

LTX-109 Is a Novel Agent for Nasal Decolonization of Methicillin-Resistant and -Sensitive *Staphylococcus aureus*

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Nasal decolonization has a proven effect on the prevention of severe *Staphylococcus aureus* infections and the control of methicillin-resistant *S. aureus* (MRSA). However, rising rates of resistance to antibiotics highlight the need for new substances for nasal decolonization. LTX-109 is a broad-spectrum, fast-acting bactericidal antimicrobial drug for topical treatment, which causes membrane disruption and cell lysis. This mechanism of action is not associated with cross-resistance and has a low propensity for development of resistance. In the present study, persistent nasal MRSA and methicillin-sensitive *S. aureus* (MSSA) carriers were treated for 3 days with vehicle or with 1%, 2%, or 5% LTX-109. A significant effect on nasal decolonization was observed already after 2 days of LTX-109 treatment in subjects treated with 2% or 5% LTX-109 compared to vehicle ($P \leq 0.0012$ by Dunnett's test). No safety issues were noted during the 9-week follow-up period. Minimal reversible epithelial lesions were observed in the nasal cavity. The systemic exposure was very low, with a maximum concentration of drug in plasma (C_{\max}) at 1 to 2 h postdosing (3.72 to 11.7 ng/ml). One week after treatment initiation, LTX-109 was not detectable in any subject. Intranasal treatment of *S. aureus* with LTX-109 is safe and reduces the bacterial load already after a single day of treatment. Hence, LTX-109 has potential as a new and effective antimicrobial agent with a low propensity of resistance development that can prevent infections by MSSA/MRSA during hospitalization. (This study has been registered at ClinicalTrials.gov under registration no. NCT01158235.)

Nasal carriage of *Staphylococcus aureus* is considered a marker of extended skin carriage and colonization by *S. aureus*. The colonization is often asymptomatic, but most severe *S. aureus* infections are caused by endogenous strains from the patient (1–5).

Persistent nasal colonization by *S. aureus*, including methicillin-resistant *S. aureus* (MRSA) strains, has shown to be a major risk factor for surgical-site (6) and renal dialysis (5, 7) infections. Such individuals have a substantially increased risk for *S. aureus* hospital-acquired infections (8), with up to as many as 11 to 22% of methicillin-sensitive and -resistant *S. aureus* carriers developing nosocomial infections during hospital admission (9). In addition, patients carrying *S. aureus* can be a source of transmission to noncarriers, which subsequently can lead to health care-related exogenous infections.

The spread of *S. aureus* remains unquestionably a serious challenge in infection control in hospitals, and in an attempt to reduce the *S. aureus* infection rates, prevention programs aiming at decolonizing individual nasal *S. aureus* carriers have been implemented. The most well-established regimen recommended in several national guidelines (e.g., in the 1998 United Kingdom guideline and the upcoming U.S. CDC guideline) is using a combination of 5 to 7 days of treatment with nasal mupirocin ointment and chlorhexidine soap (4, 5, 10–12). This treatment has been shown to reduce the incidence of nosocomial infections (5).

In areas with a low incidence of MRSA, a search-and-destroy policy is often applied (13). In such circumstances, an effective treatment for nasal decolonization is essential. However, an increasing number of reports of high-level mupirocin resistance indicate the potential loss of this major method for preventing infections and controlling MRSA (14). Hence, there is an unmet medical need for new and highly effective drugs with low pro-

ensity for resistance development to replace/complement mupirocin (8).

Lytix Biopharma is developing LTX-109, a first-in-class chemically synthesized, peptide-mimetic drug that is stable against protease degradation (15, 16) and represents a new approach to the serious challenge of *S. aureus* nasal decolonization. LTX-109 is a broad-spectrum, fast-acting bactericidal antimicrobial drug that binds to negatively charged membrane components on the bacterial cell, which is followed by membrane disruption and cell lysis (17, 18). Nonclinical and clinical studies have demonstrated that topical application of LTX-109 (1 to 5%) has a good safety profile and a low bioavailability (19). LTX-109 shows significant *in vitro* bactericidal activity against a variety of *S. aureus* strains with LTX-109 MIC values of 0.03 to 8 mg/liter and isolates resistant to several classes of antimicrobial agents, including mupirocin-resistant strains (20, 21, 22). In addition, LTX-109 has demonstrated activity against bacterial and fungal biofilms (23). Due to its novel

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mechanism of action, there is a very low propensity for resistance development compared to that of conventional antibiotics (24).

The present phase I/IIa clinical trial (registration no. NCT01158235) investigated the efficacy, safety, tolerability, and bioavailability of LTX-109 for nasal decolonization after 3 days of topical treatment of the anterior nares of persistent nasal *S. aureus* carriers.

MATERIALS AND METHODS

Study overview. This was a randomized, double-blind, dose escalation phase I/IIa study conducted at a single center during the period June 2010 to April 2011. The aim was to compare the efficacy, safety, tolerability, and bioavailability of 3 days nasal treatment with LTX-109 versus vehicle in persistent nasal carriers of *S. aureus*. Prior to the study start, the protocol and statement of informed consent were reviewed and approved by the Swedish Medicines Product Agency (MPA) and the Regional Ethical Review Board (RERB) in Lund, Sweden. The study was conducted in agreement and accordance with the Declaration of Helsinki (Seoul, October 2008) and in compliance with the International Conference on Harmonisation (ICH), good clinical practice (GCP) standard guidelines, and local regulations and laws. All subjects gave written informed consent.

Study population. Persistent nasal *S. aureus* carriers aged 16 to 75 years with at least three culture-positive nose swabs obtained during 1 month before the study start were eligible for the study. Twenty-four carriers were recruited among individuals in the mandatory register of known MRSA carriers at the Department of Infectious Diseases, Malmö, Sweden (25), and among volunteers responding to an advertisement in the local press, which invited individuals to an open-house nasal screening for *S. aureus* carriage. The household members of the MRSA carriers were also invited for MRSA screening. Positive household members were invited to participate in the study or to receive the standard eradication regimen. Positive *S. aureus* carriers were selected randomly from the open-house screening.

The main exclusion criteria were an unstable health situation, pregnancy, severe eczema, or prior disorder in the nose, as well as treatment with antibiotics during the 28 days preceding the study start or a previous attempt to eradicate MRSA colonization during the last 6 months.

Investigational drug. LTX-109, in concentrations of 1%, 2%, and 5%, was formulated as a hydrogel (Nova Laboratories Ltd., Leicester, United Kingdom). The vehicle was an identical gel without LTX-109. LTX-109 and vehicle were provided in 10-ml high-density polyethylene–low-density polyethylene (HDPE-LDPE) (1:1) tubes.

Study design. The study was conducted at the outpatient section of the Department of Infectious Diseases, Malmö, Sweden. Persistent nasal *S. aureus* carriers were verified by positive cultures from three nasal swabs collected during a 4-week period prior to the study start. Eligible subjects were enrolled sequentially in one of three treatment groups, each consisting of 8 subjects. In each group, 6 subjects were randomized to LTX-109 treatment and 2 subjects to vehicle treatment. The treatment dose in the three groups was ascending, starting with 1% LTX-109. The study design is shown in Fig. 1. The study drug was applied three times a day (TID) for three consecutive days. Approximately 250 μ l of LTX-109 or vehicle was applied with the fingertip in the anterior parts of both nostrils, and the nose was thereafter massaged for 15 to 30 s. In addition, the subjects performed a local standard hygiene program, including body and hair wash with chlorhexidine (Hibiscrub), from day 1 until day 14 of the study (25).

Study assessments. The efficacy was evaluated by quantitative cultures from the nares, throat, and perineum, and the safety was assessed by evaluation of any reported or observed adverse event (AE). The tolerability of each application was registered in a study diary by each subject. Physical examination, evaluation of vital signs, and inspection of the nasal cavity by speculum were performed daily during the treatment period and at week 2, 5, and 9 follow-up visits.

Blood samples for hematocrit (hemoglobin [Hb]), leukocytes, plate-

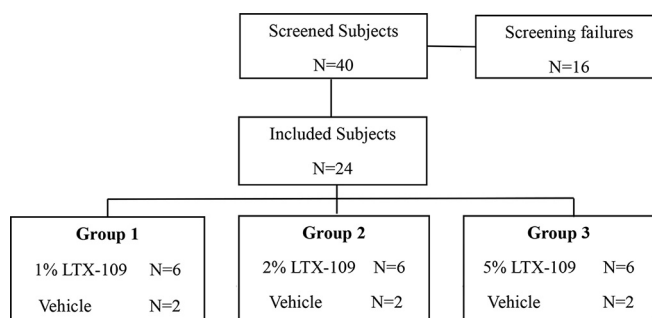


FIG 1 Disposition of subjects in the study.

lets, hematocrit, red cell count, mean corpuscular hemoglobin concentration [MCHC], mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], and differential count) and clinical chemistry (sodium, potassium, creatinine, albumin, calcium, urea, chloride, aspartate aminotransferase [ASAT], alanine aminotransferase [ALAT], glutamyltransferase [GT], alkaline phosphatase [ALP], bilirubin, C-reactive protein [CRP], total protein, and glucose) parameters were analyzed at the beginning and end of the study period at the Clinical Chemistry Department, Malmö, Sweden. Urine analysis for Hb, leukocytes, protein, and ketone bodies was done with urine sticks at the site.

Plasma concentration analysis. Systemic absorption of LTX-109 was assessed by analyzing the LTX-109 concentration in plasma collected prior to first drug administration on days 1, 2, and 3 as well as on day 4 and at the week 2 visit. Additional sampling was done at 0.5, 1, 2, and 4 h after the first dose on day 1 on volunteering subjects. Validated methods were used to analyze the plasma samples by high-performance liquid chromatography (HPLC) (Charles River Laboratories, Edinburgh, United Kingdom).

Microbiological methods. Bacterial load analysis, measured as CFU, was performed during the screening period, before the first drug application on days 1 to 3, and at the day 4 and week 2, 5, and 9 follow-up visits. Samples for microbiological analysis were collected by using flocked nylon-tip swabs from a Copan E swab kit (480CE; Copan Italia, Brescia, Italy). A swab was inserted 1 cm into one of the nostrils and rotated twice. The procedure was repeated for the other nostril using the same swab. On the day of collection, the swab was processed at the Clinical Microbiology Laboratory, Malmö, Sweden. One hundred microliters per plate was plated onto two Brilliance MRSA agar plates (PO5196A; Oxoid, Basingstoke, United Kingdom) and two CHROMagar Staph aureus plates (CHROMagar, Paris, France) as well as in a single tube containing 4 ml of CAMSA broth (15 g/liter proteose peptone [Oxoid], 2.5 g/liter liver digest [Oxoid], 5.0 g/liter yeast extract [BD Diagnostics, Sparks, MD, USA], 10 g/liter mannitol [Sigma-Aldrich, St. Louis, MO, USA], and 25 g/liter NaCl [Fisher Scientific, Gothenburg, Sweden], pH 7.0, supplemented with 8.0 mg/liter aztreonam [ICN Biomedicals Inc., Aurora, OH, USA] and 4.0 mg/liter cefoxitin [Fluka, Sigma-Aldrich]). The number of CFU was determined after 20 h and again after another 24 h. The CAMSA broth was incubated for 20 h, after which 100 μ l each was plated onto a Brilliance MRSA agar and a CHROMagar Staph aureus plate. These plates were incubated for 24 h. Pastorex Staph plus (Bio-Rad, Hercules, CA, USA) agglutination was used together with typical appearance and color to verify *S. aureus*, while MRSA colonies were also verified by *mecA*/Sa442 PCR (26). For no growth on plates, a detection level of ≤ 10 CFU/ml was recorded as 0.

The *S. aureus* strains found at the study start and at the final follow-up visit in week 9 were SPA typed by sequencing a part of the gene encoding protein A from *S. aureus* (27) using the Ridom StaphType software (Ridom GmbH, Münster, Germany) as a tool for analysis (28).

Statistical methods. The primary efficacy variable was decolonization/reduction of the bacterial load in CFU/ml. The linear contrast differ-

TABLE 1 Demographic characteristics and carriage status for treatment and vehicle groups

Demographic characteristic	Value for treatment group (<i>n</i> = 6)			
	Vehicle	1% LTX-109	2% LTX-109	5% LTX-109
Mean age, yr (range)	53 (31–71)	41 (16–60)	47 (28–65)	36 (23–65)
Race (no.)				
Asian	1	1	0	0
Black	0	0	1	0
White	5	5	5	6
MRSA carriers (no.)	1	5 ^a	1	0
MSSA carriers (no.)	5	1	5	6

^a One subject carried both MSSA and MRSA.

ence between vehicle and LTX-109 treatment was analyzed, and multiple comparisons between each treatment dose were done using Dunnett's test: repeated-measures analysis with treatment as a covariate. The assumption of normal distribution was examined, and there was no reason to believe that the assumption was violated even though the sample was rather small. The repeated-measurement analysis was performed for 2 periods: (i) baseline to day 4 and (ii) baseline to week 9. The log mean CFU values for *S. aureus* (MRSA and methicillin-sensitive *S. aureus* [MSSA]) on CHROMagar Staph aureus plates after 44 h were used for the calculations except when no colonies were found on these plates. For these low-positive MRSA samples, either the number of CFU on Brilliance MRSA agar was used or, when there was no growth on these plates, any MRSA growth after CAMSA enrichment was recorded as 10 CFU/ml. The population for this analysis was "all subjects." The number of subjects was not based on statistical justification. All statistical instruments used were exploratory.

RESULTS

Characteristics of the study population. As predefined, 24 persistent nasal *S. aureus* carriers were included and completed the study. The gender distribution was 50:50, and the races of the subjects were 21 white, 2 Asian, and 1 black (Table 1). Seven subjects carried MRSA, 17 carried MSSA, and one carried both (Table 1). Due to the dose escalation design and fewer than expected eligible subjects in the local MRSA register, all MRSA carriers except one were recruited to the 1% LTX-109 treatment group. Additional subjects were recruited from an open-house screening. In the open-house screening, 35 of the 78 screened subjects (44%) were found to be nasal *S. aureus* carriers. All strains detected in the open-house screening were sensitive to methicillin (MSSA).

Twenty-one different SPA types were observed. Among these, there were two unrelated subjects with SPA type T002, two with T008, and two with T8532 (Table 2). Throughout the study period, all subjects except one remained with the same SPA type. The deviating subject had the initial MSSA SPA type T6284 eradicated and replaced by MSSA SPA type T8352.

According to the subjects' diaries, no doses were missed.

Efficacy results. In all groups treated with LTX-109, a reduction in CFU counts compared with the baseline and the vehicle group was observed already after 1 day of treatment. The mean CFU counts of the different treatment groups are shown in Fig. 2. A significant reduction of the number of CFU below the detection limit compared to the vehicle group was demonstrated in subjects treated with 2% and 5% LTX-109 after 2 days of treatment ($P = 0.0008$ and $P = 0.0012$, respectively, by Dunnett's test). There was

TABLE 2 *S. aureus* strain and SPA identification at study start and end

Treatment group	<i>S. aureus</i>	SPA type	
		Day 1	Wk 9
Vehicle	MRSA	T002	Not done
	MSSA	T330	T330
	MSSA	T437	T437
	MSSA	T026	T026
	MSSA	T015	T015
	MSSA	Not done	Not done
1% LTX-109	MRSA	T309	T309
	MRSA	T012	T012
	MRSA	T5708	T5708
	MRSA	T008	T008
	MSSA	T002 ^a	T071 ^a
	MSSA	T3169	T3169
2% LTX-109	MRSA	T390	T390
	MSSA	T008	T008
	MSSA	T363	T363
	MSSA	T1932	Eradicated
	MSSA	T084	T084
	MSSA	T015	T105
5% LTX-109	MSSA	T8532	T8532
	MSSA	T6284 ^b	T8532 ^b
	MSSA	T1476	T1476
	MSSA	T002	T002
	MSSA	T8532*	T8532*
	MSSA	T084	T084

^a The MRSA strains found in cultures on day 1 and week 9 differed in 1 gene position, indicating that a point mutation but no reinfection had occurred.

^b The change of strain from SPA type T6284 to T8532 in one subject may be due to an eradication of the initial MSSA strain and replacement with the MSSA strain of the partner (*).

no further reduction of CFU counts in the subjects in the 1% group throughout the treatment period. After 3 days of treatment, the mean CFU count was still below the detection level in the 2% and 5% LTX-109 treatment groups, which was significant compared to vehicle treatment ($P = 0.0180$ and $P = 0.0105$, respectively, by Dunnett's test).

All agar plates exhibiting growth of *S. aureus* showed an even distribution of colonies, and no growth inhibition where the sample had been pipetted was observed (data not shown), suggesting that no carryover of remaining traces of the active compound had occurred.

The treatment effect from baseline to day 4 was explored using a linear-contrast, vehicle versus active treatment, and this was statistically significant ($P = 0.0007$ by Dunnett's test). During the follow-up period of 8 weeks, there was no significant difference between LTX-109- and vehicle-treated subjects. The repeated-measurement analysis performed for the period from baseline to week 9 showed no statistically significant treatment effect overall compared to vehicle treatment ($P = 0.2754$ by Dunnett's test).

No statistically significant treatment effect of nasal decolonization with LTX-109 was obtained for reduction of *S. aureus* in the throat, nor was there any correlation between presence of *S. aureus* in the nose and the throat (data not shown). No analysis of significance of treatment on carriage in the perineum could be done due to a limited number of readings.

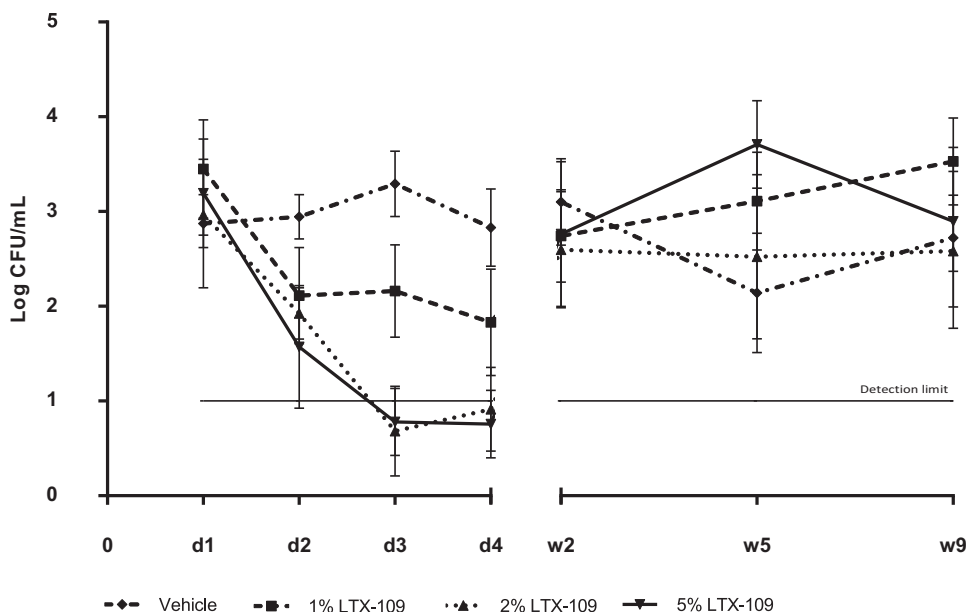


FIG 2 Nasal decolonization during days 1 to 4 and weeks 2 to 9 after treatment with vehicle or 1%, 2%, or 5% LTX-109. The mean bacterial load, analyzed as CFU/ml, with standard deviation (SD) is shown. The minimum CFU detectable is represented by a horizontal line. At days 3 and day 4 there was a statistically significant reduction in the 2% LTX-109 group ($P = 0.0008$ and $P = 0.0180$, respectively) and the 5% LTX-109 group ($P = 0.0012$ and $P = 0.0105$, respectively) compared to vehicle (Dunnett's test).

Safety and tolerability. Two serious adverse events (SAEs) were registered in weeks 6 and 8 posttreatment. They both occurred in subjects treated with 1% LTX-109 and were diagnosed as psychosis and postoperative bleeding after a prescheduled cyst eradication, respectively. Both SAEs were considered unrelated to the study drug.

The number of reported adverse events (AEs) was 132, of which 126 were classified as being mild in severity, 5 as moderate, and 1 as severe (Table 3). Seventy-four of these AEs, reported by 19 subjects, were considered possibly related to the study drug.

The most frequently reported AEs related to the application site were itching, burning, pain, and redness ($n = 26$) (Table 4). The most frequent AEs not related to the application site were common cold ($n = 12$) and headache ($n = 11$). The subjects in the 2% and 5% LTX-109 treatment groups reported more symptoms of itching, burning, and pain after application than did the 1%

LTX-109- and vehicle-treated subjects. The nasal inspections revealed 14 minimal epithelial lesions in the nasal cavity in 8 subjects (1 vehicle-treated subject and 7 LTX-109 treated subjects), of which 7 affected the septum during the treatment period. In 7 of the subjects, all lesions were healed within 1 week after completion of treatment, and the last one had healed at the week 5 inspection.

No differences regarding vital signs, physical examination, urine, clinical chemistry, hematology, and need for concomitant medications were observed in any of the subjects in the different treatment groups.

Systemic exposure to LTX-109. Nine subjects volunteered for additional plasma sampling after the first dosing on day 1, which revealed minimal plasma levels of LTX-109 during the 4-h post-

TABLE 3 Number, severity, and relationship to treatment of reported adverse events in subjects treated with LTX-109 or vehicle

Treatment ($n = 6$ /group)	No. of adverse events				
	Severity (SOC/LLT) ^a			Relationship (SOC/LLT)	
	Mild	Moderate	Severe	No reasonable possibility	Reasonable possibility
Vehicle	25	2		15	12
LTX-109					
1%	20	2	1	18	5
2%	32			4	28
5%	49	1		21	29
All	126	5	1	58	74

^a SOC, system organ class; LLT, lower-level term.

TABLE 4 Most frequently reported adverse events in subjects treated with LTX-109 or vehicle

Adverse event	No. in subjects ($n = 6$ /group) treated with:				
	Vehicle	LTX-109			Total
		1%	2%	5%	
Common cold	4	3	2	3	12
Headache	3	3	1	4	11
Runny nose	1	1	2	4	8
Application site					
Itching	1	2	4	1	26
Burning		1	3	3	
Pain	1			5	
Redness	2	1	1	1	
Minimal epithelial lesions					
Nasal cavity except septum	1	1	2	3	14
Nasal septum	1		2	4	

TABLE 5 Plasma concentrations of LTX-109 in 9 volunteering subjects in the different treatment groups at 0, 0.5, 1, 2, and 4 h after dosing on day 1

LTX-109 dose (<i>n</i>)	C_{\max} (ng/ml)	T_{\max} (h)
1% (1)	12.5	2
2% (4)	0.93–4.37	1–2
5% (4)	3.72–11.7	1–2

dosing sampling (Table 5). The highest plasma concentration measured was 12.5 ng/ml in 1 subject treated with 1% LTX-109 (lower limit of quantification [LLOQ] = 0.5 ng/ml). The time (T_{\max}) to the maximum concentration (C_{\max}) was 1 to 2 h post-dosing. Very low levels of LTX-109 were detected in the plasma in 14 out of 18 LTX-109-treated subjects at 24, 48, and 72 h after the initial dosing (Table 6). The maximum level was 16.5 ng/ml in one subject at 48 h after the first dosing of 5% LTX-109. In the remaining 4 subjects, no LTX-109 could be detected. There was no measurable plasma concentration of LTX-109 in any subject at the week 2 follow-up.

DISCUSSION

In the present placebo-controlled clinical study, we have for the first time demonstrated safety, tolerability, and a significant dose-dependent effect of the novel antimicrobial drug LTX-109 on nasal decolonization of persistent *S. aureus* carriers when administered TID for three consecutive days to the anterior nose.

Approximately 25% of all nosocomial infections are caused by *S. aureus*, affecting both surgical and nonsurgical patients and leading to increased hospital stay, antibiotic use, costs, and mortality (29–33). Data have shown that 80% of the strains are endogenous, originating from the nose (4, 34–36). Therefore, prevention programs aiming at decolonizing individual nasal *S. aureus* carriers are becoming increasingly implemented, and currently, nasally applied mupirocin combined with chlorhexidine body and hair wash is the drug of choice.

Mupirocin is bacteriostatic and has a proven effect on nasal *S. aureus* carriage, with a transient eradication rate of up to 80 to 90% in controlled studies (37); however, *S. aureus* has been evolving resistance to mupirocin (8, 14, 38–41). The mechanism of action of LTX-109 represents a new and innovative bactericidal approach via a direct membrane disruption (17, 18). The product has been shown not to be affected by cross-resistance to other available drugs and has demonstrated a low propensity for development of resistance (17, 18, 24). In the present study, a significant reduction of *S. aureus* CFU was demonstrated already after 2 days, although bacterial recurrence was observed in all but one subject 5 days after the end of treatment. The recolonization found in the treated patients could be due to a regrowth of a small amount of persistent, but not detected, intracellular *S. aureus* in the intranasal mucosa or to recolonization from other sites of the body or from close contacts carrying the same strain. An extended treatment time and/or more frequent daily applications should be implemented in further studies to investigate if a longer-lasting effect or even complete eradication can be achieved.

The 1% LTX-109 treatment demonstrated a smaller reduction of *S. aureus* CFU than the 2% and 5% treatments, consistent with a possible dose-response effect. Even though all the MRSA carriers were in the 1% group, this should not be attributed to a lesser

TABLE 6 Plasma concentrations at 24, 48, 72, and 168 h after the first dosing

LTX-109 dose	Patient no.	Plasma concn (ng/ml) ^a at:			
		24 h	48 h	72 h	168 h
1%	101	<0.5	<0.5	<0.5	<0.5
	103	<0.5	0.876	<0.5	<0.5
	104	<0.5	<0.5	<0.5	<0.5
	105	<0.5	<0.5	<0.5	<0.5
	106	<0.5	<0.5	<0.5	<0.5
	107	1.31	1.03	1.31	<0.5
	2%	201	3.19	6.63	4.84
202		0.65	0.85	1.19	<0.5
204		<0.5	<0.5	<0.5	<0.5
205		0.68	0.61	1.53	<0.5
207		<0.5	<0.5	0.929	<0.5
208		2.33	1.66	4.27	<0.5
5%		301	7.29	10.6	7.71
	302	1.15	5.27	5.02	<0.5
	304	3.25	1.11	2.01	<0.5
	306	2.71	1.27	0.87	<0.5
	307	<0.5	<0.5	<0.5	<0.5
	308	0.83	16.5	2.79	<0.5

^a Lowest level of quantification, 0.5 ng/ml.

effect on MRSA than on MSSA. In animal studies using clinical isolates of hospital-acquired and community-acquired MRSA, LTX-109 has been rapidly bactericidal against all isolates tested, with a more than 3-log reduction in CFU already after 1 day of TID treatment (42). *In vitro* studies demonstrate excellent activity of LTX-109 against multidrug-resistant *S. aureus*, including strains with low- and high-level mupirocin resistance (22), which is of particular interest in view of recent reports of cases of mupirocin-resistant *S. aureus* (14).

Among the pathogens causing health care-associated infection, MRSA has been given priority as a target of reduction efforts because of its virulence and disease spectrum, multidrug-resistant profile, and increasing prevalence in health care settings, particularly among patients in intensive care units (ICUs) (38, 43–47). Consequently, new treatment guidelines to deal with the problem are receiving increased attention.

Nasal administration of LTX-109 TID for three consecutive days was safe, and no differences in vital signs or laboratory measurements were observed between treatments. All reported adverse events were of short duration and mainly of mild severity. The study also demonstrated a very low systemic exposure of LTX-109, with detectable levels during the days of treatment only, which is consistent with the low bioavailability previously demonstrated in a comprehensive panel of good laboratory practice (GLP) toxicology and safety studies (19). LTX-109 was found to be well tolerated when applied to the anterior nose. However, local reversible adverse events related to study treatment were observed. The subjects treated with 2% or 5% LTX-109 reported more symptoms of itching, pain, and burning after application than did those treated with 1% LTX-109 or vehicle. The adverse events related to LTX-109 treatment, such as runny nose, nasal congestion, and sneezing, were probably caused by the study drug affecting the upper part of the nose and may have contributed to a removal of the study drug, resulting in shorter LTX-109 exposure

time. Hence, a more viscous formulation may induce less effect on the upper part of the nose, which may also be more effective to decolonize the nose.

Because of the spread of *S. aureus* in hospitals, leading to an increase in the infection rates, prevention programs aiming at decolonizing individual nasal *S. aureus* carriers have to be implemented. The European multicenter study by Bode et al. (6) demonstrated significant evidence that nasal mupirocin treatment reduces the incidence of surgical-site infections, and in this study, carriers of *S. aureus* were identified preoperatively by means of a real-time PCR assay. In contrast, a recent U.S. study including 43 U.S. hospitals, 74 adult intensive care units (ICUs), and 74,256 patients revealed that universal decolonization of patients in the ICU, irrespective of confirmed nasal carriage, was the most effective strategy. This significantly reduced the MRSA-positive clinical cultures by 37% and bloodstream infections from any pathogen by up to 44% (38). Thus, universal decolonization of *S. aureus* carriers as infection prophylaxis will increase the need for new antibiotics with low propensity for resistance development.

Here we showed that intranasal LTX-109 treatment of *S. aureus* is safe and reduces the bacterial load already after a single day of treatment. Hence, LTX-109 has potential as a new and effective antimicrobial agent with low propensity of resistance development that can prevent infections by MSSA/MRSA during hospitalization. The data provide a basis for the continued development of LTX-109 for nasal decolonization.

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