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

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Introduction
Palmoplantar pustulosis (PPP) is a condition of unknown etiology presenting as refractory vesicular/pustular eruption with scaly erythematosus 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.

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 erythema on her bilateral soles. A macrolide antibiotic (details unknown) was then administered. On February 2013, she developed a few small vesicles and slightly scaly erythema on her bilateral soles. A macrolide antibiotic (details unknown) was then administered.

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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 performed.

Fig. 1. Case 1. Clinical presentation of the right thenar and right plantar arches. Scales, erythema, small pustules and vesicles were visible at the first visit (a, b) and 2 months after the first visit (c, d).
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 anti-streptolysin-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 liranafate/betamethasone valerate/10% salicylic acid in the evening) and oral antibi-otic 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 2.2 after 2 months (fig. 1c, d). Treatment with CFPN-PI was then changed to roxithromycin (RXM); however, her skin eruption and joint pain recurred (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 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 metatarsophalangeal and sternoclavicular joint pain upon presentation to the rheumatology 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. 3c, 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 reached 0 at 10 months after CFPN-PI administration had been started (fig. 5 e–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 is a common antimicrobial agent 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 is commonly used for acne treatment because of its activity against *P. acnes*. Thus, azithromycin is considered the preferred treatment for SAPHO syndrome.

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.

![Fig. 4. Time course of the clinical changes caused by the treatments for case 2.](image-url)
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-

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**Table 1.** Reported antibiotic treatment trials for SAPHO syndrome

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Responders/total cases</th>
<th>First author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline (tetracycline)</td>
<td>2/2</td>
<td>Ballara [4]</td>
</tr>
<tr>
<td></td>
<td>1/1</td>
<td>Colina [5]</td>
</tr>
<tr>
<td>Minocycline (tetracycline)</td>
<td>1/1</td>
<td>Takizawa [6]</td>
</tr>
<tr>
<td>Azithromycin (macrolide)</td>
<td>7/13</td>
<td>Schilling [7]</td>
</tr>
<tr>
<td></td>
<td>1/1</td>
<td>Wagner [8]</td>
</tr>
<tr>
<td></td>
<td>8/14</td>
<td>Kirchhoff [9]</td>
</tr>
<tr>
<td></td>
<td>12/12</td>
<td>Assmann [10]</td>
</tr>
<tr>
<td>Clindamycin (lincomycin)</td>
<td>5/5</td>
<td>Matzaroglou [11]</td>
</tr>
<tr>
<td>Sulfamethoxazole-trimethoprim</td>
<td>1</td>
<td>Rozin [12]</td>
</tr>
</tbody>
</table>

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[3] 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.
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 immunoreaction 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.

References

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