International Journal of Women's Dermatology 1 (2015) 13–20

Contents lists available at ScienceDirect

International Journal of Women's Dermatology

Original Research

Clinical and bacteriological efficacy of twice daily topical retapamulin ointment 1% in the management of impetigo and other uncomplicated superficial skin infections ☆

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ARTICLE INFO

Article history:
Received 3 November 2014
Received in revised form 12 December 2014
Accepted 13 December 2014

Keywords:
Retapamulin
Impetigo
Pediatric
MRSA
MSSA

ABSTRACT

Background: Cutaneous bacterial infections are common in children and adults and frequently are caused by *Staphylococcus aureus* (*S. aureus*). Treatment failures with topical agents are not uncommon and have been shown to be secondary to bacterial resistance.
Objective: To determine clinical and bacteriological efficacy of retapamulin ointment 1% in treatment of patients with cutaneous bacterial infections caused by methicillin-resistant *S. aureus* (MRSA) and other bacteria.
Methods: Prospective, nonrandomized, uncontrolled, open label, single center trial conducted between April 2008 and November 2012 that evaluated efficacy of retapamulin ointment 1% in the treatment of impetigo, folliculitis, and other minor soft tissue infections in children and adults. Fifty patients, who presented to a dermatology outpatient clinic and were clinically diagnosed with impetigo, folliculitis, or minor soft tissue infection suitable for treatment with a topical antibiotic, were screened. Thirty-eight patients were enrolled and received treatment: topical retapamulin ointment 1% twice daily for 5 days. Seven patients were MRSA positive and qualified for the primary efficacy population. One patient withdrew due to an adverse event. Clinical and microbiological exams were performed at baseline and follow-up 5 to 7 days later to assess clinical, microbiological, and therapeutic responses. Primary outcome was clinical response at follow-up in primary efficacy population with MRSA isolated as the baseline pathogen. Secondary outcomes included clinical, microbiologic, and therapeutic responses in patients who were culture positive for any species of bacteria.
Results: Clinical response at follow-up in the primary efficacy population (MRSA-positive patients) was not sufficiently powered to demonstrate significance; however, outcomes were excellent, with 7 of 7 patients demonstrating clinical success (5 of 7) or clinical improvement (2 of 7) at follow-up. Barring lack of significance due to small total sample size for patients who were culture positive for any species of bacteria ($n = 35$), overall success rates were favorable for clinical, microbiologic, and therapeutic responses with values of 66%, 97%, and 69%, respectively. Adverse events (AEs) were mild or moderate in severity. No serious AEs were reported.
Conclusion: Safety profile appears favorable given the low number of AEs. Study design limits conclusions that can be drawn. Nevertheless, this study supports use of topical retapamulin 1% ointment in treatment of cutaneous bacterial infections, particularly those caused by *S. aureus*, including MRSA.

Introduction

Impetigo, folliculitis, and other minor soft tissue infections are common in both children and adults. Impetigo is a superficial skin infection caused by bacteria and has been shown to be the most common infection in children worldwide (Rortveit and Rortveit, 2007). *Staphylococcus aureus* and *Streptococcus pyogenes* (Group A *Streptococcus*) are the bacteria most commonly associated with this soft tissue infection (Yang and Keam, 2008). *S. aureus* has recently been shown to be responsible for most cases (70%), which is a change from years past when *S. pyogenes* was the primary pathogen leading to impetigo (Darmstadt

☆ **Funding:** Funding for this study was provided by GlaxoSmithKline plc, Research Triangle Park, NC. All research funds were paid to The University of Texas Medical School Houston, Houston, Texas. GSK was involved in the design and conduct of the study. GSK was also involved in the review and approval of the manuscript, as well as the decision to submit the manuscript for publication. GSK played no role in the collection, management, analysis and interpretation of data.
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http://dx.doi.org/10.1016/j.ijwd.2014.12.002

and Lane, 1994). Colonization coupled with minor cutaneous trauma and/or concomitant skin disease such as atopic dermatitis can predispose to infection (Bangert et al., 2012). Sites of colonization can vary throughout the body, and they include the axillae, nares, pharynx, and the perineal area among others (Durupt et al., 2007; Popovich and Hota, 2008). *S. pyogenes* tends to only infect areas of the skin where the barrier has been disrupted (Habif, 2004; Steer et al., 2007).

The presentation of impetigo can vary, with both bullous and nonbullous forms making up the spectrum of the disease. Nonbullous impetigo is the primary presenting morphology, making up 70% of cases, and presents with erythematous papules and superficial vesicles that often transition into golden-yellow-crusted (honey-crusted) plaques as they rupture and heal (George and Rubin, 2003). Acral and face involvement is common in the nonbullous form, whereas bullous impetigo often presents in the intertriginous areas of the body (e.g., axillae, neck) with vesicles and flaccid fluid-filled bullae that progress to erosions and crusting (Cole and Gazewood, 2007; Koning et al., 2012). Impetigo is contagious, and the spread of the pathogenic bacteria from person to person is via autoinoculation and fomites (Cole and Gazewood, 2007). Close contacts are at risk for acquiring infection, while other risk factors for transmission include poor hygiene, a humid environment, trauma, and atopy (Bangert et al., 2012). Most disease is self-limited even in the absence of antibacterial treatment, although rare complications such as blood, bone, joint, and lung infections do occur (Paller and Mancini, 2006). Poststreptococcal glomerulonephritis also has been shown to develop after cases of impetigo caused by *S. pyogenes* (Paller and Mancini, 2006).

In the setting of localized impetigo infections, the possibilities for autoinoculation, systemic spread and complications, and the spread of disease to close contacts has led many health care providers to treat early with antimicrobial and antibacterial agents. Treatment failures with topical and oral agents are not uncommon and have been shown to be secondary to bacterial resistance (Lee et al., 2005). Resistant strains of bacteria known to cause impetigo, such as methicillin-resistant *S. aureus* (MRSA) and macrolide-resistant *S. pyogenes,* are becoming more prevalent in an era in which the development and Food and Drug Administration approval of new antibacterial agents has slowed (Kaplan, 2008; Kaplan et al., 2005; Spellberg et al., 2004). A study of patients presenting to the emergency departments of 11 major medical centers identified community-acquired MRSA as the most common identifiable cause of skin and soft tissue infections, with an overall prevalence of MRSA at 59% (Moran et al., 2006). A more recent study of multiple centers throughout the United Stated found that MRSA was the cause of 78% of the staphylococcal-related infections of the cutaneous and soft tissues (Gorwitz, 2008). Another recent study, in otherwise healthy children aged 3 months to 18 years treated at Texas Children's Hospital (Houston, TX) for suspected *S. aureus* skin and soft tissue infection or invasive infection, examined MRSA colonization rates. MRSA was isolated from clinical cultures in 63% to 70% of children (Kaplan et al., 2014). Resistance to mupirocin among the *S. aureus* isolates tested in one international study was found to be 6.8% in the United States (Deshpande et al., 2002). Another study performed in the Unites States found mupirocin resistance as high as 24% (Raju et al., 2008). Other studies have reported an increasing resistance of MRSA isolates to common topical agents such as mupirocin and sodium fusidate (Oranje et al., 2007). Further studies have shown multi-drug resistance among MRSA strains (Silverberg and Block, 2008).

Past management options for patients affected by impetigo are many and include active nonintervention (observation), sodium hypochlorite baths, over-the-counter topical agents, topical antibacterials, and oral antibacterials (Bangert et al., 2012). Shorter duration of disease has been shown with several treatment options (Bernard, 2008; Cole and Gazewood, 2007; Koning et al., 2012), although observation alone may be reasonable given that spontaneous resolution without sequelae is common inside of a few weeks without treatment (Bangert et al., 2012). More studies are needed to determine if treating persons who are actively infected can lead to a decrease in the incidence of poststreptococcal glomerulonephritis compared with observation alone. The risk for transmission of infection to close contacts and systemic spread is not altered by active nonintervention. For this reason, among others, topical antibacterial medications remain the treatment of choice for those with limited skin disease (Bangert et al., 2012). The two most common agents that have been used by physicians to treat impetigo throughout the world are fusidic acid and mupirocin (Bangert et al., 2012). Mupirocin has been prescribed to eradicate colonization with *S. aureus* in the nares and works by inhibiting bacterial isoleucyl-t-RNA synthetase, while fusidic acid exerts its antibacterial action through inhibition of bacterial protein synthesis (Bangert et al., 2012). Emerging resistance to these traditional topical agents among the bacterial pathogens responsible for impetigo has sparked an exploration for newer and better topical treatments.

In 2007, topical retapamulin ointment 1% (Altabax; GlaxoSmithKline, Research Triangle Park, NC) was developed to help battle antibacterial resistance and is currently approved for use in adults and pediatric patients aged 9 months and older for the topical treatment of impetigo (up to 100 cm^2 in total area in adults or 2% total body surface area in pediatric patients aged 9 months or older) due to *S. aureus* (methicillin-susceptible isolates only) or *S. pyogenes* (GlaxoSmithKline, Altabax prescribing information, 2007; Rittenhouse et al., 2006). Retapamulin ointment 1% was the first member of the pleuromutilan class of antibacterial agents and possesses a threefold mode of action that helps to prevent the development of drug resistance (Bangert et al., 2012; Yan et al., 2006). Retapamulin ointment 1% has a good safety profile due to its minimal systemic absorption and has minimal side effects, such as local irritation at the application site (Dhingra et al., 2013). Previous clinical trials have shown the efficacy of retapamulin ointment 1% in the treatment of impetigo. One randomized, observer-blinded, noninferiority study comparing retapamulin ointment 1% to sodium fusidate 2% for the treatment of impetigo found similar effectiveness rates for retapamulin ointment 1% and sodium fusidate consisting of 99.1% and 94% respectively ($p = .003$) (Oranje et al., 2007). Other clinical studies have compared mupirocin cream or retapamulin ointment 1% to oral cephalexin in the treatment of secondarily infected dermatitis and found equally high success rates; however, patients and their parents preferred topical treatment over oral treatment (Bangert et al., 2012; Parish et al., 2006; Rist et al., 2002). In vitro studies have shown no differences in retapamulin ointment 1% susceptibility between methicillin-resistant and methicillin-susceptible strains of *S. aureus*; however, clinical data to support the use of retapamulin ointment 1% in the treatment of methicillin-resistant *S. aureus* remains incomplete (Traczewski and Brown, 2008; Woodford et al., 2008). Data on the prevalence of retapamulin resistance are limited. However, one study of *S. aureus* isolates from skin and soft tissue infections in children found that 9.5% of the screened isolates exhibited retapamulin resistance, of which 57.9% were MRSA (McNeal et al., 2014). Although epidemiological data specific to the Houston area is limited (Kaplan et al., 2014), an increased prevalence of MRSA infections has been noted over the past several years in patients seen at The University of Texas Houston dermatology clinic. The purpose of this study was to document the clinical and bacteriological efficacy of retapamulin ointment 1% in the treatment of patients with cutaneous bacterial infections such as impetigo, folliculitis, and other minor soft tissue infections, including secondarily infected eczema presumed to be caused by methicillin-resistant *S. aureus*.

Materials and methods

Study design and objectives

This was a prospective, nonrandomized, uncontrolled, open label, single center trial to evaluate the efficacy of retapamulin ointment 1% at treating impetigo, folliculitis, and other minor soft tissue infections

in children and adults (ClinicalTrials.gov Identifier: NCT01126268). This study was approved by the institutional review board at The University of Texas Health Science Center at Houston, also known as the Committee for the Protection of Human Subjects. Patients were recruited from The University of Texas Health Science Center at Houston outpatient dermatology clinic. The study was conducted in accordance with Good Clinical Practice and the guiding principles of the Declaration of Helsinki.

Participants

Male or female patients aged 9 months to 98 years, diagnosed with impetigo, folliculitis, or minor soft tissue infection (including secondarily infected eczema presumed to be caused by *S. aureus*) suitable for treatment with a topical antibiotic, were eligible for inclusion. If the patient was a female of childbearing potential, a negative urine pregnancy test before performing any study-related procedures was required. Exclusion criteria were as follows: use of topical antibacterial medication to the area being treated within the last 48 hours; enrollment in another clinical trial within the last 30 days; signs of systemic infection (such as fever) or evidence of abscess or cellulitis at the site to be treated; presence of a bacterial skin infection that, in the opinion of the investigator, would not be appropriately treated by a topical antibiotic; oral antibiotic use within the last 7 days; known sensitivity to the study medication; and current pregnancy or breastfeeding.

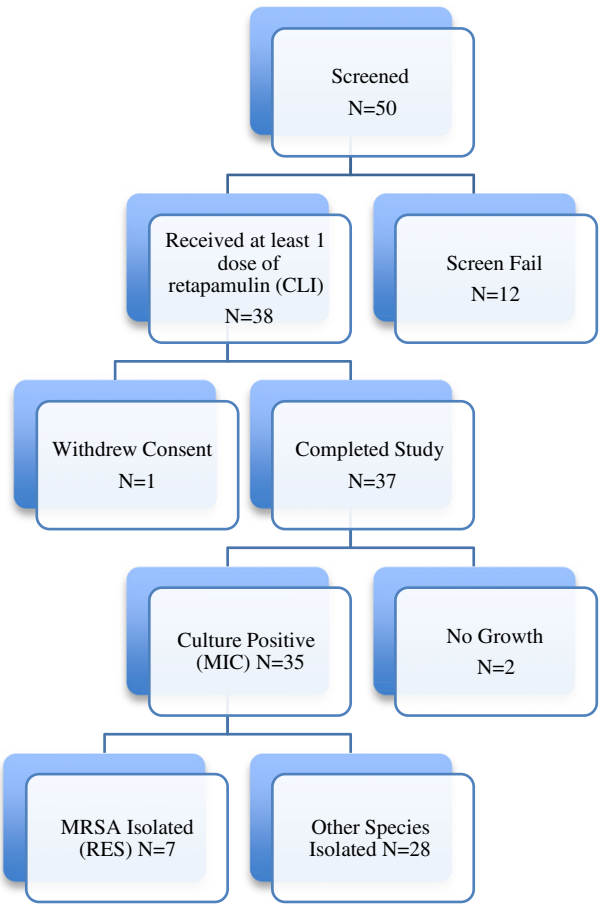

Fig. 1. Flow diagram of patient progress throughout the trial: CLI = all patients enrolled in the study who received at least 1 application of study medication, MIC = all patients in CLI who had a pathogen isolated from the treatment area at baseline upon microbiologic testing, and RES = all patients in CLI who had MRSA isolated as a baseline pathogen (primary efficacy population).

Table 1
Baseline demographic and clinical characteristics.

Characteristic		Retapamulin ointment 1% (n = 38)
Age, years, mean (SD)	All patients	18.5 (25.66)
Age, *n* (%)	< 18	28 (73.7%)
	≥ 18	10 (26.3%)
Sex, *n* (%)	Female	27 (71.1%)
	Male	11 (28.9%)
Race, *n* (%)	Eastern European descent	18 (47.4%)
	African American	10 (26.3%)
	Hispanic	5 (13.2%)
	Asian	4 (10.5%)
	Other	1 (2.6%)
Baseline pathogen, *n* (%)	All pathogens	n = 36
	Staphylococcus aureus	26 (72.2%)
	MRSA*	(7, 19.4%)
	MSSA	(19, 52.8%)
	Streptococcus pyogenes	2 (5.5%)
	Other *Streptococcus* species	1 (2.8%)
	Coagulase negative Staphylococcus	7 (19.4%)
	No growth	n = 2

* The seven patients with MRSA include six pediatric (aged < 18 years) patients and one adult (aged ≥ 18 years) patient. Three patients were male and four were female.

Interventions

Patients attended up to 2 study clinic visits over a period of 5 to 7 days (Fig. 1). Treatment was started at the first clinic visit. The infected area was first cleaned with a sterile nonantibacterial wipe. Study personnel then provided the patient (or parent/guardian if applicable) with a 10 g tube of topical retapamulin ointment 1% (10 mg retapamulin per 1 gm of ointment), a study diary to document study drug applications, and instructions for basic wound care and application of study drug. Patients were instructed to apply a thin layer of retapamulin ointment 1% to the infected lesion(s) twice daily for 5 days, for a total of 10 doses, regardless of clinical improvement. Study personnel delivered treatment at visit 1. The maximum area to be treated was 100 cm^2 in adults, and 2% of the total body surface area for pediatric patients, corresponding with a maximum retapamulin ointment 1% dose of approximately 1 g. Sterile bandage or gauze use to cover the treatment area was allowed for all patients and required for children who could have potentially put the treated lesion(s) in their mouth. Patients were allowed to withdraw themselves from the study at any time. The investigator could withdraw a patient due to failure of therapy or worsening signs of infection at any time and was available to provide them with oral antibiotics or other treatment as appropriate. Patients requiring withdrawal from the study were requested to follow-up within 48 hours of when the study medication would have been completed to record safety and adverse event data. Patients received an initial clinical

Table 2
Clinical and microbiological responses by grade at follow-up: efficacy outcomes (primary efficacy population, n = 7).

Clinical Response (Grade)	MRSA, *n/N* (%)	Microbiologic Response (Grade)	MRSA, *n/N* (%)
1. Clinical success	5/7 (71%)	1. Microbiological eradication	0/7 (0%)
2. Clinical improvement	2/7 (29%)	2. Presumed microbiological eradication	5/7 (71%)
3. No change	0/7 (0%)	3. Presumed microbiological improvement	2/7 (29%)
4. Clinical failure	0/7 (0%)	4. Microbiological persistence	0/7 (0%)
5. Unable to determine	0/7 (0%)	5. Presumed microbiological persistence	0/7 (0%)
		6. Unable to determine	0/7 (0%)
		7. New pathogen	0/7 (0%)
		8. Colonization	0/7 (0%)

Table 3
Clinical and microbiological responses by grade at follow-up: efficacy outcomes (MIC population, $n = 35$).

Clinical response (Grade)	Retapamulin ointment 1%, *n/N* (%)	Microbiologic response (Grade)	Retapamulin ointment 1%, *n/N* (%)
1. Clinical success	23/35 (66%)	1. Microbiological eradication	1/35 (3%)
2. Clinical improvement	11/35 (31%)	2. Presumed microbiological eradication	23/35 (65%)
3. No change	0/35 (0%)	3. Presumed microbiological improvement	10/35 (28%)
4. Clinical failure	1/35 (3%)	4. Microbiological persistence	1/35 (3%)
5. Unable to determine	0/35 (0%)	5. Presumed microbiological persistence	0/35 (0%)
		6. Unable to determine	0/35 (0%)
		7. New pathogen	0/35 (0%)
		8. Colonization	0/35 (0%)

and microbiological evaluation at the clinic during the baseline visit (day 1). To determine efficacy, repeat clinical and microbiological exams were performed during the follow-up visit (day 6–8) that was scheduled to occur within 48 hours of finishing all 10 doses of the retapamulin ointment 1%.

Bacteriology

Bacteriologic samples were obtained by curettage from patients at visit 1 before initiating treatment. Swab samples were collected from the treatment area with a preference for obtaining sufficient pus or exudate when present to impregnate the swab. During the post-therapy follow-up visit, bacteriologic samples were obtained if the patient was deemed a clinical failure or had withdrawn from the study. Isolated pathogens were sent to a local laboratory (Microbiology Specialists, Inc., Houston, TX) for culture and sensitivity processing according to Clinical and Laboratory Standards Institute guidelines (Clinical and Laboratory Standards Institute, 2007). Study samples that were culture positive for *S. aureus* pathogens underwent further testing to determine the presence or absence of the Panton-Valentine leukocidin genes according to published methodology (Johnsson et al., 2004; Lina et al., 1999; Wolter et al., 2007).

Analysis population

An intention-to-treat analysis was performed for four populations. The first population (CLI) included all patients enrolled in the study who received at least 1 application of study medication. The second population (MIC) included all patients in CLI who had a pathogen isolated from the treatment area at baseline upon microbiologic testing. The third population (RES) included all patients in CLI who had MRSA isolated as a baseline pathogen and serves as the primary efficacy population. The fourth population (PED) included all patients in CLI <18 years of age at the time of study completion.

Efficacy evaluations

The primary endpoint for this study was defined as the clinical response (success or failure) at follow-up in the RES population with MRSA isolated as the baseline pathogen. Secondary endpoints included clinical, microbiological, and therapeutic responses at follow-up (MIC, RES, PED) comparison of wound size from baseline to follow-up (MIC, RES, PED), comparison of signs and symptoms of infection from baseline to follow-up (MIC, RES, PED), and the safety and tolerability of topical retapamulin ointment 1% based on adverse event (AE) data (CLI).

Table 4
Clinical, microbiological and therapeutic responses by prognostic factor at follow-up: efficacy outcomes (MIC population, $n = 35$).

	Retapamulin ointment 1% Success Rate, *n/N* (%)		
	Clinical Response	Microbiological Response	Therapeutic Response
Overall	23/35 (66%)	34/35 (97%)	24/35 (69%)
Wound area* (Baseline)			
≤ Median (3.4)	14/19 (74%)	19/19 (100%)	15/19 (79%)
> Median (3.4)	9/16 (56%)	15/16 (94%)	9/16 (56%)
Sex			
Female	15/24 (63%)	23/24 (96%)	15/24 (63%)
Male	8/11 (73%)	11/11 (100%)	9/11 (82%)
Age			
< 18 years	17/25 (68%)	25/25 (100%)	18/25 (72%)
≥ 18 years	6/10 (60%)	9/10 (90%)	6/10 (60%)
MRSA at baseline			
Y	5/7 (71%)	7/7 (100%)	5/7 (71%)
N	18/28 (64%)	27/28 (96%)	19/24 (79%)
Race			
White	14/17 (82%)	16/17 (94%)	14/17 (82%)
African American	7/9 (78%)	9/9 (100%)	7/9 (78%)
Hispanic	1/5 (20%)	5/5 (100%)	2/5 (40%)
Asian	1/4 (25%)	4/4 (100%)	1/4 (25%)
Baseline pathogen			
Staphylococcus aureus	11/18 (61.1%)	17/18 (94.4%)	12/18 (66.7%)
MRSA	(5/7, 71.4%)	(7/7, 100%)	(5/7, 71.4%)
MRSA and aged < 18 years	(5/6)	(6/6)	(5/6)
MRSA and aged ≥ 18 years	(0/1)	(1/1)	(0/1)
MSSA	(6/11, 51.5%)	(10/11, 91.0%)	(7/11, 63.6%)
Streptococcus pyogenes	1/2 (50.0%)	2/2 (100%)	1/2 (50.0%)
Other *Streptococcus* species	1/1 (100%)	1/1 (100%)	1/1 (100%)
Coagulase negative Staphylococcus	5/7 (71.4%)	7/7 (100%)	5/7 (71.4%)

* Wound area was divided into two groups by its median. Median value was chosen for convenience but may lack clinical importance.

Clinical response was based on clinical evaluation by the investigator at the follow-up visit using a predefined scale with the following categories: (1) clinical success, (2) clinical improvement, (3) no change, (4) clinical failure, and (5) unable to determine. Patients who were designated as clinical success as defined in number 1 above were considered a true "clinical success" while all others were considered a "clinical failure." Patients were classified with an outcome of "unable to determine" if they missed their follow-up visit or refused clinical examination.

Microbiological response was determined by the investigator at the follow-up visit using the following microbiological outcomes: (1) microbological eradication, (2) presumed microbiological eradication, (3) presumed microbiological improvement, (4) microbiological persistence, (5) presumed microbiological persistence, (6) unable to determine, (7) new pathogen, and (8) colonization. Patients who were designated microbiological eradication, presumed microbiological eradication, presumed microbiological improvement, or colonization as defined in numbers 1, 2, 3, and 8 above were considered a "microbiological success" while all others were considered "microbiological failure."

Therapeutic response was determined from the clinical response and the microbiological response. Patients who qualified as both a "clinical success" and a "microbiological success" were deemed a "therapeutic success," and all others were deemed "therapeutic failures."

Wound size area was determined by measuring the greatest length of the wound in two perpendicular dimensions with a standard metric ruler. The two measurements were multiplied together to provide an estimate of the overall wound size. Surrounding erythema was not included in the measurement.

Signs and symptoms of the lesions were assessed based on the following factors: erythema, purulence, crusting, edema, warmth, and pain. Each factor was classified as one of the following: absent, minimal, moderate, or severe.

Samples size and statistical methods

The study was a prospective, nonrandomized, uncontrolled, open label, and single center trial to evaluate the efficacy of retapamulin ointment 1% at treating impetigo, folliculitis, and other minor soft tissue infections in children and adults. A total of 50 patients were recruited between April 2008 and November 2012. Seven of the 38 patients in the CLI safety population were culture positive at baseline for MRSA and qualified for the primary efficacy (RES) population.

Descriptive statistics were summarized for all demographic characteristics, baseline variables, and three responses (clinical, microbiological, and therapeutic). Univariate logistic regression analyses were performed to see how clinical response was related to several prognostic factors, including wound sizes at different visits, sex, age, and the presence of MRSA. Odds ratio (OR) with 95% confidence interval was reported for each factor. The comparison of wound size change at follow-up visit to baseline was conducted by paired *t* test. A *p* value of $< .05$ was considered statistically significant for the main effect. S-plus/R software was used for all statistical analyses.

Results

Study population

A total of 50 patients were recruited between April 2008 and November 2012. The disposition of patients in the study is presented in Fig. 1. The 38 patients who received retapamulin ointment 1% made up the CLI safety population, and 35 of these patients were culture positive, making up the MIC population. Of the 37 patients who completed the study, only 7 were MRSA positive and qualified for the primary efficacy population (RES). Twelve patients were culture negative and, therefore, did not qualify for any efficacy analysis. Only one patient (2.6%) withdrew from the study before completing all study procedures due to a withdrawal of consent. The demographic characteristics of patients who received treatment are presented in Table 1.

Table 5
Skin infection rating scale.

Item	Category	Score	Scale	Retapamulin ointment 1%, $n = 35$ (MIC population) Baseline *n* (%)	Follow-up *n* (%)	*p* value
1	Erythema	0	Absent	0 (0%)	9 (26%)	<.00001
		1	Minimal	10 (29%)	24 (69%)	
		2	Moderate	25 (71%)	2 (5%)	
		3	Severe	0 (0%)	0 (0%)	
2	Purulence	0	Absent	10 (29%)	34 (97%)	<.00001
		1	Minimal	14 (40%)	1 (3%)	
		2	Moderate	10 (29%)	0 (0%)	
		3	Severe	1 (2%)	0 (0%)	
3	Crusting	0	Absent	2 (6%)	25 (71%)	<.00001
		1	Minimal	8 (23%)	9 (26%)	
		2	Moderate	23 (65%)	1 (3%)	
		3	Severe	2 (6%)	0 (0%)	
4	Tissue Edema	0	Absent	3 (9%)	19 (54%)	<.00001
		1	Minimal	19 (54%)	16 (46%)	
		2	Moderate	13 (37%)	0 (0%)	
		3	Severe	0 (0%)	0 (0%)	
5	Tissue warmth	0	Absent	9 (26%)	21 (60%)	.0027
		1	Minimal	20 (57%)	14 (40%)	
		2	Moderate	6 (17%)	0 (0%)	
		3	Severe	0 (0%)	0 (0%)	
6	Pain	0	Absent	8 (23%)	26 (74%)	.000026
		1	Minimal	19 (54%)	9 (26%)	
		2	Moderate	8 (23%)	0 (0%)	
		3	Severe	0 (0%)	0 (0%)	

Bacteriology

S. aureus was the most frequently isolated pathogen at baseline (72.2%); 19.4% (7 of 36) of patients were culture positive for MRSA making up the primary efficacy population (Table 1).

Table 6
Skin infection rating scale (by age).

Item	Category	Score	Scale	Retapamulin ointment 1%, $n = 35$ (MIC population) Baseline Age < 18 years	Baseline Age ≥ 18 years	Follow-up Age < 18 years	Follow-up Age ≥ 18 years
1	Erythema	0	Absent	0	0	7	2
		1	Minimal	6	4	16	8
		2	Moderate	19	6	2	0
		3	Severe	0	0	0	0
2	Purulence	0	Absent	5	5	24	10
		1	Minimal	12	2	1	0
		2	Moderate	8	2	0	0
		3	Severe	0	1	0	0
3	Crusting	0	Absent	2	0	18	7
		1	Minimal	5	3	6	3
		2	Moderate	16	7	1	0
		3	Severe	2	0	0	0
4	Tissue edema	0	Absent	3	0	13	6
		1	Minimal	11	8	12	4
		2	Moderate	11	2	0	0
		3	Severe	0	0	0	0
5	Tissue warmth	0	Absent	5	4	15	6
		1	Minimal	14	6	10	4
		2	Moderate	6	0	0	0
		3	Severe	0	0	0	0
6	Pain	0	Absent	4	4	17	9
		1	Minimal	14	5	8	1
		2	Moderate	7	1	0	0
		3	Severe	0	0	0	0

Table 7
Skin infection rating scale (primary efficacy population).

				MRSA, $n = 7$	
Item	Category	Score	Scale	Baseline	Follow-up
1	Erythema	0	Absent	0	2
		1	Minimal	7	5
		2	Moderate	0	0
		3	Severe	0	0
2	Purulence	0	Absent	2	7
		1	Minimal	2	0
		2	Moderate	3	0
		3	Severe	0	0
3	Crusting	0	Absent	1	7
		1	Minimal	2	0
		2	Moderate	3	0
		3	Severe	1	0
4	Tissue edema	0	Absent	0	2
		1	Minimal	2	5
		2	Moderate	5	0
		3	Severe	0	0
5	Tissue warmth	0	Absent	1	4
		1	Minimal	3	3
		2	Moderate	3	0
		3	Severe	0	0
6	Pain	0	Absent	1	6
		1	Minimal	3	1
		2	Moderate	3	0
		3	Severe	0	0

Clinical efficacy

The data for the primary endpoint for this study—the clinical response (success or failure) at follow-up in the RES population with MRSA isolated as the baseline pathogen—are summarized in Table 2. Secondary endpoints included clinical responses at follow-up for RES (Table 2), MIC (Table 3), and PED (Table 4).

Microbiological efficacy

Secondary endpoints included microbiological responses at follow-up for the RES (Table 2), MIC (Table 3), and PED (Table 4) populations, as well as therapeutic responses at follow-up for RES, MIC, and PED (Table 4).

Skin infection rating scale

Other secondary endpoints included comparison of signs and symptoms of infection from baseline to follow-up for the MIC, PED, and RES populations (Tables 5–7). Table 5 describes skin infection rating scales (SIRS) along with number of patients (reported as frequency and percentage) at baseline and follow-up visit. A decreasing trend in score between two visits was observed in all infection types. For instance, in erythema, 71% of patients had score 2 (moderate) at baseline, whereas 69% had score 1 (minimal) at follow-up (Table 5). However, the interpretation here needs to be cautious, because the score at follow-up visit and baseline are correlated. In the last column, p values from the χ^2 test are provided to compare categorized scores at follow-up with scores at baseline, which indicates that patients significantly improved over time in all categories (Table 5). Table 6 summarizes SIRS data by age group, and Table 7 lists the SIRS data for the primary efficacy population.

Wound size analyses

Another secondary endpoint compared the wound areas at baseline and follow-up for the RES, PED, and MIC populations (Table 8). Their mean wound areas were 14.43 cm^2 (baseline) and 4.31 cm^2 (follow-up), and their log-transformations were tested with paired t test, yielding $p < .00001$, which confirms that wound area at visits 1 and 2 is significantly different. For PED subgroup aged < 18 years, $p = .0002$, and for the subgroup with age ≥ 18 years, $p = .002$, using paired t test. For the RES (MRSA +) group, $p = .0156$. In all cases, wound sizes at baseline and follow-up are significantly different.

Safety

The proportion of patients who experienced treatment-emergent AEs during the study was 10.5% (Table 9). AEs included burning at application site ($n = 1$), upper respiratory infection ($n = 1$), furuncle ($n = 1$), cough ($n = 1$), and a rash at a site other than the application site ($n = 1$). All AEs were mild or moderate in severity. Only one patient withdrew from the study due to an AE (2.6%; Table 9). No serious AEs were reported during the study.

Exploratory analyses

Table 4 presents the number of patients and success rates for three responses (clinical, microbiological, and therapeutic) by several prognostic factors. To further evaluate the relationship between some of these prognostic factors and clinical response, logistic regression was performed, and the results were summarized in Table 10, which focuses on the MIC population. Wound area was divided into two groups by its median value, which was chosen for convenience but may lack clinical importance. The OR associated with wound area at baseline is 2.60, which indicates that the odds of experiencing successful clinical response for patients with wound size at baseline < 3.4 cm^2 is expected be 2.60 times higher than the odds of experiencing successful clinical response for patients with wound size at baseline ≥ 3.4 cm^2. However, the related p value is .198, and wound size at baseline is not a statistically significant predictor of clinical response. No significance was found for the other variables.

Discussion

The objective of this study was to assess the clinical and bacteriological efficacy of topical retapamulin ointment 1% in the treatment of patients with cutaneous bacterial infections, such as impetigo, folliculitis, and other minor soft tissue infections, including secondarily infected eczema presumed to be caused by MRSA. The data for the primary endpoint for this study—the clinical response (success or failure) at

Table 8
Comparison of percent decrease in wound size from baseline to follow-up.

MIC population	Statistics	Baseline	Follow-up	Mean change % (SD)
Total (n = 35)	Mean (SD)	14.43 (25.38)	4.31 (17.71)	−71.3% (36.0%)
	Median	3.40	0.30	
Age <18 years (n = 25)	Mean (SD)	18.61 (29.01)	5.6 (20.92)	−73.6% (36.5%)
	Median	4.80	0.1	
Age ≥18 years (n = 10)	Mean (SD)	3.98 (4.42)	1.09 (1.37)	−65.6% (35.8%)
	Median	2.75	0.5	
MRSA (n = 7)	Mean (SD)	20.61 (24.83)	2.59 (3.21)	−87.8% (19.1%)
	Median	14.0	0.3	

The p value from paired t test that compares logarithms of wound size at visits 1 and 2 is <.00001. Mean change (%) was defined as (size at baseline – size at follow-up)/size at baseline.

Table 9
Number of patients reporting adverse events withdrawing from study due to adverse events.

	Retapamulin ointment 1%, *n*/*N* (%)
Patients reporting any AE	4/38 (10.5%)
Patients withdrawn due to AE	1/38 (2.6%)

follow-up in the primary efficacy (RES) population with MRSA isolated as the baseline pathogen—was not sufficiently powered to demonstrate significance; however, outcomes were excellent overall for this population with 7 of 7 patients demonstrating either clinical success or clinical improvement at follow-up. It remains unclear why most patients who tested positive for *S. aureus* were methicillin-sensitive. This finding is contrary to data from previous clinical trials (Gorwitz, 2008; Moran et al., 2006) and the investigators own clinical experience, in which MRSA has been found to represent the majority pathogen.

An uneven distribution between age groups (the proportion of patients aged < 18 years was 73.7%, and the proportion of those aged ≥ 18 years was 26.3%) coupled with a small overall sample size ($n = 35$) impedes the development of conclusions regarding the effect of age on clinical, microbiologic, and therapeutic responses. Barring the lack of significance due to the small total sample size for patients who received treatment and were culture positive (MIC; $n = 35$), the overall success rates were favorable for clinical, microbiologic, and therapeutic responses with values of 66%, 97%, and 69%, respectively. Subgroup analyses of these responses for PED and RES found excellent success rates overall as well.

Exploratory analyses examining correlation of several prognostic factors (wound size, sex, age, and pathogen) with clinical responses were unable to show clinical significance. The OR associated with wound area at baseline was 2.60, which indicates that the odds of experiencing successful clinical response for patients with wound size at baseline < 3.4 cm^2 is expected be 2.60 times higher than the odds of experiencing successful clinical response for patients with wound size at baseline ≥ 3.4 cm^2. However, the related p value was .198, and wound size at baseline is not a statistically significant predictor of clinical response. The odds ratio comparing *S. aureus* versus no *S. aureus* was .76, and the odds ratio from MRSA was 1.39; that is, clinical response may be different across MRSA and MSSA but the difference is not significant.

The safety profile of topical retapamulin ointment 1% appears favorable given the low number of AEs observed during the study. Of those that occurred, all were mild or moderate in severity, with no serious AEs reported. This favorable safety profile is consistent with data from previous studies.

Conclusion

Study design and execution limits the conclusions that can be drawn regarding the efficacy of topical retapamulin 1% ointment in the treatment of cutaneous bacterial infections, including those caused by *S. aureus* and MRSA. Small sample size, lack of a placebo comparator, single-site design, and failure to ensure microbiological eradication with a repeat culture post-treatment are limitations for this study. Nevertheless, this study supports the use of topical retapamulin 1% ointment in the treatment of cutaneous bacterial infections, particularly those caused by *S. aureus*, including MRSA.

Table 10
Odds ratio with 95% confidence interval investigating factors associated with clinical response by univariate logistic regression.

Variable	Odds ratio	95% confidence interval	*p* value
Wound size (baseline)			
< 3.4 vs. ≥ 3.4 (ref)	2.60	(0.607, 11.1)	.198
Male vs. female (ref)	1.60	(0.335, 7.639)	.556
Aged < 18 years vs. aged ≥ 18 years (ref)	1.42	(0.310, 6.469)	.653
MRSA: yes vs. no (ref)	1.39	(0.226, 8.508)	.722
S. aureus: yes vs. no (ref)	0.76	(0.156, 3.698)	.736

Abbreviations: ref, reference.

Acknowledgments

We acknowledge the support provided by the Biostatistics/Epidemiology/Research Design (BERD) component of the Center for Clinical and Translational Sciences (CCTS) for this project. CCTS is mainly funded by the NIH Centers for Translational Science Award (NIH CTSA) grant (UL1 RR024148), awarded to University of Texas Health Science Center at Houston in 2006 by the National Center for Research Resources (NCRR) and its renewal (UL1 TR000371) by the National Center for Advancing Translational Sciences (NCATS). The content is solely the responsibility of the authors and does not necessarily represent the official views of NCRR or the NCATS.

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