Cefcapene Pivoxil Hydrochloride Is a Potentially New Treatment for Palmoplantar Pustulosis with Pustulotic Arthro-Osteitis

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Abstract
Pustulosis palmaris et plantaris or palmoplantar pustulosis (PPP) is a refractory pustular eruption of the palms and soles with unknown etiology. In addition to skin lesions, PPP patients may present with severe joint pain and pustulotic arthro-osteitis (PAO), especially of the sternoclavicular joint. PAO is sometimes regarded as a variant of synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome. Hence, macrolide and tetracycline antibiotics are used for the treatment of PPP with PAO. We report 3 cases of PPP with PAO that did not improve upon administration of macrolide antibiotics with NSAIDs. After administration of cefcapene pivoxil hydrochloride (CFPN-PI), a third-generation cephalosporin, the swelling and sternoclavicular joint pain were promptly reduced and dramatically improved in all 3 cases. We review the conventional antibiotic treatments used currently and propose CFPN-PI as a potentially new therapy for PPP or PPP + PAO.

Introduction
Palmoplantar pustulosis (PPP) is a condition of unknown etiology presenting as refractory vesicular/pustular eruption with scaly erythematos lesions of the palms and soles. PPP is usually chronic during the course of its treatment and adversely affects patient quality of life. PPP patients may also experience severe joint pain and pustulotic arthro-osteitis (PAO), especially in the sternoclavicular joint. Thus, PAO is sometimes regarded as a variant of synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome [1]. PAO is frequently seen in Japanese patients with PPP [2]; however, acne is rarely manifested. In addition, Propionibacterium acnes, which is regarded as a possible pathogen in SAPHO syndrome, is not associated with PPP pustules, because they are sterile [3]. Thus, it is unclear whether PAO is indeed a variant of SAPHO syndrome.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally considered as first-line treatment for SAPHO syndrome to treat severe joint pain. Similar to rheumatoid arthritis treatment, methotrexate and cyclosporine can be selected as further therapeutics for SAPHO joint pain. Antibiotics such as macrolides and tetracyclines have been used for the treatment of SAPHO syndrome in several reports [4–12]. There are a few options for the treatment of PPP or PPP with PAO to date, although antibiotics have been administered to several patients with PPP and PAO, referencing SAPHO treatment.

We present 3 PPP with PAO cases who were unresponsive to macrolide antibiotics and subsequently treated successfully with cefcapene pivoxil hydrochloride (CFPN-PI). CFPN-PI is proposed as a potentially new treatment for PPP + PAO.

Case Reports
Case 1
A 42-year-old female developed slightly scaly erythema on her bilateral soles in September 2011 (fig. 1, 2). A Kampo treatment (details unknown) was started by her dermatologist. On February 2012, she developed a few small vesicles and slightly scaly lesions on her bilateral soles. A biopsy of her skin lesion revealed pustules and an inflammatory infiltrate. A diagnosis of PPP was made. She was treated with a Kampo treatment, but her illness did not improve. On October 2012, her skin lesions were more severe and she had pain in her sternoclavicular joint. She was treated with prednisolone, cyclosporine and acitretin, but her skin lesions did not improve.

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erythema on her right palm and both soles, with tenderness of the right sternoclavicular and right sternocostal joints. She was diagnosed with PPP and treated with topical steroid ointment (betamethasone valerate), minocycline (200 mg/day) and loxoprofen (300 mg/day). However, her skin condition and joint pain did not improve, and thus she discontinued treatment. In July 2012, biotin therapy was started (biotin: 9 mg/day, vitamin C: 1,200 mg/day, Clostridium butyricum: 120 mg/day). Because the patient’s joint pain did not improve, she presented to our hospital in October 2012. Clinical evaluation was per-
formed based on the Palmoplantar Pustulosis Area and Severity Index (PPPASI) [13]. The patient’s initial PPPASI score was 5.6 (fig. 1a, b) and her visual analog scale (VAS) for joint pain score 5.6 (fig. 2). No clinical tonsillar inflammation was observed at the clinic. The dental checkup was performed by the local dentist, but there was no tooth decay or abscess. Her medical history revealed no smoking or history of psoriasis.

At the initial visit, her blood count was within the normal range, negative for antistreptolysin-O, and there was no evidence of biological inflammation, as assessed by C-reactive protein (CRP), complement activities (CH50), rheumatoid factor (RF) and matrix metalloproteinase (MMP)-3. Throat swab culture confirmed the normal bacterial flora including α-streptococcus (3+), Neisseria sp. (2+), γ-streptococcus (3+) and Lactobacillus (3+).

In addition to biotin therapy, topical treatment (maxacalcitol/heparinoid conjugate administered in the morning and liranaftate/betamethasone valerate/10% salicylic acid in the evening) and oral antibiotsic therapy (CFPN-PI, 300 mg/day) were started, resulting in gradual improvement of the skin lesion to a PPPASI score of 1 and a VAS score of 2 after 2 months (fig. 1c, d). Treatment with CFPN-PI was then changed to roxithromycin (RXM); however, her skin eruption and joint pain reoccurred (PPPASI: 9, VAS: 7.2). Changing the antibiotic therapy from RXM (300 mg/day) to CFPN-PI (300 mg/day) again resulted in gradual improvement over the next 4 months (PPPASI: 1, VAS: 0). CFPN-PI was stopped and faropenem (FRPM, 600 mg/day) started, and the patient’s PPPASI score gradually increased again with no change in her VAS score; thus, we stopped FRPM and started CFPN-PI again. Her skin condition improved to a PPPASI score of 0 after 4 months, while her VAS score remained 0 (fig. 2).

Case 2
A 63-year-old male developed small vesicles and pustules on his soles in October 2003 (fig. 3, 4). A topical antifungal agent from a drug store was applied, with no improvement of the eruption. A dermatologist diagnosed PPP in December 2003, and maxacalcitol and clobetasol propionate ointments were applied topically. However, the patient experienced several subsequent remission and exacerbation cycles of the eruption.

Since 2011 he had been taking a daily oral biotin supplement as biotin therapy. Pain and tenderness of the left sternoclavicular joint commenced in January 2013. RXM (300 mg/day) and loxoprofen (300 mg/day) treatments were started; however, this regimen was unsuccessful, and the eruption gradually worsened. The patient complained of right metatarsopha langale and sternoclavicular joint pain upon presentation to the dermatology department of our hospital. Because SAPHO syndrome was suspected, he was referred to our department in September 2013. No clinical tonsillar inflammation was observed at the clinic. The dental checkup was performed by the local dentist, but there was no tooth decay or abscess. His medical history included tonsillitis, but no metal allergy to iridium or platinum, tooth decay or a family history of psoriasis. He was an active smoker for 40 years (20 cigarettes/day). His initial PPPASI and VAS scores were 21.4 and 7, respectively (fig. 3a, b, 4). At the initial visit his blood count was within the normal range, negative for antistreptolysin-O, and there was no evidence of biological inflammation (as assessed by CRP, CH50, RF and MMP-3).

In addition to biotin therapy, topical treatment (same as case 1) and oral CFPN-PI (300 mg/day) and loxoprofen (300 mg/day) were started. His PPPASI score im...
proved to 15.4, 3.6 and 1.2 at 1, 3 and 6 months after commencing treatment, respectively (fig. 3 c, d, 4). The CFPN-PI concentration was gradually reduced according to improved PPPASI and VAS scores. Loxoprofen treatment was stopped over the following 2 months, since his VAS score was 0 and his PPPASI scores gradually improved to 4.0, 3.6 and 1.2 at 2, 3 and 6 months after stopping loxoprofen, respectively.

Case 3
A 59-year-old female noticed a slight deformity of the distal interphalangeal (DIP) joint of both little fingers, without pain (fig. 5, 6). DIP joint deformity had been present on the middle finger of her left hand, with pain, since 2010, and she was admitted to orthopedist care. Though rheumatoid arthritis was excluded, the DIP joint deformity was not diagnosed, and treatment with NSAIDs was started. Erythema with itch presented on the bilateral palms in March 2012, and a dermatologist prescribed a topical steroid ointment, but the eruption was unresponsive. Another dermatologist diagnosed PPP because of pustules and erythematousquamous lesions on both palms, and clobetasol propionate ointment therapy was started. Several repeated remission and exacerbation cycles of the eruption on the palms occurred, and RXM (300 mg/day) was started in June 2012. The patient suffered from pain of the left sternoclavicular joint with nail deformity of the hands (right middle finger and little finger and left middle finger; fig. 5a, b), and she was referred to our department in July 2013. No clinical tonsillar inflammation was observed at the clinic. The dental checkup was performed by the local dentist, but there was no tooth decay or abscess. She had no relevant medical history of psoriasis in her family; however, she was an active smoker for 40 years (10 cigarettes/day). Her initial PPPASI and VAS scores were both 5.6 (fig. 5a–d, 6). Upon the initial visit, her blood count was within the normal range, negative for antistreptolysin-O, and there was no evidence of biological inflammation (as assessed by CRP,
CH50, RF and MMP-3). Throat swab culture confirmed the normal bacterial flora including α-streptococcus (3+), Neisseria sp. (3+), γ-streptococcus (3+) and Lactobacillus (3+).

Topical treatment (same as case 1) and oral FRPM (600 mg/day) and loxoprofen (300 mg/day) were started. Her PPPASI and VAS scores improved (1 and 2.2, respectively) after 2 months. However, her skin eruption and joint pain recurred soon after (PPPASI: 9, VAS: 7.2). Treatment was switched from FRPM to CFPN-PI (300 mg/day), and her skin condition and joint pain gradually improved again (PPPASI: 1, VAS: 0) after 2 months. We attempted to decrease the CFPN-PI dose; however, her PPPASI score increased such that we could not alter the CFPN-PI dose for the next 4 months. Finally, her PPPASI score reached 0 at 10 months after CFPN-PI administration had been started (fig. 5e–h). No skin eruption or joint pain recurred; thus, the CFPN-PI concentration was decreased gradually to 200 mg/day, then 100 mg/day, and currently has been stopped.

Discussion

To the best of our knowledge, this is the first report of the use of CFPN-PI for the successful treatment of PPP with PAO. SAPHO syndrome has been successfully treated with antibiotics, including azithromycin, doxycycline, minocycline, clindamycin and sulfamethoxazole-trimethoprim (table 1) [4–12]. The application of antibiotic therapy appeared to control the disease; however, disease relapse was observed after antibiotic discontinuation [10]. The authors concluded that a treatment duration of at least 4 months, or permanent administration of antimicrobial therapy in the case of azithromycin, was necessary for promising results [10]. Azithromycin has a unique antimicrobial activity that was shown in vitro to be highly concentrated in various phagocytic cells and active against bacteria within these cells [14]. Several cases of SAPHO syndrome were found to harbor P. acnes in bone lesions [15]. Azithromycin has a unique antimicrobial activity that was shown in vitro to be highly concentrated in various phagocytic cells and active against bacteria within these cells [14]. Several cases of SAPHO syndrome were found to harbor P. acnes in bone lesions [15]. Azithromycin has a unique antimicrobial activity that was shown in vitro to be highly concentrated in various phagocytic cells and active against bacteria within these cells [14].

Minocycline has anti-inflammatory, immunomodulatory and chondroprotective effects in addition to antibacterial activity [16, 17]. Tetracyclines (especially minocycline and doxycycline) are potent inhibitors of metalloproteinases, including collagenase and gelatinase [18–20]. Metalloproteinases are certainly active in rheumatoid arthritis joint destruction, as shown in animal models of arthritis (rheumatoid arthritis and osteoarthritis) [21, 22]. In addition, tetracyclines, in particular minocycline and doxycycline, inhibit the production of tumor necrosis factor [23, 24]. Based on these findings, antibiotics are considered an option for joint pain treatment in PAO and SAPHO syndrome.

Treatment for PPP or PPP with PAO remains controversial, because the difference between SAPHO syndrome and PPP with PAO is not definitive. In one perspective, PAO is regarded as a seronegative spondyloarthropathy, exhibiting joint destruction and extra-articular involvement and negativity for RF involvement [25]. A recent thorough review of PPP with PAO illuminated one possible reason for the lack of clear differentiation between PAO and SAPHO syndrome [3]. PAO is frequently seen in Japanese patients with PPP [2], but acne is rarely seen, which could be one reason why true SAPHO syndrome is rarely seen in Japan. In addition, P. acnes is responsible for acne, while PPP pustules are sterile [3]. Indeed, there are no prior reports of PAO with positive findings of P. acnes in bone lesions.

Several case reports recently revealed that in addition to NSAIDs and disease-modifying antirheumatic drugs, low-dose cyclosporine is efficacious for treating PPP with PAO [26–28] and SAPHO syndrome.
Several of our PAO patients were treated with methotrexate by rheumatologists, but it was not always effective. Thus, elucidation of the mechanisms distinguishing PAO from SAPHO syndrome is required to develop further applications for the treatment.

CFPN-PI, a third-generation cephalosporin, is a broad-spectrum antimicrobial with increased activity against Gram-negative bacteria. Cefcapene-susceptible strains include Staphylococcus sp., Streptococcus sp. and Pneumococcus sp., P. acnes among others, and the therapeutic indications for CFPN-PI include superficial and deep skin infection, pharyngolaryngitis and tonsillitis (including peritonsillitis and peritonsillar abscess).

To the best of our knowledge, there is no evidence that cephalosporins inhibit the production of tumor necrosis factor in a similar manner as tetracyclines. However, allergic reactions, associated with joint pain and swelling, to antibiotics in the cephalosporin family have been reported. PPP is associated with chronic focal infections such as tonsillitis, chronic sinusitis and dental infection [3].

It is well known that a focal infection involves bacteria localized in certain regions such as the tonsils or tissues around teeth, from which they may spread to another organ or body structure. In PPP, a focal infection such as tonsillitis is consid-
ered a major factor in the occurrence and persistence of PPP [29]. We confirmed the normal bacterial flora in their throat but no pathogenic bacterium such as *Staphylococcus aureus* or β-streptococcus. Those normal floras are regarded as commensal bacteria and are not usually considered as the pathogen of PPP. The minimal inhibitory concentration of CFPN-PI against α-streptococcus is 0.025 μg/ml (in antibiotic books in Japan; http://www.antibiotic-books.jp), and the other reported minimal inhibitory concentrations for α-streptococcus are 1.56 μg/ml with amoxicillin, 0.1–0.39 μg/ml with lincomycin and 0.39 μg/ml with vancomycin, respectively. According to this result, CFPN-PI could be considered as a strong antibiotic against α-streptococcus. One possible hypothesis about the effect of CFPN-PI for PPP treatment is that commensal bacteria in the throat such as α-streptococcus gained pathogenic character or the host (PPP patient) suffered from the disorder of immune reaction against the bacteria which was used to be a commensal. However, not all patients with PPP + PAO are treated successfully with antibiotic regimens. The mechanism of how CFPN-PI affects the pathogenesis of PPP with PAO remains unclear. Further investigation to elucidate this mechanism is necessary for the establishment of CFPN-PI as a therapy for PPP + PAO.

**Statement of Ethics**

The patients have given their informed written consent. The study protocol has been approved by the committee on human research of Ehime University, Japan.

**Disclosure Statement**

The authors have no conflict of interest to declare.

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**Fig. 6.** Time course of the clinical changes caused by the treatments for case 3.

**References**


