A single cohort, open-label study of the efficacy of pamidronate for palmoplantar pustulosis in synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome

Sirs,

Palmoplantar pustulosis (PPP) is the most common skin manifestation of synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome and affects 55.1–92.3% of patients. The lesions are usually painful and significantly decrease life quality (1). However, some current treatments are with limited efficacy (1). In a retrospective study that was designed to systematically investigate the efficacy of intravenous pamidronate in alleviating spinal bone marrow edema in a cohort with SAPHO syndrome (2), we found an impressive improvement in PPP.

Patients who had PPP at the baseline assessment in the reported cohort (2) were included and those without PPP were excluded. Treatments were administered pamidronate disodium 1 mg/kg/d intravenously for 3 days at baseline and again 3 months later. We collected the pictures of skin lesions at baseline and at 3, 6 and 12 month follow-ups. Two experienced dermatologists evaluated and calculate the palmoplantar pustular psoriasis area and severity index (PPPASI). The primary outcome parameter was the PPPASI, and a decrease in score >50% was considered an effective reponse. Wilcoxon rank test was performed. All data are presented as mean values ± standard deviation if not otherwise indicated.

Twenty-five patients (16 females and 9 males) were included. The median age was 50.0 (interquartile range [IQR] 14.5) years. A total of 13 and 11 patients responded effectively to the first and second treatments, respectively, and 21 (84%) had more than 50% remission at the 12-month follow-up. Compared with baseline, the PPPASI revealed a significant decrease at 3, 6 and 12-month follow-ups (14.18±9.73 *vs*. 8.70±2.40, 7.23±9.48, 2.78±4.26, respectively) and a similar decrease was seen for the Visual Analogue Scale (5.7±1.7 *vs*. 4.3±2.0, 2.6±1.1, 2.4±1.3 cm, respectively) (all $p<0.05$, Fig. 1A-B). Furthermore, the inflammation factors also demonstrated a considerable drop at 3, 6 and 12 months from baseline (hs-CRP:11.991±10.484 *vs*. 9.720±14.108, 5.282±5.267 and 6.023±5.710 mg/L; ESR: 31.2±26.6, 22.2±17.8, 20.3±15.1, and 19.4±20.1 mm/h, respectively. All $p<0.05$, Fig. 1C-D).

In this study, the most common side effects were fever (71.5%), hypocalcaemia (30.0%) and mild gastrointestinal discomfort (22.0%), without severe symptoms. We did not observe any osteonecrosis of the jaw. This study demonstrated considerable efficacy of bisphosphonate treatment for PPP in SAPHO syndrome. Ninety-six percent patients showed improvement in symptoms at the one-year follow-up, and was much higher than the reported spontaneous remission rate which varied from 12.5% to 28% (3). These observations provide preliminary evidence of a new treatment strategy for PPP, especially for SAPHO syndrome patients.

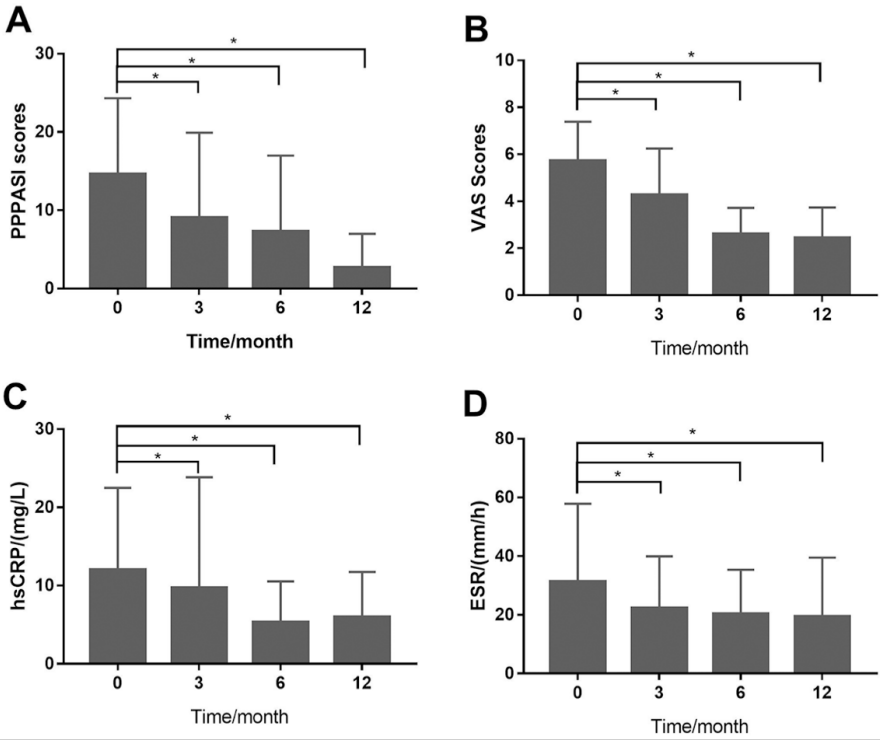

Fig. 1. Symptom assessments and inflammation factors show a significant decrease at three follow-ups compared with baseline.
A: PPPASI scores; **B**: Visual Analogue Scale (cm); **C**: hs-CRP (mg/L), and **D**: ESR (mm/h). Bar charts show the mean ± standard deviation, *$p<0.05$.

Bisphosphonates may relieve the syndromes by strengthening the innate immune system. Zimmermann reviewed publications about autoinflammatory bone disorders, and reported 48 of 98 patients had cultures positive for *P. acnes* (4). In acne patients, *P. acnes* promotes Th17 cells and IL-17 (5), which are reportedly involved in the progression of SAPHO syndrome (6, 7). SAPHO syndrome patients may have a genetic predisposition for impaired clearance of *P. acnes* (4). Compared with controls, SAPHO syndrome patients have lower proportion and absolute number of natural killer (NK) cells (7). The FoxO1 downregulation impedes bacterial clearance and then P. acnes triggers SAPHO syndrome (8). Pamidronate, as reported by Tu *et al*., controls influenza pathogenesis and lung inflammation by expanding the γδT cell population (9). Pamidronate could reduce the chronic infection, lower the inflammation level caused by that infection, and finally relieve the bone marrow oedema and PPP. The effects of antibiotics in SAPHO syndrome and tonsillectomy in PPP also support this (4, 10).

In conclusion, we found dramatic efficacy of pamidronate for PPP in SAPHO syndrome patients. By controlling chronic infections, bisphosphonates could be a potential treatment for PPP patients.

Written informed consent was obtained from each patient. The Ethics Committee of Peking Union Medical College Hospital (PUMCH) approved this trial (Identifier: ZS-944).

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Funding: this work was supported by the National Natural Science Foundation of China (81501852, 81472045, 81772299), Beijing Natural Science Foundation (7172175), Beijing Nova Program (Z161100004916123), Beijing Nova Program Interdisciplinary Collaborative Project (xxjc201717), The National Key Research and Development Program of China (2016YFC091501), and Capital Medical Research and Development Fund (2016-4-40112).

Competing interests: none declared.

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