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IL17 in Sarcoidosis – A level playing field?

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To the editor,

Sarcoidosis is a multisystem antigen driven granulomatous disease for which there are limited treatment options. The mainstay of treatment is corticosteroids, alongside steroid-sparing agents such as methotrexate, mycophenolate, azathioprine and hydroxychloroquine. More recently, NHS England has approved a commissioning pathway for the use of infliximab (a TNF inhibitor) in pulmonary sarcoidosis (1) with a previous pathway for neurological disease. Given the limited treatment options, multiple clinical trials are underway of additional targeted therapies, including namilumab (GM-CSF inhibitor) and efzofitimoid (neuropilin-2 inhibitor) (2). Emerging evidence suggests that cytokines, such as IL-6 and IL-17 have a role in the development of sarcoidosis. Despite this, the use of IL-6 inhibitors in cutaneous sarcoidosis did not observe any meaningful benefit (3), with further evidence through Mendelian randomisation demonstrating that IL-6 blockade may be detrimental in sarcoidosis (1). In contrast, IL-17 and the Th17 axis are associated with granuloma formation and have been found to be increased in both granulomas from mucosal biopsies and the broncho-alveolar lavage of people with pulmonary sarcoidosis, suggesting a potential role for IL-17 blockade in the management of sarcoidosis (2-3). A broader range of cytokine signatures were found in Lofgren syndrome (LS), a self-limiting form of sarcoidosis, including increased IL17A levels. There are two case reports of successful treatment of pulmonary sarcoidosis following treatment with secukinumab (an IL-17A inhibitor), with complete resolution of clinical symptoms within 12 months of therapy (2-3). Contrasting this evidence of potential benefit for IL-17 inhibition in sarcoidosis are several case reports reporting paradoxical sarcoidosis following treatment with IL-17 inhibitors. Paradoxical sarcoidosis refers to the development or worsening of sarcoidosis-like granulomatous inflammation and is a recognised adverse effect following treatment with TNF inhibitors. This is less widely reported following treatment with other targeted therapies (4). There are 6 case reports of paradoxical sarcoidosis following treatment with IL-17A inhibitors, 5 were reported following treatment with secukinumab (5-9), and one case following treatment with ixekizumab, both of which are IL-17A inhibitors (2) (Figure 1). The mean exposure to the IL-17 inhibitor was 10 months. A further 12 cases of IL-17 inhibitor-associated paradoxical sarcoidosis have been registered with VigiBase, the WHO's pharmacovigilance registry (2). Beyond case reports of IL-17-induced paradoxical sarcoidosis, clinical trial data for the IL-17 inhibitors, secukinumab, ixekizumab, brodalumab, bimekizumab, has yet to report a case of sarcoidosis in a combined pool of over 20,000

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Author/Year	IL17i	Gender	Age	Dose	Exposure length (months)	Indication	Sarcoid Presentation	Sarcoid Phenotype	Management	Outcome	Biopsy Site	CT	Biochemical	Other
Donzella, 2024	Secukinumab	male	55	150	60	ankylosing spodylitis	cough, fever, dysphonia	Pulmonary	prednisolone 37.5 to taper	stability	unk	BHL and nodularity		
Halca, 2022	Secukinumab	male	56	300	20	plaque psoriasis	tender nodules (erytematous & firm) at radiocarpal joint	Cutaneous	cessation of IL17 for 1 month and transition to risankizumab	resolution	Skin	Nil	normal ACE	
Haptipoglu, 2021	Ixekizumab	male	58	80	1.5	plaque psoriasis	dyspnea, tachycaridia, peripheral odema	Cardiac	cessation IL17, IV Methylprednisolone (dose unknown) followed by oral (dose unknonw)	improvement in EF from 25% to 56% at 6 months	Lymph node	BHL with nodularity	negative/normal ANA, EBV, HIV, TB, TSH	
Kirby, 2021	Secukinumab	female	52	300	6	plaque psoriasis	dry cough, dyspnoea, polyarthralgia, dacytulitis, violaceous rash around eyes	Pulmonary	30mg prednisolone reduced by 5mg a month.	resolution	Lymph node	Nodularity with BHL and ground glass opacities	ESR 40, CRP 20, normal LDH & ACE, negative IGRA	Restrictive PFT - TLCO 80%
Lu, 2021	Secukinumab	male	36	300	2	plaque psoriasis	nontender subcutaenous nodules	Cutaneous	cessation IL17 for 2 months	resolution	Skin	nil	ACE 465.5 , IGRA negative,	Normal ECG
Nyckowsk, 2017	Secukinumab	female	45	150	unk	psoriatic arthritis	linear subdermal nodules	Pulmonary and Cutaneous	cessation of IL17	unknown	Skin	nil		

Figure 1. Summary of case reports for IL-17i-induced paradoxical sarcoidosis. Data summarized include the age and gender of the patient, the indication for the IL17i, the sarcoid phenotype, management of the paradoxical reaction, outcome of the reaction, CT findings, biochemical findings and other relevant findings.

patients from 150 clinical trials and an adverse event reporting period of up to 2.5 years (3-5). Notably over 1 million people have been treated worldwide with secukinumab alone across multiple disease indications. One potential explanation for the conflicting evidence or benefit and harm might stem from the presence of excipients, such as polysorbate 80, which are known to cause immune-mediated reactions. Polysorbate 80 is the most prevalent excipient in the five TNF inhibitors and four IL-17 inhibitors licensed by the EMA. Immunological reactions from biologics containing polysorbate 80 have previously been explored (6) associating it to anaphylactoid like reactions and allergenic responses raising the question of whether polysorbate 80 is a key mediator of paradoxical sarcoidosis, rather than cytokine blockade itself. Additional studies are needed to further elucidate this. The immunobiology of IL17 inhibitors in granuloma formation and their known safety profile from their use in psoriasis, axial spondyloarthropathy and psoriatic arthritis alongside positive clinical trial outcomes in other granulomatous diseases such as giant cell arteritis would suggest a role for their use in sarcoidosis (7). In the TitTAIN study secukinumab was associated with a 70% remission rate and reduced corticosteroid burden. If these results were mirrored in patients with sarcoidosis, it would be a considerable advancement in the tools available to treat sarcoidosis. To our knowledge, there are no known clinical trials for the use of IL17 inhibition in sarcoidosis. Given the need for further treatment options, and the potential for benefit, consideration should be given to a clinical trial programme of IL-17 inhibition in pulmonary and extrapulmonary sarcoidosis, with the potential to stratify patients based on serum and broncho-alveolar lavage IL-17 levels Paramount importance must be given to a useful primary outcome measure and selecting patients accordingly to reduce heterogenicity and improve clinical trial design.

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