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Activity of nadifloxacin and three other antimicrobial agents against *Cutibacterium acnes* isolated from patients with acne vulgaris

Dear Sir,

Nadifloxacin[1] (OPC-7251) represents an established antimicrobial agent belonging to the quinolone group and was developed exclusively for topical administration[4]. Nadifloxacin is effective in treating a variety of bacterial skin infections and acne.[2,3,5,7,8,9] Here, the *in vitro* activity of nadifloxacin was assessed and compared with those of erythromycin, clindamycin and tetracycline against *Cutibacterium* (*C.*) *acnes*, formerly *Propionibacterium acnes*, to gain a picture of the resistance situation in Germany. The study was approved by the Ethics Committee of the Bayerische Landesärztekammer (Munich, Germany; EC-No.17088) and registered at Deutsches Register Klinische Studien (ID: DRKS00014231). Samples were collected between March and May 2018 at 45 sites. Each sample was obtained from a pustule of the facial area using a sterile sample collection swab and directly inserted in the transport tube medium (Amies medium, Sarstedt AG & Co. KG, Nümbrecht, Germany, order number 80.1361.500). Further information was acquired to characterize the patient population, acne score (Leeds revised Acne Grading System[6]) and prior antibiotic treatment of acne. The VITEK 2 ANC Card System for Identification of Clinical Isolates of Anaerobic Bacteria (bioMérieux sa, Marcy-l´Etoile, France, distributed by bioMérieux Deutschland GmbH, Nürtingen, Germany) was used. Reference standards of antimicrobial agents were purchased by Sigma-Aldrich Chemie GmbH (Taufkirchen, Germany): nadifloxacin (Order no. SMB00375-1G), clindamycin phosphate (Order no. PHR1021-1G), erythromycin (Order no. E5389-1G) and tetracycline hydrochloride (Order no. T7660-5G). Nadifloxacin was dissolved in 0.1 N NaOH, erythromycin in ethanol 96% (Dr. K. Hollborn & Söhne GmbH & Co. KG, Leipzig, Germany), clindamycin and tetracycline in sterile distilled water.

Before susceptibility testing, the isolates were transferred on Columbia 5% SB (sheep blood) agar (BD, Heidelberg, Germany) to ensure purity and good growth. The antimicrobial susceptibility against the different drugs was determined by an agar dilution method using Gifu Anaerobic Medium agar modified 'Nissui' (Nissui Pharmaceutical Inc. Ltd., Tokyo, Japan; pH 7.3, distributed by HyServe GmbH & Co. KG, Uffing, Germany) and a bacterial cell inoculum of 10^6 cfu per ml as it was previously described[5]. The plates were incubated at 37°C in anaerobic atmosphere using the Anaerocult system (Merck, Darmstadt, Germany) and analysed after 48 h incubation for anaerobic *C. acnes*.

Minimum inhibitory concentration for clindamycin was determined by E-test (Liofilchem, Roseto degli Abruzzi, Italy) on Mueller-Hinton agar plates (BD, Heidelberg, Germany), which covered a continuous concentration range from 0.016 to 256 µg/mL.

Two control organisms (*C. acnes* DSM 1897 and 108415, Braunschweig, Germany) were tested simultaneously (MIC [µg/mL]: nadifloxacin: 0.195; erythromycin: 0.049; tetracycline: 0.78; clindamycin: 0.016; [n = 2]).

A total of 73 strains of *C. acnes* from 115 samples were isolated. Of these 73 samples, 23 (31.5%) came from patients who had been pretreated with antibiotics. More than half of the patients (51.4%) were ≤21 years old (Table 1). Most of the patients suffered from mild to moderate acne, represented by a Leeds score of 6 for the 3rd quartile (75%) and 4 for the median (Table 1).[6]

*Registered in Germany as Nadixa, Ferrer International S.A., Gran Via Carlos III, 94, ES-08028 Barcelona, Distributor: Dr. Pfleger Arzneimittel GmbH.

Table 1 Patient age [years] and severity of acne at time of sample collection

Characteristics	N	Missing	Minimum	1st quartile	Median	3rd quartile	Maximum
Age [years]	72	1	10.0	18.0	21.0	26.0	64.0
Severity grade of acne*	73	0	1.0	3.0	4.0	6.0	11.0

*According to Leeds revised acne grading system (O'Brien *et al.* [6]).

Table 2 Minimal inhibitory concentration (MIC) range, MIC_{50}, MIC_{90} of antimicrobial agents against *C. acnes*; breakpoint resistance, percentage and no. of resistant strains

Antimicrobial agent	Test	MIC range (min to max) [μg/mL]	MIC_{50} [μg/mL]	MIC_{90} [μg/mL]	Breakpoint resistance [μg/mL]	% resistance (no. of strains)
Nadifloxacin	Agar dilution	0.097 to 0.390	0.195	0.195	≥4†	0.00 (0)
Clindamycin	E-Test	0.023 to >256	0.047	0.750	≥8†,‡,§,¶	4.11 (3)
Erythromycin	Agar dilution	<0.024 to >200	0.024	200	≥2‡ ≥8†	For both breakpoints: 15.07 (11)
Tetracycline	Agar dilution	0.390 to 3.125	0.390	0.780	≥16‡,§	0.00 (0)

†Alba *et al.* [1].
‡Sardana *et al.* [8].
§Clinical and Laboratory Standards Institute (CLSI) Performance Standards for Antimicrobial Susceptibility Testing, 29th Edition, CLSI Supplement M100, Wayne PA: Pennsylvania; 2019.
¶The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 9.0, 2019. http://www.eucast.org.

None of the 73 strains revealed elevated minimum inhibitory concentration (MIC) levels against nadifloxacin or tetracycline. Table 2 shows the number of samples in which resistance was detected according to the applied clinical breakpoints. The highest percentage (15.07%, 11 strains) was shown for erythromycin, followed by clindamycin (4.11%, 3 strains).

As for erythromycin a significant number of resistances was found (n = 11), an investigation into possible influencing factors on occurrence of resistant strains was carried out by means of contingency tables. There is no evidence of an influence of age, severity of acne or antibiotic pretreatment on the occurrence of resistant strains.

In summary, nadifloxacin was found to be highly active against *C. acnes* isolated from patients with acne vulgaris. However, a considerable number of *C. acnes* strains showed *in vitro* resistance against erythromycin and clindamycin.

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Conflict of interest

C Neumeister, M R Götz and U Schwantes are employees of Dr. Pfleger Arzneimittel GmbH. P Nenoff, D Koch and C Krüger are employees of the laboratory for medical microbiology, which was commissioned by Dr. Pfleger Arzneimittel GmbH with the isolation of *C. acnes* and susceptibility testing. R-H Bödeker and C. Borelli have received honoraria for their advisory activities from Dr. Pfleger Arzneimittel GmbH.

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Morphea-like changes in the setting of cancer immunotherapy

Editor,

Immune checkpoint inhibitors (ICI) are monoclonal antibodies targeting cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1).[1] The spectrum of immunotherapy-induced adverse reactions is unique and referred to as immune-related adverse events (irAEs). Cutaneous toxicities account for approximately 30% of all irAEs; the most common include eczema-like maculopapular rash, pruritus, lichenoid reactions, vitiligo-like lesions, psoriasis, and, less frequently, bullous pemphigoid or sarcoidosis.[2] Sclerotic reactions as scleroderma and morphea have been rarely described. A recent review reported 6 cases of scleroderma and 4 cases of morphea.[3] We describe two cases of ICI-related morphea-like reactions.

Case 1. In January 2021, a 74-year-old female patient was examined for the presence of diffuse skin indurated abdominal plaques, loss of skin appendages and hypo- and hyper abdominal pigmentary changes (Fig. 1a). The lesions were rapidly developed during the previous month, and the patient reported a bothering sensation of skin tight impairing her quality of life. Four months earlier (September 2020), the patient started treatment with ipilimumab (3 mg/kg every 3 weeks) for a metastatic vaginal mucosal melanoma (pT4bN1aM1c). Concurrent medications included furosemide 25 mg/die and irbesartan 150 mg/die for hypertension. The patient denied any concomitant digestive, vascular or pulmonary symptoms. Laboratory examinations including anti-nuclear antibodies, anti-centromere, anti-Scl-70 and anti-RNA-polymerase III antibodies were negative. A histologic examination of a biopsy specimen showed diffuse dermal sclerosis, atrophy of the adnexal structures, and perivascular and interstitial lympho-plasmacytic infiltrates, consistent with the clinical suspicion of localized morphea. Based on the temporal proximity between the beginning of ipilimumab and the occurrence of the cutaneous manifestations, the causative role of immunotherapy was postulated. The drug was not discontinued; due to increasing cutaneous symptoms, the patient was started on oral prednisone 25 mg/die, progressively tapered, with partial clinical benefit of the cutaneous manifestations.

Case 2. In October 2019, a 37-year-old female patient presented to the Cancer University Institute of Toulouse Oncopole for the development of two whitish, indurated abdominal sclerotic plaques (Fig. 1b), one located on the right hypochondrium and measuring 2cm, the other located on the left flank and measuring 6cmx4cm. The patient had a diagnosis of cutaneous melanoma (pT2aN0M0) since 2016. In September 2019, a follow-up examination revealed metastatic involvement of 3 inguinal lymph nodes; following lymphadenectomy, the patient started nivolumab in adjuvant setting, 480 mg every 4 weeks for 12 months. The indurated whitish plaques occurred 3 weeks after the first infusion, the patient was otherwise asymptomatic. ANA, anti-centromere, anti-Scl-70 and anti-RNA-polymerase III antibodies were all negative. Histopathologic examination of an incisional skin biopsy showed sclerosis in the dermis, and some perivascular and interstitial lympho-plasmacytic infiltrates (Fig. 2). On the basis of clinico-pathologic findings, the

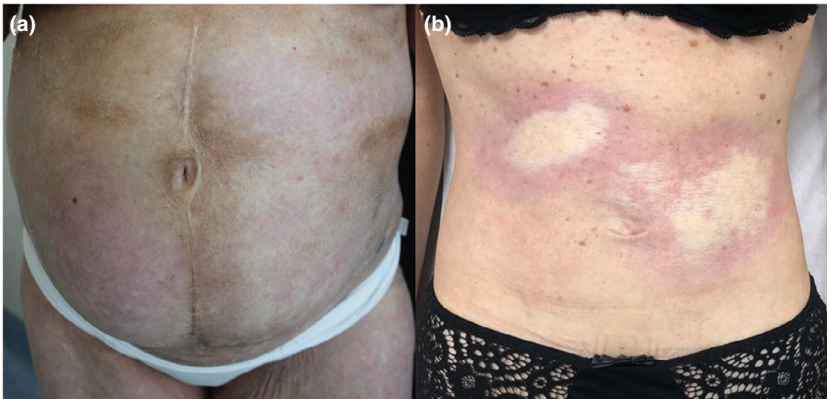

Figure 1 Clinical presentation of morphea-like changes: (a) diffuse skin induration and pigmentary changes on the abdomen and (b) two indurated whitish abdominal plaques, one on the right hypochondrium and one on the left flank.