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Original Research

Safety and efficacy profile of ozenoxacin 1% cream in pediatric patients with impetigo ☆

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ABSTRACT

Background: Ozenoxacin is a topical antibiotic approved in the United States for treatment of impetigo in adults and children age ≥2 months. This analysis evaluated the efficacy and safety of ozenoxacin in specific pediatric age groups.
Methods: Data for children aged 2 months to <18 years recruited from eight countries who had participated in phase 1 and 3 trials of ozenoxacin were extracted and analyzed by age range.
Results: Across studies, 644 pediatric patients with impetigo received ozenoxacin 1% cream (n = 287) or vehicle (n = 247). One study included retapamulin 1% ointment as the internal validity control (n = 110). The clinical success rate at the end of treatment and bacterial eradication rates after 3 to 4 days of treatment and at the end of treatment were significantly higher with ozenoxacin than vehicle (all $p < .0001$). The clinical and microbiologic success rates were higher with ozenoxacin than vehicle in the age groups of 0.5 to <2 years, 2 to <6 years, 6 to <12 years, and 12 to <18 years and were comparable to vehicle in the 2 to <6 months age group, although patient numbers were low (≤5 per treatment arm). No safety concerns with ozenoxacin were identified. Of the 362 plasma samples derived from 38 patients, four slightly exceeded the lower limit of quantification, indicating negligible systemic absorption.
Conclusion: The results of this analysis suggest that ozenoxacin 1% cream is an effective and safe treatment for impetigo in pediatric patients aged 2 months to <18 years.

Introduction

Impetigo is a highly contagious bacterial skin infection that most commonly occurs in young children (Brown et al., 2003; Cole and Gazewood, 2007; Lewis, 2019; Sladden and Johnston, 2004, 2005). The estimated global median prevalence is 2.5-fold higher in children than adults (Bowen et al., 2015). In the United States, the number of cases of impetigo is estimated at >3 million per year (U.S. Food and Drug Administration, 2016). Major predisposing factors for impetigo are hot and humid climates, socioeconomic deprivation, crowded environments, malnutrition, and certain lifestyle activities such as involvement in close-contact sports (Bowen et al., 2015; Cole and Gazewood, 2007; Rabbani Khorasgani, 2019; Sladden and Johnston, 2004).

The main causative pathogen of impetigo is *Staphylococcus aureus*, although *Streptococcus pyogenes* alone or in combination with *S. aureus* is also implicated. The condition is characterized by erythematous pustules or vesicles (red sores) that quickly evolve into superficial erosions with a characteristic honey-colored crust. Lesions are typically localized on the face, neck, and hands but can spread to other parts of the body due to scratching or can be transmitted to close contacts (Cole and Gazewood, 2007; Lewis, 2019; Sladden and Johnston, 2004; 2005). Because impetigo is highly contagious, the condition is of particular concern for schools and daycare centers. To limit the spread of infection, the American Academy of Pediatrics recommends that children with impetigo be kept at home until at least 24 hours after initiation of appropriate antimicrobial therapy (American Academy of Pediatrics, 2019). Clinical practice guidelines recommend the use of topical antibacterial agents for localized patches of impetigo and recommend oral antibiotics for treatment of numerous or extensive lesions that are

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not responding to topical therapy and for systemic infection (Stevens et al., 2014).

Ozenoxacin is a novel, nonfluorinated quinolone antibiotic approved in the United States for the topical treatment of impetigo due to *S. aureus* or *S. pyogenes* in adult and pediatric patients aged 2 months or older (Food and Drug Administration, 2017). In comparative studies against a range of other antimicrobial agents, ozenoxacin demonstrated potent bactericidal activity against pathologically relevant Gram-positive organisms, particularly staphylococci and streptococci (Canton et al., 2018). Ozenoxacin exhibits an expanded spectrum against methicillin-, mupirocin-, and ciprofloxacin-resistant strains of *S. aureus* (Canton et al., 2018; López et al., 2013) and has a better safety profile than fluorinated quinolones, including a lack of chondrotoxic potential, due to the absence of a fluorine atom in its molecular structure (González Borroto et al., 2018). Importantly, ozenoxacin's mechanism of action against both DNA gyrase A and topoisomerase IV protects it from the development of resistance (Vila et al., 2019). Topical ozenoxacin is negligibly absorbed (Gropper et al., 2014a) and shows excellent dermal tolerability (Gropper et al., 2014b). Together, these properties suggest that ozenoxacin may be a valuable option for empirical treatment of impetigo.

Evaluation of topical ozenoxacin 1% cream in children and adults with impetigo in a phase 1 study (Gropper et al., 2014c) and two well-controlled, adequately powered phase 3 clinical trials (Gropper et al., 2014d; Rosen et al., 2018) demonstrated that this treatment is effective and well tolerated. To gain insight into the clinical profile of ozenoxacin solely in the pediatric population, study data from participating children aged 2 months to <18 years were pooled and analyzed. This analysis is complementary to a similar analysis conducted of pediatric patients in the same clinical studies, which involved children and adolescents aged 6 months to <18 years with nonbullous impetigo as per the indication for ozenoxacin in Europe (Medicine & Healthcare Products Regulatory Agency, 2019).

Methods

Patients

Data for pediatric patients enrolled in a phase 1 study (Gropper et al., 2014c) and two phase 3 clinical trials (Gropper et al., 2014d; Rosen et al., 2018) of ozenoxacin for treatment of impetigo were analyzed to evaluate its efficacy and safety profile by age group. The phase 1 study included 38 patients aged ≥2 months to <18 years. The first phase 3, multicenter, randomized, placebo-controlled trial of ozenoxacin included 335 patients aged ≥2 years from Germany, Romania, South Africa, Ukraine, and the United States. The second phase 3, multicenter, randomized, placebo-controlled trial of ozenoxacin included 271 patients aged ≥2 months from Germany, Romania, Russia, Spain, South Africa, and the United States. In both phase 3 trials, placebo treatment consisted of ozenoxacin 1% cream vehicle, which contains emollients, emulsifying agents, an aqueous cosolvent, and benzoic acid as a preservative agent. For the analyses, data for the pediatric population were extracted, pooled, and stratified into age groups: 2 to <6 months, 6 months to <2 years, 2 to <6 years, 6 to <12 years, and 12 to <18 years.

All studies applied similar inclusion/exclusion criteria with regard to extent and severity of disease, and all studies used the same therapeutic schedule (i.e., topical application of ozenoxacin 1% cream or vehicle twice daily for 5 days). Although the main outcome of the phase 1 study was safety, a measure of clinical efficacy was also included. The pivotal phase 3 studies evaluated the efficacy and safety of ozenoxacin versus vehicle, and one study also included retapamulin 1% ointment as an internal validity control. All studies were conducted in accordance with the principles outlined in the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. Written informed consent was obtained from all study participants (or their legal guardians) prior to entry.

Analyses

Patients' demographic parameters (age, sex, and race), baseline clinical characteristics, clinical and microbiologic outcomes, and safety evaluation were analyzed by treatment and by treatment stratified by age group. Baseline clinical characteristics included number and extent of lesions, Skin Infection Rating Scale (SIRS) score, impetigo type (bullous/nonbullous), microbiologic susceptibility (if a sample was available), and pharmacokinetic data (if available).

The primary efficacy endpoint was the clinical response rate, which was defined in the studies as clinical success (cure) or clinical failure (improvement, failure, or unable to determine) in the intent-to-treat population at the end of treatment (visit 3; days 6–7). However, to facilitate comparison with studies of other antimicrobials approved for the treatment of impetigo that also included clinical improvement in their definition of clinical success, the broader definition was applied in the current analysis. Thus, clinical success was defined as cure (total SIRS score of 0 for exudates/pus, crusting, tissue warmth, and pain; ≤1 for each instance of erythema/inflammation, tissue edema, and itching; and no requirement for additional antimicrobial therapy of baseline-affected areas) or improvement (SIRS score decreased by >10% compared with baseline and not fulfilling SIRS score criteria for a cure). A patient who showed clinical improvement at the end of therapy could continue treatment with another antimicrobial at the discretion of the investigator. Clinical failure was defined as no change in total SIRS score or total SIRS score increased or decreased by ≤10% compared with baseline, and a requirement for additional antimicrobial therapy of affected areas. A patient who did not meet any of the outcomes listed was classified as unable to determine and considered a clinical failure.

The phase 3 studies also evaluated microbiological response at visit 2 (day 3–4 of treatment) and visit 3 (day 6–7 of treatment, end of therapy). Microbiologic success/eradication was defined as the absence of the original pathogen(s) identified in the specimen culture from the affected area at baseline (visit 1) with or without the presence of any new microorganisms. Microbiologic failure/persistence was defined as the presence of the original pathogen(s) in the specimen culture from the affected area at baseline with or without the presence of any new microorganisms. Adverse events (AEs) and adverse drug reactions in all age groups of children treated with ozenoxacin, vehicle, or retapamulin were monitored to assess treatment safety. Blood samples were collected to determine ozenoxacin plasma concentrations for potential pharmacokinetic analyses. Plasma concentrations <0.5 ng/mL were considered to be below the lower limit of quantification (0.489 ng/mL).

Statistical analyses

Statistical significance (p-value) for clinical success rates and microbiologic response rates between ozenoxacin and vehicle was calculated in the overall pediatric population. The Fisher's exact test was applied in both analyses. Due to the selection of pediatric patients for re-analysis and consequent decrease in statistical power relative to the entire patient population per study, comparisons by age group were analyzed descriptively.

Results

Demographic and baseline clinical characteristics

The pooled efficacy and safety pediatric population consisted of 644 patients aged ≥2 months to <18 years who were enrolled in a phase 1 study or two phase 3 clinical trials of ozenoxacin in the treatment of impetigo. Patients were recruited from eight countries (Germany, Puerto Rico, Romania, Russia, South Africa, Spain, Ukraine, and the United States), although most patients came from South Africa (n = 368), the United States (n = 113), and Germany (n = 75). Demographic and baseline characteristics of the combined efficacy and safety population are summarized according to treatment with ozenoxacin (n = 287), vehicle (n = 247), or retapamulin (n = 110; Table 1).

The treatment groups were well matched with respect to demographic parameters, impetigo type, and clinical characteristics. Most patients were in the 6 to <12 years (n = 285; 44.3%) or 2 to <6 years (n = 209; 32.5%) age group. Most patients were male (57.3%), and the most common ethnic groups were black (44.9%) and Caucasian/white (38.7%). Patients had mainly nonbullous impetigo (n = 535; 83.1%). At baseline, patients had a mean (standard deviation [SD]) SIRS total score of 11.5 (4.7), a mean (SD) of 3.3 (3.6) affected areas, and a mean (SD) total affected area of 7.1 (10.4) cm^2, with no notable differences in any parameter between ozenoxacin- and vehicle-treated groups. The majority of patients (95.5%) had microbiologic susceptibility.

Demographic and baseline characteristics of the combined efficacy and safety population treated with ozenoxacin or vehicle and stratified by age group are shown in Table 2. The mean (SD) number of affected areas at baseline ranged from 5.0 (3.9) in the 2 to <6 months age group to 3.0 (3.1) in the 12 to <18 years age group in patients treated with ozenoxacin and from 3.7 (4.2) in the 2 to <6 years age group to 1.9 (1.5) in the 12 to <18 years age group in patients treated with vehicle. The mean (SD) total affected area at baseline ranged from 3.5 (2.1) cm^2 in the 2 to <6 months age group to 8.1 (10.1) cm^2 in the 6 to <12 years age group in patients treated with ozenoxacin and from 4.1 (3.2) cm^2 in the 2 to <6 months age group to 9.1 (11.6) cm^2 in the 12 to <18 years age group in patients treated with vehicle. The mean (SD) baseline SIRS total score ranged from 9.0 (3.3) in the 2 to <6 months age group to 12.4 (5.3) in the 12 to <18 years age group in patients treated with ozenoxacin and from 6.7 (0.6) in the 2 to <6 months age group to 11.3 (4.9) in the 2 to <6 years age group in patients treated with vehicle.

Clinical outcomes

The clinical success rate in the overall combined pediatric population was significantly higher with ozenoxacin than with vehicle ($p < .0001$; Fig. 1). Both ozenoxacin and vehicle had a 100% clinical success rate in children aged 2 to <6 months, although patient numbers in each treatment arm were low (5 and 3, respectively). In each of the other four age groups, ozenoxacin had a higher clinical success rate than vehicle. The respective clinical success rates by age group for ozenoxacin versus vehicle were 100% versus 58.5% for 0.5 to <2 years; 83.8% versus 72.7% for 2 to <6 years; 90.8% versus 76.8% for 6 to <12 years; and 94.1% versus 78.0% for 12 to <18 years.

Microbiologic response

The microbiologic response after treatment with ozenoxacin or vehicle was evaluated at visit 2 (day 3–4 of treatment) and visit 3

Table 1
Demographic and baseline characteristics of the combined safety and efficacy population by treatment.

	Total (n = 644)	Ozenoxacin (n = 287)	Vehicle[a] (n = 247)	Retapamulin (n = 110)
Study, n (%)				
Phase 1 (Gropper et al., 2014c)	38 (5.9)	38 (13.2)	0 (0.0)	0 (0.0)
Phase 3 (Gropper et al., 2014d)	335 (52.0)	113 (39.4)	112 (45.3)	110 (100.0)
Phase 3 (Rosen et al., 2018)	271 (42.1)	136 (47.4)	135 (54.7)	0 (0.0)
Age range, n (%)				
2 to <6 months	8 (1.2)	5 (1.7)	3 (1.2)	0 (0.0)
6 months to <2 years	35 (5.4)	23 (8.0)	12 (4.9)	0 (0.0)
2 to <6 years	209 (32.5)	99 (34.5)	66 (26.7)	44 (40.0)
6 to <12 years	285 (44.3)	109 (38.0)	125 (50.6)	51 (46.4)
12 to <18 years	107 (16.6)	51 (17.8)	41 (16.6)	15 (13.6)
Sex, n (%)				
Female	275 (42.7)	124 (43.2)	110 (44.5)	41 (37.3)
Male	369 (57.3)	163 (56.8)	137 (55.5)	69 (62.7)
Race, n (%)				
Black	289 (44.9)	131 (45.6)	93 (37.7)	65 (59.1)
Caucasian/white	249 (38.7)	102 (35.5)	122 (49.4)	25 (22.7)
Mixed race/multiracial	81 (12.6)	43 (15.0)	19 (7.7)	19 (17.3)
Asian	25 (3.9)	11 (3.8)	13 (5.3)	1 (0.9)
No. of affected areas				
Mean (SD)	3.3 (3.6)	3.4 (3.4)	3.0 (3.2)	3.8 (4.6)
Total affected area (cm^2)				
Mean (SD)	7.1 (10.4)	7.2 (10.1)	7.4 (10.4)	5.9 (10.9)
Baseline Skin Infection Rating Scale total score				
Mean (SD)	11.5 (4.7)	11.2 (4.8)	10.9 (4.8)	13.8 (3.8)
Impetigo type, n (%)				
Nonbullous	535 (83.1)	244 (85.0)	202 (81.8)	89 (80.9)
Bullous	109 (16.9)	43 (15.0)	45 (18.2)	21 (19.1)
Microbiological susceptibility, n (%)				
N	286	101	99	86
Resistant	13 (4.5)	6 (5.9)	4 (4.0)	3 (3.5)
Susceptible	273 (95.5)	95 (94.1)	95 (96.0)	83 (96.5)

SD, standard deviation
[a] Vehicle refers to ozenoxacin 1% cream formulation without active ingredient.

Table 2
Demographic and baseline characteristics of the combined safety and efficacy population by treatment and age group.

	Oxenoxacin					Vehicle[a]				
	2 to <6 months (n = 5)	0.5 to <2 years (n = 23)	2 to <6 years (n = 99)	6 to <12 years (n = 109)	12 to <18 years (n = 51)	2 to <6 months (n = 3)	0.5 to <2 years (n = 12)	2 to <6 years (n = 66)	6 to <12 years (n = 125)	12 to <18 years (n = 41)
Study, n (%)										
Phase 1 (Gropper et al., 2014c)	3 (60.0)	13 (56.5)	9 (9.1)	4 (3.7)	9 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Phase 3 (Gropper et al., 2014d)	0 (0.0)	0 (0.0)	50 (50.5)	44 (40.4)	19 (37.3)	0 (0.0)	0 (0.0)	31 (47.0)	63 (50.4)	18 (43.9)
Phase 3 (Rosen et al., 2018)	2 (40.0)	10 (43.5)	40 (40.4)	61 (56.0)	23 (45.1)	3 (100.0)	12 (100.0)	35 (53.0)	62 (49.6)	23 (56.1)
Sex, n (%)										
Female	2 (40.0)	9 (39.1)	38 (38.4)	47 (43.1)	28 (54.9)	1 (33.3)	7 (58.3)	26 (39.4)	62 (49.6)	14 (34.1)
Male	3 (60.0)	14 (60.9)	61 (61.6)	62 (56.9)	23 (45.1)	2 (66.7)	5 (41.7)	40 (60.6)	63 (50.4)	27 (65.9)
Race, n (%)										
Black	2 (40.0)	11 (47.8)	53 (53.5)	50 (45.9)	15 (29.4)	0 (0.0)	2 (16.7)	31 (47.0)	53 (42.4)	7 (17.1)
Caucasian/white	1 (20.0)	4 (17.4)	28 (28.3)	42 (38.5)	27 (52.9)	3 (100.0)	10 (83.3)	26 (39.4)	54 (43.2)	29 (70.7)
Mixed race/multiracial	2 (40.0)	6 (26.1)	16 (16.2)	11 (10.1)	8 (15.7)	0 (0.0)	0 (0.0)	7 (10.6)	9 (7.2)	3 (7.3)
Asian	0 (0.0)	2 (8.7)	2 (2.0)	6 (5.5)	1 (2.0)	0 (0.0)	0 (0.0)	2 (3.0)	9 (7.2)	2 (4.9)
No. of affected areas										
Mean (SD)	5.0 (3.9)	4.9 (3.2)	3.5 (3.5)	3.2 (3.4)	3.0 (3.1)	3.3 (2.3)	2.5 (1.7)	3.7 (4.2)	2.9 (3.0)	1.9 (1.5)
Total affected area (cm^2)										
Mean (SD)	3.5 (2.1)	5.0 (6.4)	7.6 (12.5)	8.1 (10.1)	5.7 (5.8)	4.1 (3.2)	4.5 (3.2)	7.4 (7.6)	7.3 (11.7)	9.1 (11.6)
Baseline Skin Infection Rating Scale total score										
Mean (SD)	9.0 (3.3)	10.8 (3.7)	11.5 (5.0)	10.4 (4.5)	12.4 (5.3)	6.7 (0.6)	8.3 (3.0)	11.3 (4.9)	11.1 (4.6)	10.9 (5.4)
Impetigo type, n (%)										
Nonbullous	5 (100.0)	17 (73.9)	83 (83.8)	94 (86.2)	45 (88.2)	1 (33.3)	7 (58.3)	49 (74.2)	106 (84.8)	39 (95.1)
Bullous	0 (0.0)	6 (26.1)	16 (16.2)	15 (13.8)	6 (11.8)	2 (66.7)	5 (41.7)	17 (25.8)	19 (15.2)	2 (4.9)
Microbiological susceptibility, n (%)										
N	0	1	48	39	13	0	0	30	59	10
Resistant	0 (0.0)	0 (0.0)	4 (8.3)	2 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.7)	1 (1.7)	1 (10.0)
Susceptible	0 (0.0)	1 (100.0)	44 (91.7)	37 (94.9)	13 (100.0)	0 (0.0)	0 (0.0)	28 (93.3)	58 (98.3)	9 (90.0)

SD, standard deviation.
[a] Vehicle refers to ozenoxacin 1% cream formulation without active ingredient.

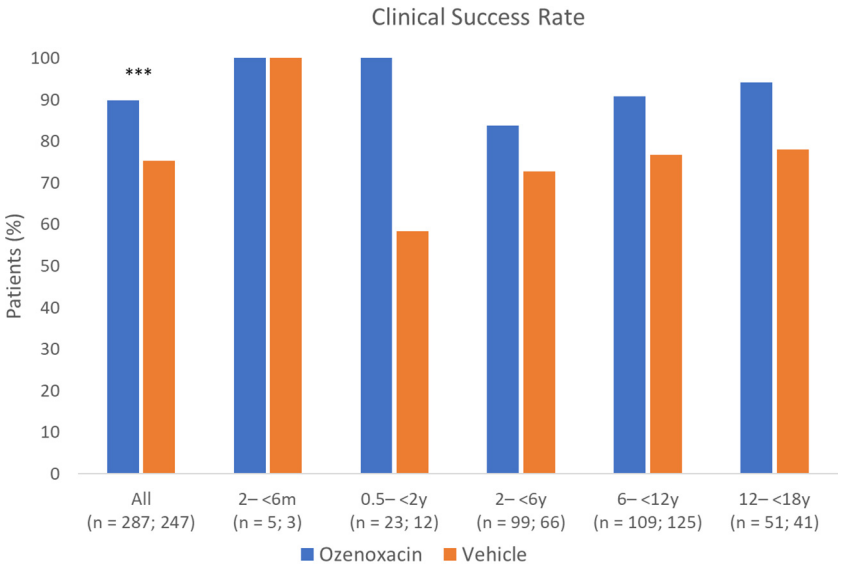

Fig. 1. Clinical success rates in ozenoxacin- and vehicle-treated pediatric patients stratified by age group. Clinical success was defined as cure or improvement according to predefined criteria. Vehicle refers to ozenoxacin 1% cream formulation without active ingredient. *** $p < .0001$.

(day 6–7 of treatment, end of therapy). Significantly higher microbiologic success rates were achieved with ozenoxacin than with vehicle in the overall combined population at visit 2 (Fig. 2) and visit 3 (Fig. 3; $p < .0001$ at both time points). Both ozenoxacin and vehicle had a microbiologic success rate of 100% in the 2 to 6 months age group at visits 2 and 3, but patient numbers were low (two patients in each treatment arm at both visits).

In each of the other four age groups, ozenoxacin had a higher microbiologic success rate at visits 2 and 3 compared with vehicle. At visit 2, the respective microbiologic success rates for ozenoxacin and vehicle were 100% versus 60% for 0.5 to <2 years, 79.7% versus 59.2% for 2 to <6 years, 85.5% versus 55.4% for 6 to <12 years, and 83.3% versus 40.7% for 12 to <18 years (Fig. 2). At visit 3, the respective microbiologic success rates for ozenoxacin and vehicle

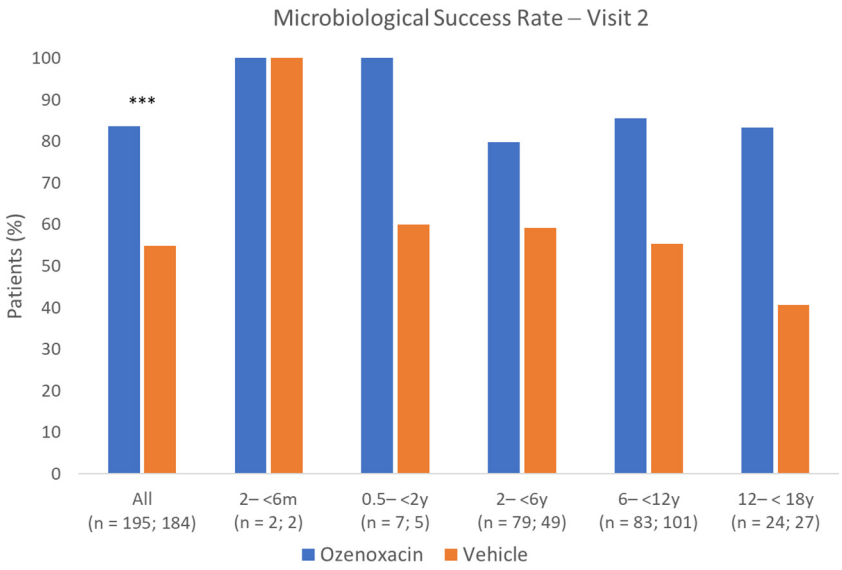

Fig. 2. Microbiologic success rates at visit 2 (day 3–4 of treatment) in ozenoxacin- and vehicle-treated pediatric patients stratified by age group. Microbiologic success was defined as the absence of original pathogen(s) in culture of the baseline specimen with or without the presence of new microorganisms. Vehicle refers to ozenoxacin 1% cream formulation without active ingredient. *** $p < .0001$.

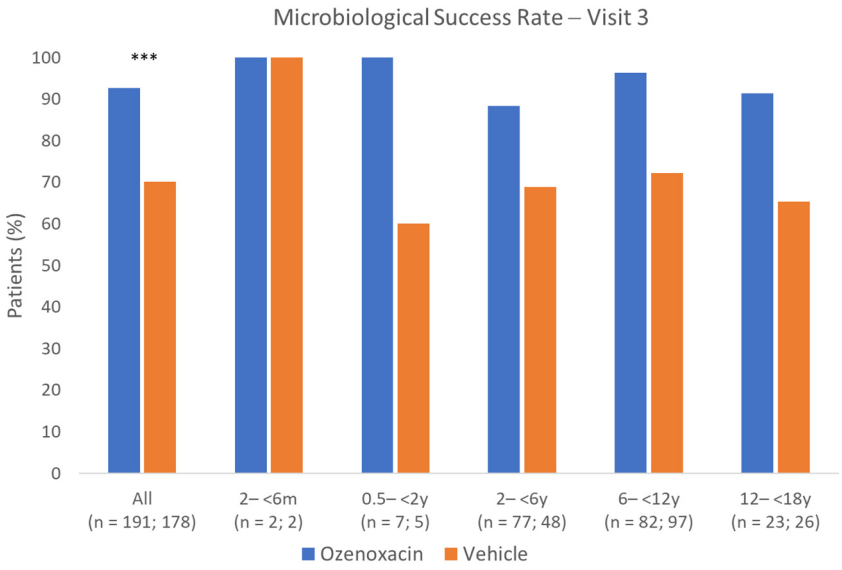

Fig. 3. Microbiologic success rates at visit 3 (day 6–7, end of treatment) in ozenoxacin- and vehicle-treated pediatric patients stratified by age group. Microbiologic success was defined as the absence of original pathogen(s) in culture of the baseline specimen with or without the presence of new microorganisms. Vehicle refers to ozenoxacin 1% cream formulation without active ingredient. *** $p < .0001$.

were 100% versus 60% for 0.5 to <2 years, 79.7% versus 63.5% for 2 to <6 years, 85.5% versus 64.8% for 6 to <12 years, and 83.3% versus 60.7% for 12 to <18 years (Fig. 3).

Outcomes in patients with resistant strains

Ten patients had resistant bacterial strains at baseline. At visit 3 (day 6–7 of treatment, end of therapy), the clinical success rate (cure or improvement) was 100% (6 of 6 patients) with ozenoxacin and 100% with vehicle (4 of 4 patients). The microbiologic eradication rate with ozenoxacin was 100% at visit 2 (day 3–4 of treatment) and 100% at end of therapy. Two of four vehicle-treated patients (50%) achieved microbiologic success at the end of therapy.

Safety

Across the studies, 49 AEs were reported in 38 patients (5.9%) during the course of treatment, all of which were mild (n = 37) or moderate (n = 12) in intensity. No serious AEs were reported. No reported AE for ozenoxacin or vehicle was considered drug related. One AE reported with retapamulin (0.9%), which occurred in the 6 to <12 years age group, was considered drug related.

Blood samples for the analysis of ozenoxacin plasma concentrations were collected from 38 pediatric patients in the phase 1 study (Table 3). Four of 362 samples (1.1%) derived from 38 patients showed plasma ozenoxacin concentrations above the lower limit of quantification (range: 0.539–0.681 ng/mL), three in the 2 to <6 months age group, and one in the 2 to <6 years age group.

Table 3
Ozenoxacin plasma samples above the lower limit of quantification (Gropper et al., 2014c).

Patients (n)	Ozenoxacin plasma samples					
	All (n = 38)	2 to <6 months (n = 3)	0.5 to <2 years (n = 13)	2 to <6 years (n = 9)	6 to <12 years (n = 4)	12 to <18 years (n = 9)
Samples, n	362	21	88	64	36	153
Samples above lower limit of quantification, n (%)	4 (1.1)	3 (14.3)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)

Detected concentrations (range: 0.539–0.681 ng/mL) were close to the lower limit of quantification (0.489 ng/mL), indicating negligible systemic absorption.

Concentrations indicated negligible systemic absorption; therefore, further pharmacokinetic analyses were not performed.

Discussion

The efficacy and safety of ozenoxacin in the pediatric population with impetigo were examined by extracting and pooling data for all patients aged <18 years who participated in phase 1 (Gropper et al., 2014c) or phase 3 (Gropper et al., 2014d; Rosen et al., 2018) trials. Patients were stratified into five age groups, ranging from 2 to <6 months to 12 to <18 years. In the pooled population of pediatric patients, clinical and microbiologic success rates with ozenoxacin were significantly superior to those with vehicle, confirming overall results of the pivotal phase 3 trials. The clinical success rates with ozenoxacin at the end of treatment ranged from 83.8% to 100% across age groups and were higher than those with vehicle (58.3%–100%).

The bacterial eradication rates with ozenoxacin were similar across age groups, ranging from 79.7% to 100% after 3 to 4 days of treatment and from 88.3% to 100% at the end of treatment. Clinical and microbiologic success rates of 100% were achieved with both ozenoxacin and vehicle in the 2 to <6 months age group, but because patient numbers were low ($\leq$5 in each treatment arm), the results must be interpreted with caution. In all other age groups, ozenoxacin demonstrated clinical and microbiologic superiority to vehicle in patients with susceptible or resistant strains.

Safety and tolerability are important features of any medication intended for use in the pediatric population, especially one that includes infants. Among 287 children treated with ozenoxacin across the three studies, no safety concerns were identified. None of the 17 mild or moderate AEs reported with ozenoxacin during the course of the studies was considered treatment related. The absence of local reactions to ozenoxacin or its vehicle, and the negligible systemic absorption of ozenoxacin, are consistent with the results of phase 1 studies conducted during its clinical development (Gropper et al., 2014a, 2014b).

The main limitation of this subgroup analysis of ozenoxacin clinical trials data is the low patient numbers in the 2 to <6 months and 0.5 to <2 years age categories, although this is consistent with the disease pattern; impetigo is more common in older children, who typically have greater outward contact through daycare, school, and social/sporting activities (Sladden and Johnston, 2004). Ozenoxacin showed excellent clinical and microbiologic efficacy and was well tolerated even in the youngest age groups, supporting its use in children as young as 2 months of age.

A strength of the analysis is the homogeneity of the respective patient populations, which facilitated data pooling to evaluate outcomes in a large population treated with ozenoxacin or vehicle. Possible reasons for the high cure rates observed in the vehicle-treated group include the self-limiting nature of impetigo, the high overall standard of care for patients treated within the context of a clinical trial, and the presence of benzoic acid in the ozenoxacin cream vehicle.

The global emergence and spread of antibiotic resistance has negatively affected treatment outcomes of patients with impetigo, with various world regions reporting resistance to the commonly used topical agents fusidic acid (Alsterholm et al., 2010; Castanheira et al., 2010a, 2010b; Howden and Grayson, 2006; Pfaller et al., 2010) and mupirocin (Antonov et al., 2015; McNeil et al., 2011; Poovelikunnel et al., 2015; Simor et al., 2007). Increasing rates of antimicrobial resistance are a particular concern for diseases such as impetigo, where treatment is often initiated empirically in the absence of microbial culture and/or susceptibility testing. As the need for alternative antibacterial agents with activity against resistant strains and a low propensity to induce resistance is increasing simultaneously with the decline in new antibiotic development (Doron and Davidson, 2011; Poovelikunnel et al., 2015), the introduction of a new agent with broad bactericidal activity is a major event.

Conclusion

Delivering a high concentration of antibiotic directly to infected areas of skin can overcome its potential to develop bacterial resistance. Minimal dermal absorption avoids the risk of systemic adverse effects associated with oral therapy. The fact that ozenoxacin is bactericidal, is intended for use in a short-term therapeutic schedule (two applications daily for 5 days), and achieves high concentrations in the upper layers of the epidermis matches the current principles of antibiotic stewardship which aim to avoid the emergence of bacterial resistance. (Doron and Davidson, 2011).

The antibacterial spectrum of activity of ozenoxacin and its preclinical and clinical efficacy and safety are well characterized (Canton et al., 2018; López et al., 2013; Vila et al., 2019). The current analysis addressed a relevant clinical question about the efficacy and safety of topical ozenoxacin in the primary intended patient population (i.e., children and adolescents). The results confirm that topical ozenoxacin 1% cream is effective and safe for treating impetigo in children aged 2 months to <18 years.

Conflict of Interest

None.

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Study Approval

The authors confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

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