



Goenka, A., Roderick, M. R., Finn, A. H. R., & Ramanan, A. V. (2020). The jigsaw puzzle of chronic non-bacterial osteomyelitis: are anti-IL7 therapies the next piece? *Rheumatology*, 59(3), 459-461. <https://doi.org/10.1093/rheumatology/kez492>

Peer reviewed version

Link to published version (if available):
[10.1093/rheumatology/kez492](https://doi.org/10.1093/rheumatology/kez492)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Oxford University Press at <https://academic.oup.com/rheumatology/article/59/3/459/5599882?searchresult=1>. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: <http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

Title

The jigsaw puzzle of chronic non-bacterial osteomyelitis: are anti-IL7 therapies the next piece?

Authors

Anu Goenka¹, Marion Roderick¹, Adam Finn^{1,2}, Athimalaipet V. Ramanan^{3,4}

1. Paediatric Immunology and Infectious Diseases Service, Bristol Royal Hospital for Children, University Hospitals Bristol NHS Foundation Trust, Bristol, UK
2. Bristol Children's Vaccine Centre, Schools of Cellular and Molecular Medicine and of Population Health Sciences, University of Bristol, UK
3. Department of Paediatric Rheumatology, Bristol Royal Hospital for Children, University Hospitals Bristol NHS Foundation Trust, Bristol, UK
4. Translational Health Sciences, University of Bristol, Bristol UK

Corresponding Author

Professor Athimalaipet V. Ramanan

Department of Paediatric Rheumatology

Bristol Royal Hospital for Children

Bristol BS6 6BT

UK

Email: avramanan@hotmail.com

Telephone: +44 117 342 0149

Conflict of Interest

The authors declare no conflict of interest

Main Text

Chronic non-bacterial osteomyelitis (CNO) is an inflammatory disorder of unknown aetiology characterised by painful sterile osteitis. It is also known as chronic recurrent multifocal osteomyelitis. Bone inflammation is followed by hyperostosis and osteolytic lesions, most commonly in the clavicles, long bones and spine [1]. Extra-osseous features include psoriasiform dermatoses such as palmoplantar pustulosis in approximately one-fifth of patients, as well as spondyloarthropathy and inflammatory bowel disease [2, 3]. The median age of onset of CNO is 10 years, although an adult-onset equivalent is known as SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome [2, 4]. Current understanding of the natural history of CNO is constrained by a lack of large prospective cohort studies. The available data suggest that approximately 20-35% of patients suffer long-term morbidity including growth retardation, bone deformities and kyphosis [5, 6]. As might be expected, such poor outcomes appear to be more common in children with longer periods of active inflammation due to delays in making the diagnosis of CNO, or disease that is refractory to current treatments [1, 6]. Therefore, as well as improving awareness of CNO among clinicians, there is also an urgent need to identify novel treatment approaches that reliably induce complete and sustained remission. Current treatments include non-steroidal anti-inflammatory drugs which achieve remission in approximately 39% of patients, and bisphosphonates which achieve 51% [2]. There are also observational reports to support the use of targeted treatments such as therapeutic blockade of the innate cytokines TNF α and IL1 β , although the molecular aetiology of CNO remains unknown [2]. Here, we outline the biological plausibility of using anti-17 therapy as a novel candidate treatment for CNO.

An important feature of the bone tissue microenvironment is the tightly-regulated process of extracellular matrix turnover [7]. Bone resorption and remodelling is primarily performed by osteoclasts, multinucleated giant cells derived from haematopoietic stem cells [7]. Osteoclastogenesis is dependent on the conditioning of myeloid precursors with macrophage colony stimulating factor (M-CSF) and receptor activator of nuclear factor- κ B ligand (RANKL) [7]. Osteoclast function (and RANKL expression) is upregulated by innate cytokines including TNF α , IL1 β and IL6 [7]. Although excessive osteoclast activity is the purported mechanism for the osteolytic lesions in CNO, this has not yet been specifically demonstrated. However, investigators have observed elevated innate cytokine production in patients with CNO that could drive osteoclastogenesis and excessive osteoclast activity (Fig. 1) [8]. For example, peripheral monocytes from treatment-naïve patients with CNO exhibit elevated TNF α and IL1 β (and diminished IL10) production compared with equivalent cells from healthy controls [9]. These observations have helped inform the prevailing theory that CNO is an autoinflammatory disorder involving disinhibited inflammasome activation. The inflammasome is an intracellular multiprotein complex that potentiates IL1 β release and pyroptotic cell death in response to damage-associated molecular patterns and pathogens [10]. A receptor involved in activating the inflammasome, NLRP3, is highly expressed in monocytes and bone regions from patients with CNO [11]. Furthermore, the clinical phenotype of CNO is similar to that observed in monogenic autoinflammatory diseases featuring sterile osteitis such as Majeed syndrome and IL1RA deficiency [10]. However, no monogenic cause has been found for CNO and only 2.8% of patients report an affected family member [2]. This might be, in part, due to factors influencing epigenetic regulation such as the intestinal microbiome, as demonstrated in the *pstpip2*^{-/-} mouse model of CNO [12]. In summary, experimental observations suggest that CNO is likely to have a complex aetiology

that extends beyond the disinhibited inflammasome activation observed in high-penetrance monogenic autoinflammatory diseases. The presence of lymphocytic infiltrate in the chronic bony lesions of affected patients also raises the question whether CNO is caused by both autoinflammatory and autoimmune mechanisms, involving a final common pathway of lymphocyte-mediated inflammation with tissue specificity for skin, bones, and the intestine [11].

Osteoclastogenesis and osteoclast activation is also dependent on IL17, produced by a subset of inflammatory CD4⁺ T cells known as Th17 cells, as well as mast cells and granulocytes [13, 14]. Naïve CD4⁺ T cells are polarised into Th17 cells following exposure to IL6, IL23 and TGF β . Although most Th17 cells reside within the gut mucosa where they regulate intestinal barrier immunity, this subset of T helper cells has diverse roles throughout the body including neutrophil recruitment and defence against extracellular pathogens including fungi [13]. Th17 overexpression is implicated in autoimmune inflammatory diseases such as rheumatoid arthritis [13]. There are several reasons to suspect that IL17 may be an important driver of pathology in CNO (Fig. 1). First, IL6 (a major Th17-polarising cytokine) is found in high concentrations in the serum of patients with CNO and was the single most discriminative factor of 18 soluble mediators (IL17 was not studied) tested in differentiating CNO from a range of other inflammatory bone conditions as well as healthy individuals [8]. Second, the clinical spectrum of CRMO includes phenotypes such as psoriasis, palmoplantar pustulosis and ankylosing spondylitis, which are mediated by IL17 [2, 3, 14]. Finally, individuals with SAPHO syndrome exhibit significantly elevated peripheral Th17 cells compared with both healthy controls as well as patients with psoriasis [4]. Taken together, these observations suggest that the neutralisation of IL17 would be a plausible therapeutic strategy in CNO.

The therapeutic application of IL17 blockade has proven highly effective in the treatment of psoriasis, and has also been used in patients with SAPHO syndrome [13, 15]. Treatments include monoclonal antibodies directed against IL17A (secukinumab and ixekizumab) or against the IL17 receptor (brodalumab) [13]. These treatments are well tolerated and are not associated with significant adverse events [16]. A significant therapeutic response to anti-IL17 therapies in patients with CNO would not only be of immediate benefit to patients but could potentially further our understanding of disease pathogenesis. Alongside IL17 blockade, other therapies targeting the IL6-IL23-Th17 axis should also be tested in CNO clinical efficacy trials including IL6 blockade (e.g. tocilizumab) which has been used previously [17], and IL23 blockade which has been used in SAPHO syndrome [15]. We advocate that multicentre randomised placebo-controlled trials of such treatments should be conducted alongside prospective observation of patients with CNO. These studies should employ rigorous clinical data collection, whole genome sequencing, deep immunophenotyping and functional immunological evaluation, including the measurement of IL17 levels and the capacity for its production. Such collaborative research is the most likely way to understand the aetiology and improve outcomes for patients with this chronic disease.

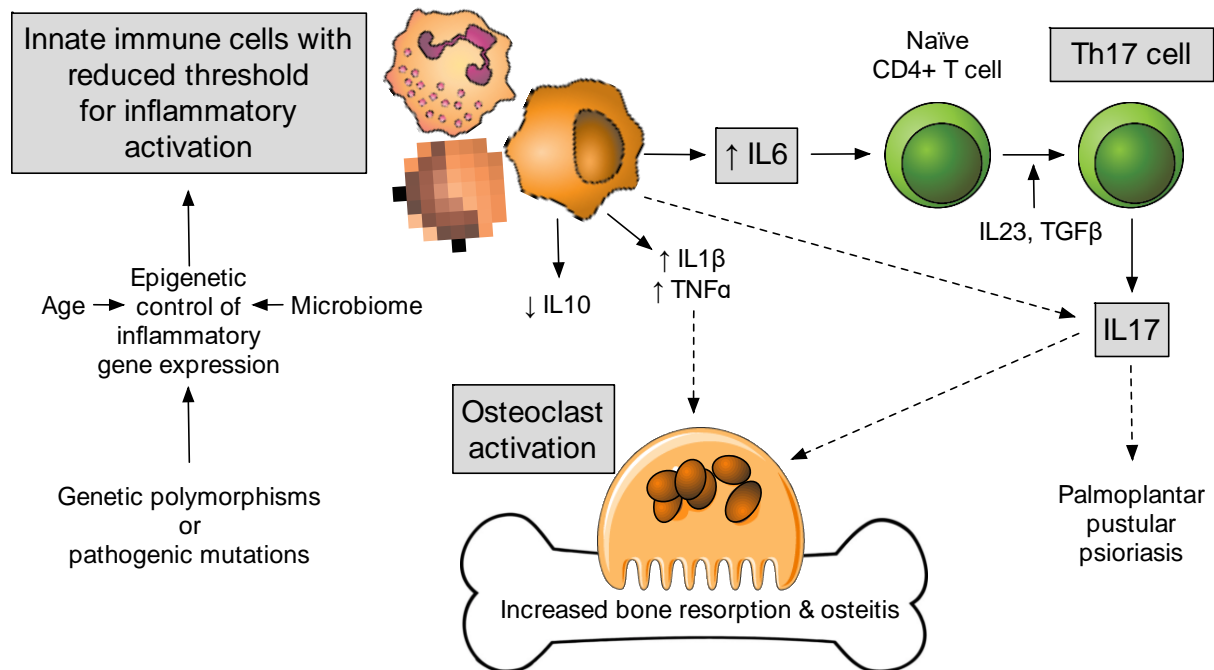


Fig. 1 Autoinflammatory cytokine production may result in CNO through IL17-mediated osteoclast activation. Increased inflammatory responsiveness of monocytes, macrophages and neutrophils is potentiated by unknown genetic/epigenetic mechanisms, resulting in chronic IL6-mediated expansion of the Th17 cell compartment and IL17 production. Overexpression of IL17 and innate cytokines drives excessive osteoclast activation and osteitis, as well as palmoplantar pustular psoriasis.

References

- 1 Schnabel A, Range U, Hahn G, Siepmann T, Berner R, Hedrich CM. Unexpectedly high incidences of chronic non-bacterial as compared to bacterial osteomyelitis in children. *Rheumatol Int* 2016;36(12):1737-45.

- 2 Girschick H, Finetti M, Orlando F, et al. The multifaceted presentation of chronic recurrent multifocal osteomyelitis: a series of 486 cases from the Eurofever international registry. *Rheumatology (Oxford)* 2018;57(7):1203-11.
- 3 Vittecoq O, Said LA, Michot C, et al. Evolution of chronic recurrent multifocal osteitis toward spondylarthropathy over the long term. *Arthritis Rheum* 2000;43(1):109-19.
- 4 Firinu D, Barca MP, Lorrai MM, et al. TH17 cells are increased in the peripheral blood of patients with SAPHO syndrome. *Autoimmunity* 2014;47(6):389-94.
- 5 Catalano-Pons C, Comte A, Wipff J, et al. Clinical outcome in children with chronic recurrent multifocal osteomyelitis. *Rheumatology (Oxford)* 2008;47(9):1397-9.
- 6 Schnabel A, Range U, Hahn G, Berner R, Hedrich CM. Treatment Response and Longterm Outcomes in Children with Chronic Nonbacterial Osteomyelitis. *J Rheumatol* 2017;44(7):1058-65.
- 7 Nakashima T, Takayanagi H. Osteoclasts and the immune system. *J Bone Miner Metab* 2009;27(5):519-29.
- 8 Hofmann SR, Bottger F, Range U, et al. Serum Interleukin-6 and CCL11/Eotaxin May Be Suitable Biomarkers for the Diagnosis of Chronic Nonbacterial Osteomyelitis. *Front Pediatr* 2017;5:256.
- 9 Hofmann SR, Morbach H, Schwarz T, Rosen-Wolff A, Girschick HJ, Hedrich CM. Attenuated TLR4/MAPK signaling in monocytes from patients with CRMO results in impaired IL-10 expression. *Clin Immunol* 2012;145(1):69-76.
- 10 Hedrich CM, Hofmann SR, Pablik J, Morbach H, Girschick HJ. Autoinflammatory bone disorders with special focus on chronic recurrent multifocal osteomyelitis (CRMO). *Pediatr Rheumatol Online J* 2013;11(1):47.

- 11 Brandt D, Sohr E, Pablik J, et al. CD14(+) monocytes contribute to inflammation in chronic nonbacterial osteomyelitis (CNO) through increased NLRP3 inflammasome expression. *Clin Immunol* 2018;196:77-84.
- 12 Lukens JR, Gurung P, Vogel P, et al. Dietary modulation of the microbiome affects autoinflammatory disease. *Nature* 2014;516(7530):246-9.
- 13 Patel DD, Kuchroo VK. Th17 Cell Pathway in Human Immunity: Lessons from Genetics and Therapeutic Interventions. *Immunity* 2015;43(6):1040-51.
- 14 Lin AM, Rubin CJ, Khandpur R, et al. Mast cells and neutrophils release IL-17 through extracellular trap formation in psoriasis. *J Immunol* 2011;187(1):490-500.
- 15 Wendling D, Aubin F, Verhoeven F, Prati C. IL-23/Th17 targeted therapies in SAPHO syndrome. A case series. *Joint Bone Spine* 2017;84(6):733-5.
- 16 Kamata M, Tada Y. Safety of biologics in psoriasis. *J Dermatol* 2018;45(3):279-86.
- 17 Sato H, Wada Y, Hasegawa E, et al. Adult-onset Chronic Recurrent Multifocal Osteomyelitis with High Intensity of Muscles Detected by Magnetic Resonance Imaging, Successfully Controlled with Tocilizumab. *Intern Med* 2017;56(17):2353-60.