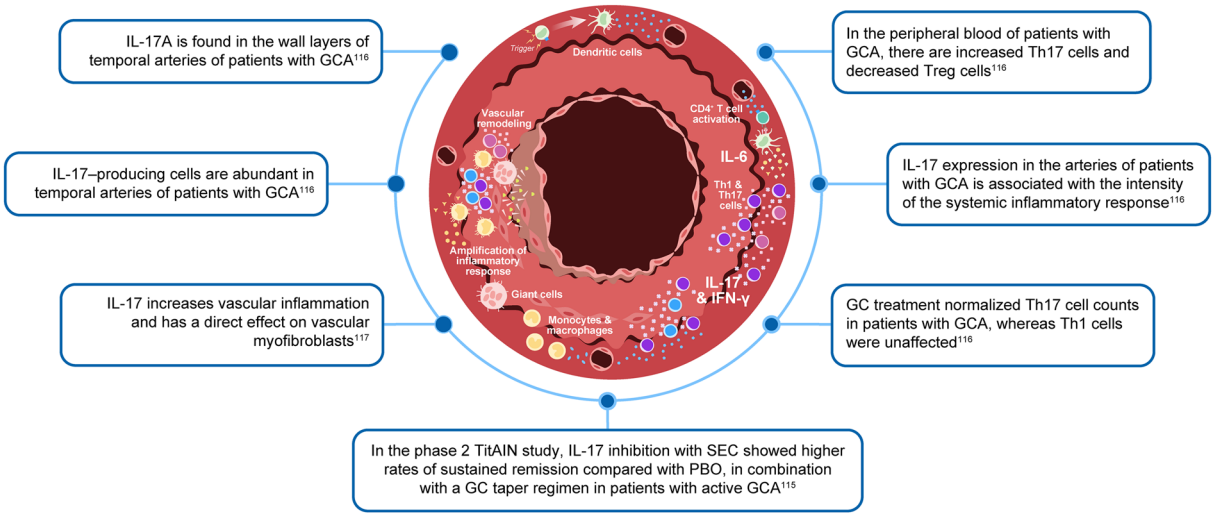

Fig. 2 Rationale for IL-17A inhibition in GCA [115–117]. *GC* glucocorticoids, *GCA* giant cell arteritis, *IFN* interferon, *IL* interleukin, *PBO* placebo, *SEC* secukinumab, *Th* T helper. Figure adapted courtesy of Zeisbrich M, et al. "The IL-17 pathway as a target in giant cell arteritis", licensed under CC BY 4.0 [116]

Box 1 Targets for GCA and PMR Therapies

IL-6 inhibitors

Tocilizumab

GCA: Tocilizumab was approved for the treatment of GCA [107]

PMR: Two RCTs suggest efficacy of tocilizumab in PMR [108, 109]

Sarilumab

GCA: RCT of sarilumab in GCA was terminated early due to the impact of COVID-19, so no efficacy conclusions can be drawn from this study [82]

PMR: RCT of sarilumab in PMR was also terminated early; however, significant efficacy in achieving sustained remission and reducing cumulative glucocorticoid dose led to FDA and EMA approvals in relapsing disease or where response to glucocorticoids has been inadequate [105, 110–112]

Sirukumab

GCA: RCT in GCA was terminated early and development for GCA and other diseases has been discontinued [113]

JAK inhibitors

Upadacitinib

GCA: Phase 3 RCT of upadacitinib in GCA showed positive results [106]

GM-CSF inhibitors

Mavrilimumab

GCA: Phase 2 RCT of mavrilimumab in GCA showed efficacy; however, no phase 3 trial is currently planned [104, 114]

IL-17 inhibitors

Secukinumab

GCA: TitAIN – Phase 2 RCT of secukinumab in GCA showed efficacy [115]; two ongoing phase 3 RCTs of secukinumab in GCA: GCAptAIN [11] and GigAINt [13]

PMR: There is one ongoing phase 3 RCT of secukinumab in PMR: REPLENISH [12]

EMA European Medicines Agency, *FDA* United States Food and Drug Administration, *GCA* giant cell arteritis, *GM-CSF* granulocyte–macrophage colony-stimulating factor, *IL* interleukin, *JAK* Janus kinase, *PMR* polymyalgia rheumatica, *RCT* randomized controlled trial.

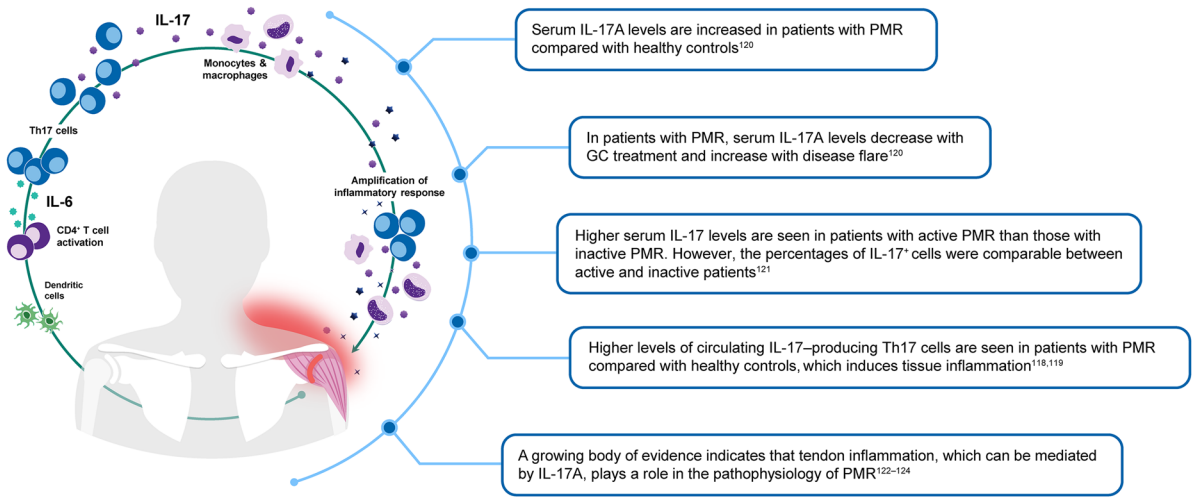

Fig. 3 Rationale for IL-17A inhibition in PMR [118–124]. *GC* glucocorticoid, *IL* interleukin, *PMR* polymyalgia rheumatica, *Th* T helper

Inhibition of the IL-17 pathway represents a potential therapeutic option for GCA and PMR. Figure 2 provides an overview of the rationale for IL-17A inhibition in GCA [116, 117]. In the temporal arteries of patients with GCA, IL-17-producing cells are abundant, with IL-17A found in the wall layers [116]. IL-17 increases vascular inflammation and has a direct effect on vascular myofibroblasts, which increase pro-inflammatory cytokines [117]. IL-17 expression in the arteries of patients with GCA is associated with the intensity of the systemic inflammatory response [116]. In the peripheral blood of patients with GCA, increased levels of T helper 17 (Th17) cells and decreased regulatory T cells have been found [116]. Additionally, glucocorticoid treatment normalized increased Th17 cell counts, whereas Th1 cells were unaffected [116].

Regarding the rationale for IL-17A inhibition in PMR, IL-17-producing Th17 cells, which induce tissue inflammation, have been seen in patients with PMR [118, 119], and higher serum levels have been observed in patients with PMR compared with healthy controls [120] (Fig. 3). Additionally, when comparing patients with active PMR with those with inactive PMR, serum levels of IL-17 were higher in those with active PMR, but the percentages of IL-17 + cells were comparable between active and inactive patient groups [121]. Finally, serum IL-17A levels decreased with glucocorticoid use and increased with disease flare-ups, suggesting a role for IL-17A in the mechanism of disease of PMR [120].

This was the rationale for the phase 2 TitAIN study, which evaluated the safety and efficacy of secukinumab, an IL-17A-inhibiting monoclonal antibody, in patients with GCA [115]. Findings demonstrated that patients with active GCA had a higher sustained remission rate with secukinumab (70%) compared with placebo (20%) at week 28, in combination with a glucocorticoid taper regimen. Together with the safety findings, which aligned with the known secukinumab safety profile, this study provided proof-of-concept for IL-17A inhibition as a treatment for GCA and paved the way for further phase 3 studies [115]. There are three studies ongoing for secukinumab in GCA and in PMR: GCAptAIN, in adults with active, new-onset or relapsing GCA (primary endpoint: proportion of patients with sustained remission at 52 weeks) [11]; GigAINt, in adults with new-onset GCA who are in clinical remission (primary endpoint: time to first clinical relapse [at ≥ week 24]) [13]; and REPLENISH, for adults with PMR who have had a relapse within the 12 weeks before baseline (primary endpoint: proportion of participants with sustained remission at 52 weeks) [12].

CONCLUSIONS

Targeting the IL-17 pathway has already transformed the way PsA and axSpA are managed. Monitoring psoriatic disease through metabolic and mechanical changes is promising with new imaging techniques; these may aid the early identification and potential prevention of PsA when combined with early management strategies. In patients with axSpA, new guidance on defining early disease will allow us to better understand how early treatment may support the management of axSpA—more research is needed in this area. In GCA and PMR, several treatment targets have been or are being explored, with secukinumab, an IL-17A inhibitor, in late-stage development for these conditions.

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Declarations

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