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Letter to the Editor (Matters arising from published papers)

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Comment on: The neglected and untreated pains of CRMO and SAPHO syndrome

Dear Editor, With interest, we read the recent article by Sinnappurajar *et al.* in which the authors reconstruct the evident need for advancement of therapeutic options in Chronic Recurrent Multifocal Osteomyelitis (CRMO) and SAPHO syndrome [1]. They also deduce a potential therapeutic role for various biologics from their pathogenesis. We gladly respond to the author's discussion on therapeutic unmet needs, also highlighting our running randomized controlled PAPS study (PAmidronate for Pain in Sternocostoclavicular hyperostosis) evaluating the efficacy of pamidronate.

Prior to the treatment discussion, the authors touch upon the complex diagnostic classification of CRMO and SAPHO. Both diseases are commonly regarded subtypes of the chronic nonbacterial osteomyelitis (CNO) spectrum which may, as the authors point out, affect children and adults [2]. We would like to add that another distinguished CNO subtype is localized in the sternum, clavicles and upper ribs, and is also descriptively referred to as sternocostoclavicular hyperostosis (SCCH: ORPHA 178311). CNO/SCCH contrasts with CRMO in its localization in the axial skeleton and adult onset (whereas CRMO is mostly a paediatric and peripheral disease), and differentiates from full SAPHO due to frequent absence of synovitis and dermatologic manifestations [3, 4].

CNO/SCCH is specifically characterized by sclerosis, hyperostosis, erosions and ankylosis of the sternocostoclavicular region, accompanied by strongly increased isotope uptake on nuclear imaging. Similar to what the authors describe for CRMO/SAPHO, CNO/SCCH is poorly recognized and is associated with severe diagnostic delay (5 years median [4]). We therefore fully concur that all CNO patient populations are ill-served, facing excessive (and expensive) diagnostic trajectories during which irreversible tissue damage may manifest due to delay of potentially adequate treatment. We deliberately state 'potentially', as CNO/SCCH deals with a similar mayhem of off-label, physician-dependent, non-trialled treatment options that the authors describe for CRMO/SAPHO [3, 4].

Pamidronate, as the authors summarize, is found to be effective in various observational studies and one pilot randomized placebo-controlled trial (RCT) [5]. We would like to point out that the Leiden University Medical Center, The Netherlands, is currently running an RCT on the treatment of CNO/SCCH with pamidronate. The PAPS study includes adult patients with active disease as demonstrated by persistent pain and increased isotope uptake in the sternocostoclavicular region, and randomizes them for 6 months to receive 3-monthly i.v. pamidronate or placebo, followed by a 6 month open label phase (EudraCT 2020-001068-27).

The rationale for treating CNO/SCCH with pamidronate is twofold. First, CNO/SCCH consistently reveals increased isotope uptake on nuclear imaging, reflecting increase in local bone turnover. This increased metabolic activity is the main driver of bone pain and long-term secondary degenerative damage. Anti-resorptive agents may therefore reduce pain and disease progression, just like in other metabolic bone diseases such as Paget's disease [6]. The second part of the rationale for pamidronate lies in its anti-inflammatory properties, through its interference with the mevalonate pathway and inhibition of farnesyl pyrophosphate synthase, which is essential for the survival of osteoclasts and farnesyl pyrophosphate–dependent macrophages. Moreover, bisphosphonates significantly decrease the number of gamma/delta T cells, a specific subset of CD3+ T cells that are capable of recognizing antigens without MHC presentation, thereby thus also reducing the inflammatory cascade [7, 8].

Pamidronate's mechanistic foundation is also supported by our 25-year experience; our CNO/SCCH cohort demonstrates marked clinical improvement after pamidronate treatment (personal observations). On top of its efficacy in an observational setting, pamidronate is safe, well-tolerated—with known and preventable adverse effects—and inexpensive.

We entirely support the author's call for trials on the treatment of CNO (including CRMO, SAPHO and SCCH). An expansion of well-reasoned treatment options is critical, especially because first-line treatment with NSAIDs is often insufficient to achieve remission. Effective second-line treatments may include pamidronate, as will be assessed in the running randomized placebo-controlled PAPS study, and biologicals targeting IL-6, TNF-α, IL-17 and IL-23 as the authors suggest. Not only will adequate RCTs contribute to install the first evidence-based therapies for these diseases; they will also further increase awareness which will decrease diagnostic delay and improve prognosis, making a diagnosis of CNO a less debilitating one than it is at present.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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