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REVIEW

Ozenoxacin: a review of preclinical and clinical efficacy

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ABSTRACT

Introduction: Impetigo is the most common bacterial skin infection in children. Treatment is becoming complicated due to the development of antimicrobial resistance, especially in the main pathogen, *Staphylococcus aureus*. Ozenoxacin, a novel non-fluorinated topical quinolone antimicrobial, has demonstrated efficacy in impetigo.

Areas covered: This article reviews the microbiology, pharmacodynamic and pharmacokinetic properties of ozenoxacin, and its clinical and microbiological efficacy in impetigo.

Expert opinion: In an environment of increasing antimicrobial resistance and concurrent slowdown in antimicrobial development, the introduction of a new agent is a major event. Ozenoxacin is characterized by simultaneous affinity for DNA gyrase and topoisomerase IV, appears to be impervious to certain efflux pumps that confer bacterial resistance to other quinolones, shows low selection of resistant mutants, and has a mutant prevention concentration below its concentration in skin. These mechanisms protect ozenoxacin against development of resistance, while the absence of a fluorine atom in its structure confers a better safety profile versus fluoroquinolones. *In vitro* studies have demonstrated high potency of ozenoxacin against staphylococci and streptococci including resistant strains of *S. aureus*. Clinical trials of ozenoxacin in patients with impetigo reported high clinical and microbiological success rates. Preserving the activity and availability of ozenoxacin through antimicrobial stewardship is paramount.

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Ozenoxacin; impetigo; topical antibiotics; pediatric population; quinolones

1. Introduction

Impetigo is one of the most common bacterial skin infections in children, particularly those aged two to five years [1–8]. Globally, the median prevalence of impetigo in the general population is 11.2%, but is 2.5-fold higher in children (12.3%) than adults (4.9%) [9], thus representing a high disease burden, especially for children residing in low and low-middle income countries or in socioeconomically disadvantaged areas of high-income countries [9].

Impetigo lesions are typically located on the face, neck, and hands, although scratching of pruritic lesions can transfer the infection to other parts of the body and to close contacts. The main causative pathogens of impetigo are *Staphylococcus aureus* and *Streptococcus pyogenes*, both of which cause the non-bullous form which occurs in around 70% of cases [7,10]. Bullous impetigo is caused exclusively by *S. aureus* due to the production of exfoliative toxins [7,11].

The highly contagious nature of impetigo makes the condition a particular concern for schools and day care centers [1–4,7,8,10,12,13]. To limit the spread of infection, it is recommended that children be kept at home until 24 h after the start of appropriate antimicrobial therapy [14]. Disease control is also important to relieve symptoms (itching, sores), minimize scarring due to scratching, and prevent rare but serious complications such as rheumatic heart disease [15] or glomerulonephritis [8].

Antimicrobial treatment of impetigo can produce a rapid resolution of symptoms [10,13], thus limiting the risk of person-to-person transmission. Clinical practice guidelines recommend use of topical antibacterial agents for localized impetigo and recommend use of oral antibiotics for patients with extensive lesions unresponsive to topical therapy, for those with systemic infection, and for managing outbreaks that affect several people [16]. Topical antibacterial treatment delivers a high concentration of drug directly to infected areas of skin, facilitating the potential of the antimicrobial to overcome bacterial resistance. Additionally, topical therapies are minimally absorbed, which largely avoids the systemic side effects associated with oral therapies [1]. Topical treatment has been shown to be equally or more effective than oral therapy for treating impetigo [13,16].

An increasing number of Gram-positive pathogens, especially *S. aureus*, have developed resistance to topical antimicrobial agents typically used in clinical practice. Antimicrobial resistance, particularly methicillin-resistant *S. aureus* (MRSA) isolates, is a major concern worldwide, and the emergence of community-

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Article highlights

- Ozenoxacin is a novel non-fluorinated topical quinolone used for the treatment of impetigo.
- Ozenoxacin simultaneously inhibits both enzymes responsible for bacterial DNA replication and appears unaffected by the activity of certain efflux pumps; this dual mechanism of antibacterial activity affords protection from development of resistance.
- *In vitro* studies of the antibacterial activity of ozenoxacin showed potency against staphylococci and streptococci including resistant strains of *Staphylococcus aureus*.
- An *in vivo* study using a mouse model of *S. aureus*-induced dermal infection showed superior efficacy of topical ozenoxacin 1% formulations versus mupirocin 2% ointment and retapamulin 1% ointment, as indicated by significant reductions in mean microbiological counts in infected skin samples and superior bacterial eradication rates.
- Preclinical trials showed the absence of chondrotoxic potential with ozenoxacin.
- Phase I studies showed that ozenoxacin has negligible transdermal absorption and does not induce phototoxicity, photoallergy or contact allergy.
- In two pivotal phase III studies of patients as young as 2 months with impetigo, ozenoxacin 1% cream significantly improved clinical and microbiological success rates compared with placebo (vehicle) cream and was well tolerated.
- This review of preclinical and clinical data of ozenoxacin supports its use for the treatment of impetigo.
- The role of ozenoxacin is likely to expand in future to include the treatment of other skin and soft tissue infections.
- Antimicrobial stewardship is essential to protect this valuable resource.

This box summarizes key points contained in the article.

acquired MRSA infections has aided the spread of resistant isolates [17]. Fusidic acid resistance in *S. aureus* has emerged in several countries, potentially limiting its overall efficacy [18–23]. Resistance has also been described to the commonly used topical agent mupirocin [24–27]. A recent large study of *S. aureus* isolates (n = 358) from skin and soft tissue infection samples from a mainly outpatient pediatric population found that 31.3% were resistant to mupirocin [26]. Increasing rates of antimicrobial resistance are a concern for patients with empirically managed diseases such as impetigo [16] where treatment is often provided without the benefits of microbial culture and/or susceptibility testing results to guide appropriate care. Newer antimicrobial agents with different modes of action to current drugs for impetigo, and with activity against resistant isolates, are clearly desirable.

This review discusses the microbiological and pharmacokinetic properties of the novel non-fluorinated topical quinolone ozenoxacin and highlights new studies reporting its therapeutic efficacy in impetigo.

2. Pharmacological properties

2.1. Mechanism of action

Quinolones act by inhibiting the enzymes DNA gyrase and topoisomerase IV, both of which are involved in bacterial DNA synthesis [28]. DNA gyrase catalyzes the negative supercoiling of DNA, and thus plays an important role in the replication and transcription of DNA, and in organization of the chromosome [29]. The main function of topoisomerase IV is to decatenate the two daughter molecules of DNA after replication [30]. Both enzymes are tetrameric: DNA gyrase consists of two A subunits (GyrA, encoded by the *gyrA* gene) and two B subunits (GyrB, encoded by the *gyrB* gene); topoisomerase IV also has two A subunits (ParC or GrlA, the latter in *S. aureus*, encoded by the *parC* or *grlA* genes) and two B subunits (ParE or GrlB, the latter in *S. aureus*, encoded by the *parE* or *grlB* genes) [28]. Some quinolones (e.g. levofloxacin and ciprofloxacin) act preferentially against topoisomerase IV over DNA gyrase [31].

Ozenoxacin has been shown to inhibit DNA gyrase supercoiling activity and topoisomerase IV decatenation simultaneously at the lowest concentrations in *S. aureus* SA113 compared with other quinolones [32]. This high inhibitory activity of ozenoxacin at low concentrations might be explained by its rapid penetration inside the bacterial cell in the first minute after exposure and high intrabacterial concentrations compared with other quinolones in all studied microorganisms, among them *S. aureus* and *S pyogenes*, causal agents of impetigo [33]. High accumulation of ozenoxacin inside the Gram-positive bacterial cell may reflect its apparent imperviousness to the activity of certain efflux pumps that affect other quinolones [34].

The bactericidal capacity of ozenoxacin against *S. aureus* and *S. pyogenes* compared to mupirocin and fusidic acid was demonstrated in killing curves experiments [35]. In *S. aureus*, ozenoxacin at two times the minimum inhibitory concentration (MIC) showed bactericidal activity by means of a 3-log reduction in colony-forming units (CFU) after 4 h, whereas mupirocin and fusidic acid at concentrations equivalent to 32 times the MIC showed bacteriostatic activity after 24 h (Figure 1).

Collectively, the characteristics of ozenoxacin indicate a high level of activity against Gram-positive bacteria [32–35].

2.2. In vitro antibacterial activity

In the most recent ozenoxacin surveillance study conducted using isolates collected in 2014, the *in vitro* activity of ozenoxacin was compared with other antimicrobial agents against Gram-positive clinical isolates from skin and soft tissue infections [36]. A total of 1,031 isolates were collected from single centers located in Spain, Argentina, Brazil, Colombia, Germany, Romania, South Africa, Sweden, and two sites in the United States (US). *S. aureus* isolates accounted for 49% of all isolates collected. MICs were determined for 11 antimicrobial agents, including topical agents such as mupirocin, fusidic acid, and retapamulin. Isolates were stratified by species and by their methicillin susceptibility/resistance and/or levofloxacin susceptibility/nonsusceptibility status. Summary data for the six most relevant comparators are shown in Table 1. Ozenoxacin showed high *in vitro* activity against all *S. aureus* isolates, inhibiting 99.4% of isolates at a MIC of ≤0.05 mg/L. Ozenoxacin MIC_{50} and MIC_{90} values were higher for levofloxacin-non-susceptible *S. aureus* isolates (0.06 mg/L and 0.5 mg/L, respectively) than for levofloxacin-susceptible *S. aureus* isolates (0.002 mg/L and 0.002 mg/L, respectively). Corresponding MIC values for levofloxacin were much higher for non-susceptible isolates (8 and

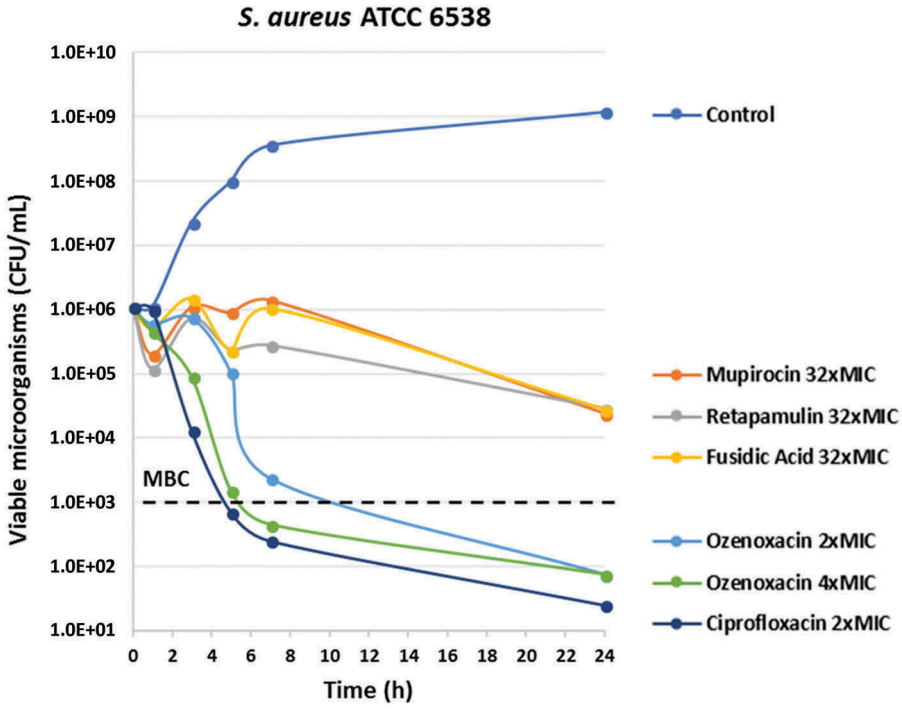

Figure 1. Bactericidal activity of ozenoxacin compared with mupirocin, fusidic acid and retapamulin against *S. aureus* ATCC 6538, evaluated by kill curves [35]. MBC: minimal bactericidal concentration. MIC: minimal inhibitory concentration; CFU: colony-forming units; xMIC: number of times the MIC.

>16 mg/L, respectively) and were similar for susceptible isolates (0.12 mg/L and 0.25 mg/L, respectively). Ozenoxacin was the most potent agent tested against *Staphylococcus epidermidis* isolates with MIC_{50} and MIC_{90} values of 0.008 and 0.25 mg/L, respectively. Ozenoxacin inhibited 94.8% of *S. epidermidis* isolates at a MIC of ≤0.05 mg/L. The activity of ozenoxacin was higher against levofloxacin-susceptible versus levofloxacin-non-susceptible *S. epidermidis* isolates, irrespective of their methicillin resistance status. Ozenoxacin was the most potent agent tested against *S. pyogenes*, inhibiting 98.3% of isolates at a MIC of ≤0.03 mg/L, and against *S. agalactiae*, inhibiting 95.5% of isolates at a MIC of ≤0.03 mg/L.

2.3. In vivo antibacterial activity

In a mouse model of *S. aureus*-induced dermal infection, ozenoxacin (1% ointment and 1% cream formulations) significantly reduced mean microbiological counts in infected skin samples compared with mupirocin 2% ointment (positive control) and retapamulin 1% ointment ($p < 0.05$ for comparisons of ozenoxacin formulations with mupirocin and retapamulin). Bacterial eradication rates (relative $\log_{10}$ transformation of CFU counts per gram of skin for control and test treatments) for ozenoxacin 1% cream and 1% ointment were 53% and 47%, respectively, compared with 31% for retapamulin and 28% for mupirocin after a single application [37].

2.4. Resistance

Acquisition of quinolone resistance follows two main mechanisms. The first is through chromosomal mutations in bacterial genes (*gyrA, gyrB, parC*, and *parE*) which encode the A and B subunits of target proteins. The second is through mutations which reduce accumulation of drug inside the cell, either by decreased uptake (porin mutations) or increased efflux (overexpression of efflux pumps) [38–40]. Quinolone resistance genes associated with plasmids have been described in certain Gram-negative bacteria [28]. In Gram-positive bacteria, the plasmid-mediated efflux pump QacB variant QacBIII was shown to confer capability for fluoroquinolone efflux in *S. aureus* [41]. Elsewhere, however, and based on a low prevalence of the plasmidic gene QacB in MRSA isolates and its absence in methicillin-susceptible *S. aureus* isolates, investigators concluded that QacBIII-mediated plasmidic mechanism of resistance to quinolones is likely to be of low relevance, even in quinolone-resistant MRSA strains [42]. Therefore, in Gram-positive bacteria, quinolone resistance is associated mainly with mutations in genes encoding GyrA and ParC and is complemented by overexpression of some efflux pumps [28].

The development of quinolone resistance is caused by point mutations in a specific region of the *gyrA* and *parC* genes, called the Quinolone Resistance-Determining Regions (QRDR). These genes encode the A subunit of DNA gyrase and topoisomerase IV, respectively [43].

The activity of ozenoxacin was not influenced by mutations in the *grlA* gene of *S. aureus*, and the degree of MIC increase for ozenoxacin with *gyrA-grlA* double and triple mutants was lowest among the quinolones tested (levofloxacin, nadifloxacin, ofloxacin) [32]. In another *in vitro* study which compared the antimicrobial activity of ozenoxacin, moxifloxacin, levofloxacin and ciprofloxacin on quinolone-susceptible and quinolone-resistant strains of *S. aureus*, ozenoxacin showed high antimicrobial activity in methicillin-resistant strains, even those with two, three, and/or four mutations in the *gyrA*

Table 1. *In vitro* activity of ozenoxacin and comparators against worldwide isolates of *S. aureus*, *S. epidermidis*, *S. pyogenes*, and *S. agalactiae* from skin and soft tissue infections.

Microorganism (no. of isolates)	Antibacterial agent	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)
S. aureus (all) (504)	Ozenoxacin	≤0.001–2	0.002	0.06
	Mupirocin	0.06–>256	0.25	0.5
	Fusidic acid	≤0.015–>16	0.12	0.25
	Retapamulin	0.03–>1	0.12	0.12
	Levofloxacin	0.06–>16	0.25	16
	Ciprofloxacin	0.12–>16	0.25	>16
MSSA (279)	Ozenoxacin	≤0.001–0.25	0.002	0.004
	Mupirocin	0.06–>256	0.25	0.5
	Fusidic acid	≤0.015–>16	0.12	0.25
	Retapamulin	0.03–>1	0.12	0.25
	Levofloxacin	0.06–>16	0.12	0.25
	Ciprofloxacin	0.12–>16	0.25	1
MRSA (225)	Ozenoxacin	≤0.001–2	0.004	0.12
	Mupirocin	0.06–>256	0.25	0.5
	Fusidic acid	0.06–>16	0.12	0.25
	Retapamulin	0.03–>1	0.12	0.12
	Levofloxacin	0.06–>16	0.25	>16
	Ciprofloxacin	0.12–>16	0.5	>16
Levofloxacin-susceptible *S. aureus*(383)	Ozenoxacin	≤0.001–0.03	0.002	0.002
	Mupirocin	0.06–>256	0.25	0.25
	Fusidic acid	0.03–>16	0.12	0.25
	Retapamulin	0.03–>1	0.12	0.25
	Levofloxacin	0.06–1	0.12	0.25
	Ciprofloxacin	0.12–4	0.25	0.5
Levofloxacin non-susceptible *S. aureus* (121)	Ozenoxacin	0.008–2	0.06	0.5
	Mupirocin	0.06–>256	0.25	2
	Fusidic acid	≤0.015–>16	0.12	0.25
	Retapamulin	0.03–0.25	0.12	0.12
	Levofloxacin	2–>16	8	>16
	Ciprofloxacin	4–>16	>16	>16
S. epidermidis (all) (195)	Ozenoxacin	≤0.001–2	0.008	0.25
	Mupirocin	0.06–>256	0.25	>256
	Fusidic acid	0.06–>16	0.12	8
	Retapamulin	0.03–>1	0.06	0.25
	Levofloxacin	0.12–>16	0.25	>16
	Ciprofloxacin	0.06–>16	0.5	>16
Methicillin susceptible *S. epidermidis* (MSSE) (86)	Ozenoxacin	≤0.001–2	0.004	0.03
	Mupirocin	0.06–>256	0.25	256
	Fusidic acid	0.06–>16	0.12	8
	Retapamulin	0.03–>1	0.06	0.25
	Levofloxacin	0.12–>16	0.25	4
	Ciprofloxacin	0.06–>16	0.25	4
Methicillin resistant *S. epidermidis* (MRSE) (109)	Ozenoxacin	0.002–2	0.06	0.5
	Mupirocin	0.06–>256	0.25	>256
	Fusidic acid	0.06–>16	0.12	16
	Retapamulin	0.03–>1	0.06	0.12
	Levofloxacin	0.12–>16	4	>16
	Ciprofloxacin	0.12–>16	8	>16
Levofloxacin-susceptible *S. epidermidis* (105)	Ozenoxacin	≤0.001–0.015	0.004	0.008
	Mupirocin	0.06–>256	0.25	>256
	Fusidic acid	0.06–>16	0.12	4
	Retapamulin	0.03–>1	0.06	0.25
	Levofloxacin	0.12–0.5	0.25	0.25
	Ciprofloxacin	0.06–1	0.25	0.5
Levofloxacin-non-susceptible *S. epidermidis* (90)	Ozenoxacin	0.008–2	0.06	1
	Mupirocin	0.06–>256	0.25	>256
	Fusidic acid	0.06–>16	0.12	16
	Retapamulin	0.03–>1	0.06	0.12
	Levofloxacin	2–>16	8	>16
	Ciprofloxacin	2–>16	>16	>16
Streptococcus pyogenes (124)	Ozenoxacin	≤0.001–0.25	0.008	0.015
	Mupirocin	≤0.015–0.5	0.06	0.25
	Fusidic acid	≤0.015–>16	4	4
	Retapamulin	≤0.015–0.25	0.03	0.06
	Levofloxacin	≤0.015–2	0.5	1
	Ciprofloxacin	≤0.015–8	0.5	1
Streptococcus agalactiae (88)	Ozenoxacin	0.002–0.5	0.015	0.03
	Mupirocin	0.5–8	1	1
	Fusidic acid	4–16	8	16
	Retapamulin	0.03–0.5	0.06	0.12
	Levofloxacin	0.25–>16	0.5	1
	Ciprofloxacin	0.25–>16	0.5	1

and/or *grlA* genes, and was not affected by the efflux pump inhibitor reserpine [44].

As discussed previously, overexpression of some efflux pumps can affect the MIC of some quinolones. In *S. aureus*, the efflux pumps involved in quinolone resistance are NorA, NorB, and NorC, belonging to the Major Facilitator Superfamily (MFS) of proteins [45]. Another efflux pump involved in quinolone resistance is MepA, which belongs to the Multiple Antibiotic and Toxin Extrusion (MATE) family of proteins [28,45]. In a recent study which tested several *S. aureus* strains presenting overproduction of some efflux pumps (e.g. NorA and MepA) against ozenoxacin, moxifloxacin, levofloxacin, ciprofloxacin and norfloxacin, the MICs of ozenoxacin were considerably lower than those for the other quinolones and were unaffected in strains with overexpression of these efflux pumps [34].

For some antibiotics, of which fluoroquinolones are probably the paradigm, it has been established that resistant mutants are selected in the so-called 'mutant selection window', which is the concentration range starting from the MIC to that required to inhibit the growth of the least susceptible single-step mutant. The upper boundary of the mutant selection window is also known as the mutant prevention concentration (MPC). The antibiotic concentration at a site of infection must always be maintained above the MPC to prevent generation of resistant mutants and to eradicate any growing resistant subpopulations [46–48]. The MPC of ozenoxacin determined in strains of methicillin-susceptible *S. aureus*, either wild-type or with a single mutation in the *gyrA* and/or *parC* genes, ranged from 0.05 to 1.2 mg/L, and that for methicillin-resistant *S. aureus* was 0.6 mg/L for strains with a mutation in the amino acid codon Ser-83 of the *gyrA* gene [49].

A single topical application of ozenoxacin cream delivers approximately 5 mg of active ingredient to the skin. Gropper and colleagues reported a mean ozenoxacin concentration of ~22,000 ng/mg (22 mg/L) in the stratum corneum (tape stripping samples) in human volunteers after twice daily administration of ozenoxacin cream for 3 days [50]. These concentrations are markedly higher than the predicted MIC of ozenoxacin (MIC range 0.008–0.25 mg/L) [36] and predicted MPC values for common impetigo pathogens including resistant strains of *S. aureus* [49].

Ozenoxacin has shown no cross-resistance with other families of commercial antibacterial agents against Gram-positive organisms and retains its activity below breakpoints for mutant species resistant to other marketed quinolones [36]. Ozenoxacin showed the same level of activity against

methicillin-susceptible and methicillin-resistant strains of all studied bacterial species [36].

3. Pharmacokinetic properties

3.1. Absorption

Analysis of tape stripping samples and skin punch biopsy samples following topical application of ozenoxacin 2% cream to healthy volunteers (n = 24) showed that ozenoxacin does not penetrate the skin. Ozenoxacin concentrations were high in the stratum corneum, low in the epidermis, and below the limit of quantitation in the dermis on most study days [50].

Clinical pharmacokinetic phase I studies conducted in healthy adult volunteers (n = 84) [51] and subjects with impetigo (aged 2 months to 65 years; n = 46) [52] found no or negligible systemic absorption following repeated topical application of varying strengths (1% or 2%) of ozenoxacin cream or ointment to intact or abraded skin [53]. Ozenoxacin plasma concentrations above the lower limit of quantification (0.5 ng/mL) were found in two children treated with ozenoxacin 1% cream for impetigo, with respective values of 0.539 and 0.681 ng/mL [52].

3.2. Distribution, metabolism, and elimination

As either no or negligible systemic absorption of ozenoxacin was observed in phase I clinical studies [51,52], the tissue distribution, metabolism and elimination of ozenoxacin in humans have not been investigated.

4. Therapeutic efficacy

4.1. Clinical efficacy

The efficacy and safety of ozenoxacin 1% cream in the treatment of impetigo have been demonstrated in two pivotal placebo-controlled phase III clinical trials [54,55]. In both studies, placebo consisted of cream vehicle without the active ingredient ozenoxacin. The vehicle contains benzoic acid among other excipients.

The first randomized, double-blind, multicenter phase III study compared ozenoxacin 1% cream (n = 155) with placebo (vehicle) cream (n = 156) in adults and children aged >2 years with impetigo [54]. The study included a retapamulin 1% ointment arm (n = 154) for internal validation. Study drug was applied twice daily for 5 days and clinical, microbiological and laboratory evaluations were performed over a 2-week follow-up. Total affected area (mean ± standard deviation [SD]) was 9.34 ± 16.73 cm^2, 12.85 ± 21.40 cm^2, and 12.12 ± 22.51 cm^2 for ozenoxacin, placebo, and retapamulin, respectively. Analysis of the primary efficacy endpoint, the clinical success rate (i.e. clinical cure) in the intention-to-treat (ITT) population at the end of therapy (day 6–7), demonstrated that ozenoxacin was significantly superior to placebo (34.8 *vs*. 19.2%, p = 0.003). The internal control retapamulin was also superior to placebo (37.7 *vs*. 19.2%, p < 0.001). In this study, clinical success was determined by means of the Skin Infection Rating Scale (SIRS), similar to that used in phase III retapamulin trials, which assesses seven signs/symptoms scored from 0 (absent) to 6 (severe). As clinical success rates reported for other marketed topical antibiotics include both clinical cure and improvement, a post hoc analysis was performed to obtain comparable efficacy results. Ozenoxacin was again superior to placebo in this analysis (85.2 *vs*. 73.7%; p = 0.028), and the results compare favorably with clinical success rates from randomized controlled trials of other topical antibiotics versus placebo: 68–82% *vs*. 29–42% for mupirocin (1980s); 55 *vs*. 13% for fusidic acid (2003); and 85 *vs*. 52% for retapamulin (2006) [13].

In the second randomized, double-blind, phase III study, patients aged 2 months and older with impetigo were randomized to receive topical ozenoxacin 1% cream (n = 206) or placebo (vehicle) cream (n = 206) twice daily for 5 days [55]. Total affected area (mean ± SD) was 10.29 ± 13.04 cm^2 and 8.84 ± 8.12 cm^2 for ozenoxacin and placebo, respectively. In this study, the primary efficacy outcome of clinical response (clinical cure) in the ITT population at the end of therapy was based on SIRS scores for five signs/symptoms, scored from 0 (absent) to 3 (severe) as per recommendations of the FDA Draft Guidance on mupirocin [56]. Ozenoxacin was significantly superior to placebo, with clinical success rates of 54.4% and 37.9%, respectively, at the end of 5 days' therapy (p = 0.001). A secondary outcome was clinical success inclusive of clinical cure and improvement. In this analysis, 88.8% of patients in the ozenoxacin group achieved clinical success at the end of therapy compared to 78.2% in the placebo group (p = 0.003).

A subsequent pooled analysis of individual patient data from both phase III trials in patients with impetigo treated with ozenoxacin (n = 361) or placebo (n = 362) confirmed the superior efficacy of ozenoxacin [57]. Clinical success rates in the ITT population at the end of therapy were 47.3% and 31.4%, respectively (p < 0.001). The proportion of subjects achieving clinical success at the end of therapy, inclusive of clinical cure and improvement, also significantly favored ozenoxacin (p < 0.0001; Figure 2).

4.2. Microbiological efficacy

The phase III clinical trials also evaluated the microbiological efficacy of ozenoxacin 1% cream and comparators [54,55]. Microbiological responses were assessed following culture of specimens taken from baseline affected area(s) at all study visits if culturable material was present. Since *S. aureus* and *S. pyogenes* alone or in combination are responsible for the majority of cases of impetigo, other microorganisms were considered as pathogens only if neither of these two bacterium was identified at baseline [58].

In the first phase III trial in patients aged 2 years and older, microbiological clearance rates were significantly higher with ozenoxacin than placebo [54]. Respective microbiological success rates were 70.8% and 38.2% (p < 0.0001) after 2–3 days' treatment, and 79.2% and 56.6% (p < 0.0001) at the end of treatment (days 6–7). Compared with retapamulin, microbiological clearance rates with ozenoxacin were higher after 2–3 days' treatment (70.8 *vs*. 56.9%; p = 0.0087) and comparable after 5–6 days' treatment (79.2 *vs*. 81.7%; p = 1.000).

Similarly, in the second phase III trial in patients aged 2 months and older, microbiological clearance rates were significantly greater with ozenoxacin than placebo [55].

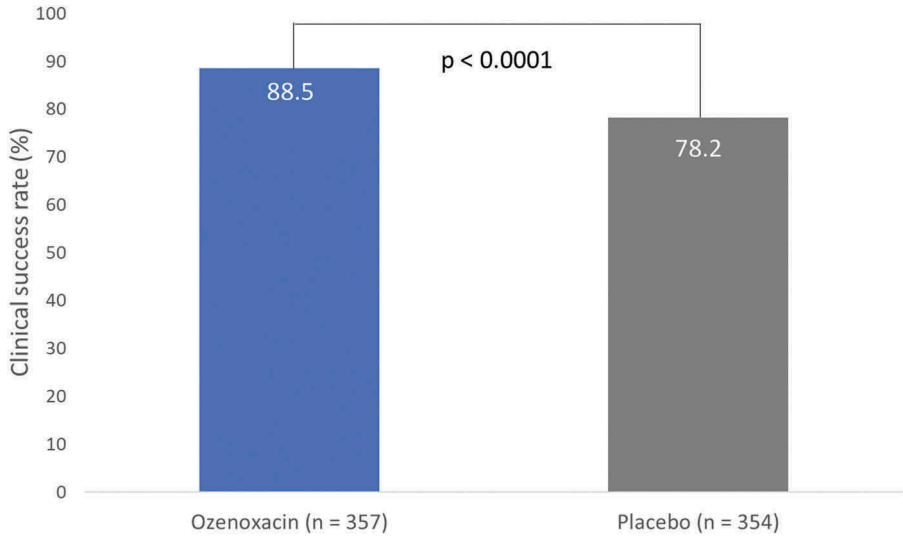

Figure 2. Clinical success rate at the end of treatment (day 6–7) in a pooled analysis of phase III studies of ozenoxacin 1% cream versus placebo (vehicle) cream. Clinical success was defined as clinical cure or improvement. The clinical success rate for the internal control retapamulin was 84.2% [57].

Microbiological success rates reported in the ozenoxacin and placebo groups were 87.2% and 63.9% (p = 0.002), respectively, after 2–3 days of therapy, and 92.0% and 73.1% (p = 0.005), respectively, after 5 days' therapy.

Pooled analysis of data from both phase III trials indicated that microbiological success rates were significantly higher with ozenoxacin (n = 279) than placebo (n = 271) after 2–3 days of therapy and at the end of therapy (both p < 0.0001; Figure 3) [57]. Available culture-based pooled microbiologic data suggested superior early eradication of bacterial etiology in the ozenoxacin versus placebo group. Eradication + presumed eradication rates of *S. aureus* with ozenoxacin and placebo were 86.6% and 50%, respectively, after 2–3 days' therapy, and 75.8% and 39.5% at the end of treatment. Corresponding figures for *S. pyogenes* were 75.8% and 39.5% after 2–3 days' therapy, and 87.9% and 60.4% at the end of treatment [58].

4.3. Activity against antimicrobial-resistant strains

In the pooled analysis of phase III trials, *S. aureus* strains showing demonstrable resistance to at least one of the antibacterial agents tested, i.e. methicillin (oxacillin), ciprofloxacin, retapamulin, mupirocin, and fusidic acid, were identified in 36 ozenoxacin-treated patients at baseline; two patients had *S. pyogenes* strains resistant to at least one of these antibacterial agents [57]. All patients with resistant infections achieved clinical cure or improvement at the end of treatment, including 11 of 11 patients with mupirocin-resistant *S. aureus*, and 10 of 10 patients with methicillin-resistant *S. aureus*. Of 23 ciprofloxacin-resistant *S. aureus* strains treated with ozenoxacin, two were microbiologic failures although, in both cases, the clinical result was improvement; thus, all patients achieved clinical improvement or cure at the end of treatment.

Ozenoxacin demonstrated similar clinical and microbiological success rates irrespective of the presence of the virulence genes Panton–Valentine leukocidin (*PVL*) and phenol-soluble modulin (*PSM*) [59] in *S. aureus* isolates [57].

5. Safety

Molecular modifications to moieties on the basic quinolone pharmacophore, specifically the addition of fluorine at position 6 and other substitutions at positions 1, 5, 7 and 8, led to development of a series of fluoroquinolone compounds with enhanced antibacterial efficacy and superior pharmacokinetic characteristics [60,61]. However, a relationship exists between specific structural alterations and adverse effects observed with individual agents [60,61]. Ozenoxacin, in contrast, has no fluoride substituent at the C-6 position and is devoid of halogen substituents in other positions [32]. As such, ozenoxacin is expected to have a better safety profile relative to other quinolones.

As quinolones have recognized chondrotoxic effects in juvenile animals, preclinical studies were conducted to assess the potential toxicity of ozenoxacin [62]. Typical quinolone-induced articular cartilage lesions with chondromucinous degeneration were observed in 3 of 10 juvenile rats treated with oral ofloxacin, whereas no histopathological toxicologically relevant changes were observed in the group treated with ozenoxacin. Likewise, in juvenile dogs, oral administration of ozenoxacin for 14 days was not associated with any chondrotoxicity or toxicologically relevant findings in selected target organs (brain, thymus, lung, liver, and kidney).

As part of the ozenoxacin clinical development program, a series of randomized placebo-controlled phase I studies using industry methods were conducted in healthy adult volunteers to assess its potential to cause local toxicity under occlusive patch conditions [63]. Ozenoxacin 1% and 2% cream formulations both showed excellent dermal tolerability. Across eight studies, there was little to no evidence of cumulative irritation, sensitizing potential, phototoxicity or photoallergy. Almost all adverse events reported in repeated-dose studies were deemed unlikely to be related or unrelated to ozenoxacin application.

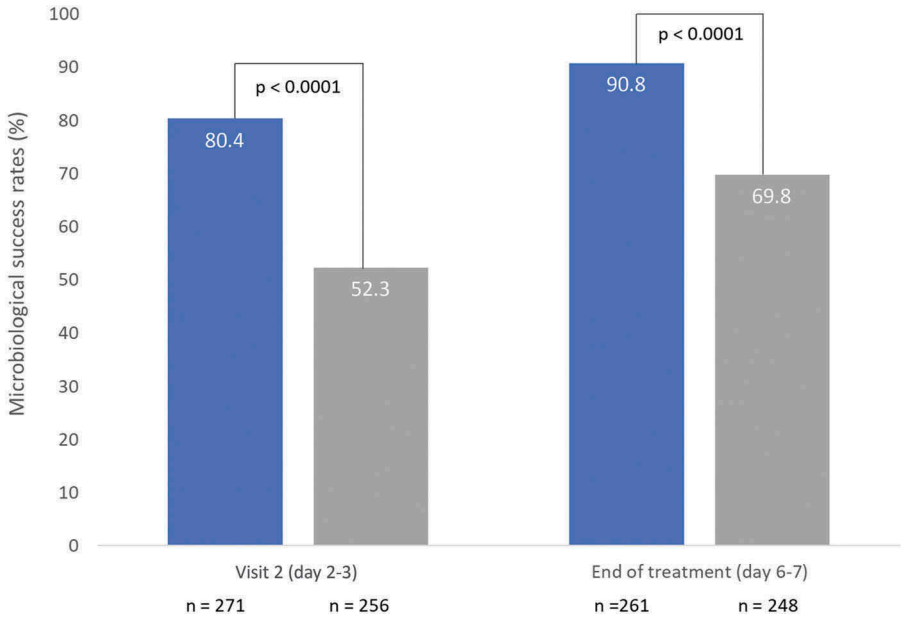

Figure 3. Microbiological success rates at the second visit (day 2-3) and at the end of treatment (day 6–7) in a pooled analysis of phase III studies of ozenoxacin 1% cream versus placebo (vehicle) cream. Microbiological success was defined as microbial eradication [57].

Blue=Ozenoxacin; Grey=Placeblo.

Of 875 patients who participated in phase III clinical trials of ozenoxacin [57], a single adult patient (<0.1%) receiving ozenoxacin had two adverse events (worsening of pre-existing rosacea and seborrheic dermatitis) which were considered possibly or probably related to treatment. Placebo-related events were dermatitis and skin tightness, and events related to retapamulin 1% ointment were application site pain and urticaria. As no treatment-related adverse event occurred in more than one subject, no patterns or safety signals were identified.

6. Dosage and administration

Topical ozenoxacin 1% cream is indicated in the European Union for short-term treatment of non-bullous impetigo in adults, adolescents, children and infants aged 6 months and older [64], and in the US and Canada for treatment of impetigo due to *S. aureus* or *S. pyogenes* in adult and pediatric patients 2 months of age and older [65,66]. No dosage adjustments are required in patients with renal or hepatic impairment, or in elderly patients [64].

The approved posology and method of administration of ozenoxacin is to apply a thin layer of ozenoxacin 1% cream (10 mg/g) to the affected area twice daily for 5 days. The affected area may be up to 100 cm^2 in adult and pediatric patients 12 years of age and older, or up to 2% of the total body surface area and not exceeding 100 cm^2 in pediatric patients less than 12 years of age [64–66]. The treated area may be covered by a sterile bandage or gauze dressing as desired [64–66].

Since systemic exposure to ozenoxacin is negligible, no effects are anticipated during pregnancy. Whether ozenoxacin is excreted in human breast milk is unknown; however, due to the minimal systemic exposure observed in adults, exposure of a breastfeeding infant to ozenoxacin is likely to be negligible. Nevertheless, it is recommended to avoid applying ozenoxacin to the breast area during breastfeeding to protect the nursing infant from unintentional oral drug uptake [64–66].

7. Expert opinion

The ability to treat infectious diseases is under serious threat due to the emergence and global spread of antibiotic resistance. The situation is intensified by a simultaneous decline in the development of new antimicrobial agents, severely limiting the options available to treat increasingly resistant infections [67]. Development and introduction of a new antibiotic is thus a significant event, and responsible management of antimicrobials by health-care professionals to preserve their use in future is of paramount importance [68].

Ozenoxacin is a novel non-fluorinated topical quinolone approved for treatment of impetigo due to *S. aureus* or *S. pyogenes*. The characteristics of ozenoxacin set it apart from other members of the quinolone family. Whereas most quinolones act by binding irreversibly to either DNA gyrase or topoisomerase IV in the bacterial cell, ozenoxacin has simultaneous affinity for both enzymes. Ozenoxacin also appears to be unaffected by the activity of certain efflux pumps which commonly confer bacterial resistance to other quinolones. As a result, ozenoxacin accumulates inside the bacteria much more quickly and at higher concentrations compared with other quinolones. Ozenoxacin shows low selection of resistant mutants and has a MPC below the concentration it achieves in skin. Collectively, these properties reduce the susceptibility of ozenoxacin to resistance development. The absence of a fluorine atom at position 6 of its molecular structure affords ozenoxacin a more favorable safety profile than fluorinated quinolones.

Antibiotics with a rapid bactericidal effect are important for symptoms resolution. This is especially relevant in the pediatric setting to limit person-to-person transmission of infection. *In*

vitro studies which compared the activity of ozenoxacin with an extensive range of other antimicrobial agents against Gram-positive clinical isolates from skin and soft tissue infections demonstrated that ozenoxacin was the most potent agent tested against staphylococci and streptococci. Ozenoxacin susceptibility studies were conducted using the ISO standard broth microdilution technique as per European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical & Laboratory Standards Institute (CLSI) guidance; breakpoints have yet to be defined by EUCAST or CLSI. Ozenoxacin was shown to be bactericidal against methicillin-susceptible *S. aureus*, methicillin-resistant *S. aureus*, methicillin-susceptible *S. epidermidis*, and methicillin-resistant *S. epidermidis* – including levofloxacin-susceptible and levofloxacin-resistant isolates – as well as against *S. pyogenes*, and *S. agalactiae*. Clinical trials of ozenoxacin in patients with impetigo demonstrated high clinical and microbiological success rates as early as two days after initiation of therapy, including in patients with mupirocin-resistant or methicillin-resistant *S. aureus*. Culture-based data indicated early eradication rates 1.7 and 1.9-fold higher with ozenoxacin than placebo for *S. aureus* and *S. pyogenes*, respectively, the major pathogens implicated in impetigo.

In view of the emerging resistance to fusidic acid and mupirocin, ozenoxacin represents a valuable addition to the antibacterial arsenal for treating impetigo and deserves to be treated as such. Use of ozenoxacin may decrease numbers of circulating mupirocin-resistant or methicillin-resistant isolates. An antimicrobial agent such as ozenoxacin with inherent defenses against the development of resistance is a valuable commodity that must be protected for future generations. Antimicrobial stewardship is essential to optimize the use of ozenoxacin and improve patient outcomes now and in future.

8. Five-year view

Over the next few years, it is expected that clinical practice guidelines for managing impetigo will be updated to include recommendations about the use of ozenoxacin. Further studies will be conducted to follow up on antimicrobial resistance patterns and the impact of ozenoxacin in quinolone resistance as well as mupirocin and methicillin resistance. Importantly, even with greater use of ozenoxacin to treat impetigo, no increase in ozenoxacin-resistant strains is expected on account of its dual mechanism of antibacterial activity and low potential to select resistant mutants. In future, the role of ozenoxacin is likely to expand to include treatment of other types of skin and soft tissue infections.

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