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A STUDY TO ASSESS SKIN LESION MEASUREMENT TECHNIQUES RELATED TO ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS

Michael Dunne,[1] Purvi Mehra,[2] Sinikka Green,[2] Wade Sears,[2] Robert Cockrell,[2] Paul Manos,[2] George Talbot,[3] Anita Das[4]

[1]Durata Therapeutics, Inc., Morristown, NJ; [2]eStudySite, San Diego, CA; [3]Talbot Advisors LLC, Anna Maria, FL; [4]Axistat, Inc., San Francisco, CA

ABSTRACT

Background

The US Food and Drug Administration recently issued a Draft Guidance that redefines the primary endpoint to be used in registrational studies to support an indication of acute bacterial Skin and Skin Structure Infections (abSSSI). The endpoint requires documentation of both cessation of spread of any cellulitis associated with the infection as well as resolution of fever. This study was designed to provide evidence of reproducibility of the measurements of the erythema associated with these lesions.

Methods

This was a multicenter, observational study in patients with an abSSSI enrolled sequentially. All measurement/procedures were performed at the baseline visit. At least two, and not more than three, observers measured the erythema associated with the abSSSI by ruler; correlation with other techniques such as digital imaging, planimetric assessment of transparencies and thermal imaging was also performed. The primary endpoint was assessment of the intra-observer and inter-observer variability of the erythema as measured by ruler and determined by the intraclass correlation coefficient (ICC).

Results

42 patients meeting criteria for an abSSSI were enrolled; 39 were evaluated for efficacy. Overall, both the repeated (intra-) observer and between (inter-) observer ruler measurements showed almost perfect reliability with ICC's >0.9 for area, length and width. The percent differences in ruler measurements between different observers were slightly larger than between repeated measurements by the same individual (17.4% vs. 4.1%, respectively). Variability was higher in smaller lesions. There was almost perfect intra-observer reliability (ICC>0.9) comparing the longest and shortest lesion measurements by ruler compared to measurements derived programmatically from a computer-assisted planimetry assessment of lesion taken from the transparency grid. Lesions measured by digital camera and transparency were 35% and 31% smaller than the ruler, respectively.

Conclusions

Measurement of the erythema associated with an abSSSI can be reliably performed using a ruler.

OBJECTIVES

- The primary objective was to characterize the size of erythema associated with presenting skin lesions in patients with an acute bacterial skin and skin structure infection (abSSSI) as measured by different techniques. Additional objectives were to characterize local and systemic signs/symptoms of abSSSI, and to correlate lesion measurements obtained with various techniques with other related clinical information such as relevant medical history, previous and concomitant drug and non-drug therapies, and other signs and symptoms of infection such as the presence of fever at baseline.

METHODS

- In this multicenter, observational (non-drug) study, approximately 40 patients with an abSSSI meeting enrollment criteria were planned to be enrolled sequentially. All measurement/procedures were performed at the baseline visit (Day 1). Evaluations included medical history and clinical assessments. Prior drug and non-drug treatments and concomitant drug and non-drug adjunctive therapy were reviewed. Infection sites were assessed through measurement of lesion size. At least two, and not more than three, observers made some or all of these assessments using various measurement techniques (ruler, transparent dressing with measurement grid, digital imaging, thermal imaging). Patients were monitored for adverse events (AE).

Inclusion Criteria

Patients enrolled in this study:

- Were 18–85 years old who signed informed consent
- Had an abSSSI (suspected/ confirmed due to Gram-positive bacteria) defined as:
  - infections involving deeper soft tissue or requiring significant surgical intervention (major cutaneous abscess, surgical site/traumatic wound infection, cellulitis).
  - ≥2 signs/symptoms of abSSSI infection (purulent drainage/ discharge, fluctuance, heat/localized warmth, tenderness to palpation, swelling/induration) and,
  - ≥1 systemic signs of infection (body temperature ≥38°C/100.4°F, white blood cell [WBC] count >12,000 cells/mm^3, WBC differential count with ≥10% band forms, regardless of peripheral WBC count).

Assessment of abSSSI Lesion Measurement Techniques

- Ruler measurements of infection sites were determined twice by the first observer for an assessment of intra-observer variability. The first observer also measured the same lesion using digital imaging and a transparency grid for an assessment of inter-technique variability (vs. ruler). The lesions were also measured once by one to two other observers using a ruler, and compared to the first ruler measurement by the first observer for an assessment of inter-observer reliability.
- Measurements by thermal imaging were obtained at selected sites.
- The primary outcome was ruler measurement of the skin lesion area, defined as length x width. Secondary outcomes included measurements of lesion area by other imaging techniques.
- Patients were also assessed for the presence of local clinical signs/symptoms of infection and evidence of systemic infection. The analysis population was the "enrolled population" (signed informed consent and met all enrollment criteria). Exploratory analyses were also performed. Inflammatory markers of disease and patient pain assessment were also listed as secondary outcome measures.

Statistical Methods

- To assess variability in measurements (intra-and inter-observer, inter-technique), the intraclass correlation coefficient (ICC) and coefficient of variation (COV) were determined with 95% confidence intervals (CI). Differences between measurement techniques were also assessed using the paired t-test (significance at p<0.05). Bland-Altman plots of ruler versus other measurement techniques were created.
- Descriptive statistics were utilized, providing numbers and percentages for categorical variables, and numbers, means, standard deviations, medians, and minimum and maximum values for continuous variables.

RESULTS

Table 1. Infection Site by Type of abSSSI — Enrolled Population

	Enrolled Population (N=39)		
Infection Type	**n**	**Mean (SD)**	**Minimum, Maximum**
Major Cutaneous Abscess	19		
Length of shortest peripheral margin of erythema (cm)	19	8.62 (6.523)	3.0, 32.0
Length of induration (cm)	19	17.87 (9.368)	6.5, 47.0
Width of induration (cm)	19	14.58 (8.455)	5.0, 43.5
Area of induration (cm^2)	19	321.15 (435.667)[a]	40.0, 2044.5
Traumatic Wound Infection	5		
Length of greatest peripheral margin of erythema (cm)	4	15.63 (9.810)	5.5, 29.0
Cellulitis	15	—	—

[a] Median=240.00

N=Number of patients in enrolled population; n=Number of patients in specific category; SD=standard deviation.

Table 2. Systemic Signs/Symptoms of Infection

	Enrolled Population (N=39)					
	Abscess (N=19)		Traumatic Wound Infection (N=5)		Cellulitis (N=15)	
Systemic Sign/Symptom	**n**	**Measure**	**n**	**Measure**	**n**	**Measure**
Temperature (°C) (mean, SD)	19	37.18 (0.774)	5	36.98 (0.476)	15	37.27 (1.024)
Febrile (≥38°C/100.4°F) (%)	4	21.1%	0	0.0%	3	20.0%
WBC ≥12,000 cells/mm^3 (%)	17	89.5%	5	100.0%	15	100.0%
Immature Neutrophils ≥10 (%)	0	0.0%	0	0.0%	0	0.0%
CRP (mg/dL) above normal[a] (%)	18	94.7%	5	100.0%	12	80.0%
CRP (mg/dL) (mean, SD) (median, range)	19	39.2 (76.4) 12.5 (1.6–288.4)	5	7.6 (7.6) 4.7 (1.1–19.0)	13	22.9 (41.9) 8.6 (0.5–149.8)
Lymphadenopathy (%)[b] (%)	12	63.2%	4	80.0%	11	73.3%
Painful lymphadenopathy[b] (%)	9	47.4	4	80.0%	9	60.0
Pain (scale 0–10)[c] (Mean, SD)	18	5.9 (2.74)	5	6.4 (4.04)	14	6.6 (2.06)

N=Number of patients in enrolled population; n=Number of patients in specific category; SD=standard deviation; CRP=C-reactive protein; WBC=white blood cell.

[a] The upper limit of normal for CRP at the various sites ranged from 0.35–0.7 mg/dL.

[b] Refers to lymphadenopathy proximal to the abSSSI.

[c] Patient assessment of pain from the Brief Pain Inventory.

Table 3. Ruler Measurements of abSSSI Lesion Area (cm^2): Intra-observer and Inter-observer Variability by Lesion Size

	Enrolled Population (N=39)			
	n	**Mean (SD)**	**ICC (95% CI)**	**COV (95% CI)**
All Lesion Sizes				
Intra-observer				
Measurement 1	39	524.99 (543.038)	0.999 (0.998, 1.000)	3.08 (2.89, 3.27)
Measurement 2	39	526.13 (545.783)		
Intra-observer				
Observer 1	39	524.99 (543.038)	0.990 (0.981, 0.995)	10.38 (9.70, 11.06)
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Lesions 75–150 cm^2				
Intra-observer				
Measurement 1	8	116.19 (22.354)	0.686 (0.122, 0.915)	10.70 (10.56, 10.83)
Measurement 2	8	111.26 (21.202)		
Intra-observer				
Observer 1	8	116.19 (22.354)	0.107 (−0.544. 0.678)	26.69 (26.26, 27.11)
Observer 2	8	111.05 (40.934)		
Lesions >150–300 cm^2				
Intra-observer				
Measurement 1	9	219.16 (46.293)	0.866 (0.567, 0.963)	9.22 (9.08, 9.36)
Measurement 2	9	212.71 (61.598)		
Intra-observer				
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Lesions >300–600 cm^2				
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Measurement 1	13	417.41 (57.135)	0.922 (0.781, 0.974)	3.70 (3.66, 3.74)
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Intra-observer				
Observer 1	13	417.41 (57.135)	0.598 (0.134, 0.847)	13.76 (13.58, 13.94)
Observer 2	13	423.92 (116.880)		
Lesions >600 cm^2				
Intra-observer				
Measurement 1	9	1349.59 (580.636)	0.999 (0.997, 1.000)	1.18 (1.15, 1.21)
Measurement 2	9	1353.14 (581.259)		
Intra-observer				
Observer 1	9	1349.59 (580.636)	0.984 (0.940, 0.996)	5.43 (5.30, 5.57)
Observer 2	9	1338.50 (571.353)		

Source: Tables 14.2.2.1 and 14.2.2.1.1

N=Number of patients in the enrolled population; n=Number of patients with two ruler measurements (length and width) obtained by the same observer (intra-observer) or by two different observers (inter-observer).

Note: Descriptive statistics for the intra-observer ruler measurements are for the two ruler measurements conducted by the first observer. Descriptive statistics for the inter-observer ruler measurements are for the first of two measurements made by the first observer and the ruler measurement of the second observer.

Note: Lesion size is defined as the average of the two ruler measurements by the first observer.

SD=standard deviation; ICC=Intraclass correlation coefficient; COV=Coefficient of variation.

Figure 1. Patient 103

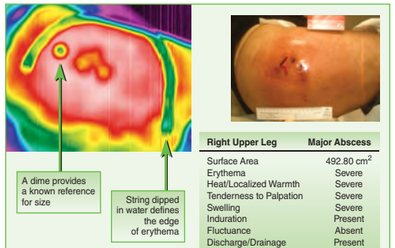

Figure 2. Patient 504

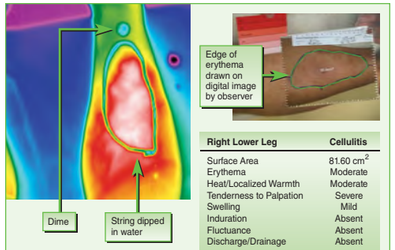

Figure 3. Patient 505

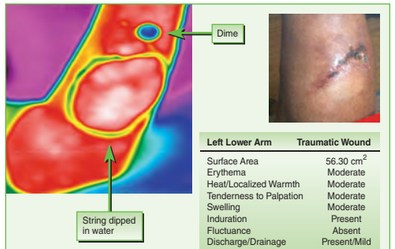

Table 4. Measurements of Intra-observer Variability of Lesion Area by Imaging Technique

	Enrolled Population (N=39)		
Lesion Size (cm^2)	**n**	**Mean (cm^2) (SD)**	**Difference (cm^2)**
All Sizes			
Ruler	33	396.93 (377.017)	
Digital Imaging	33	257.08 (241.830)	139.85
Ruler	32	401.71 (393.051)	
Transparent Dressing	32	276.48 (238.997)	125.23
Digital Imaging	32	302.56 (295.491)	
Transparent Dressing	32	360.17 (360.743)	−57.61

N=Number of patients in the enrolled population; SD=standard deviation.

n=Number of patients with a measurement obtained 1) using a ruler and other specified technique, or 2) using digital imaging and transparent dressing.

Note: Lesion size is defined as the average of the two ruler measurements conducted by the first observer.

Note: Paired difference is calculated 1) as ruler measurement minus other measurement within each patient paired by observer, or 2) as digital imaging measurement minus transparent dressing measurement within each patient.

Note: Mean area for the ruler measurements is based on the first ruler measurement taken by the observer with a paired measurement using either digital imaging or transparency grid.

CONCLUSIONS

- For all lesions without regard to size, the intra- and inter-observer ruler measurements showed almost perfect reliability with ICCs >0.9 for area (primary outcome).
- The percent differences in lesion measurements between different observers (17.4% for area) was larger than for repeated measurements by the same observer (4.1% for area). Results were similar for length and width.
- With ruler measurements of the abSSSI lesion area, there was a trend towards lower ICC scores with smaller lesions.
- Intra- and inter-observer reliability of ruler measurements (area, length, width) was almost perfect (ICC>0.9) regardless of infection type (abscess with or without incision/drainage, traumatic wound infection, cellulitis).
- As expected, in all comparisons the estimates of mean lesion area were nominally larger with the ruler (which measures a rectangle or square) compared to either digital imaging or transparency grid (which measure the actual lesion).
- Thermal imaging can identify involvement of infection beyond that defined by the surface representation of erythema.
- There was almost perfect intra-observer reliability (ICC>0.9) in the longest and shortest lesion measurements by ruler versus transparency grid.

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Source: Tables 14.2.2.1 and 14.2.2.1.1

N=Number of patients in the enrolled population; n=Number of patients with two ruler measurements (length and width) obtained by the same observer (intra-observer) or by two different observers (inter-observer).

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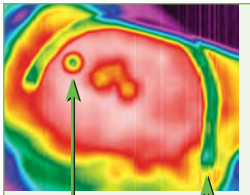
Note: Lesion size is defined as the average of the two ruler measurements by the first observer.

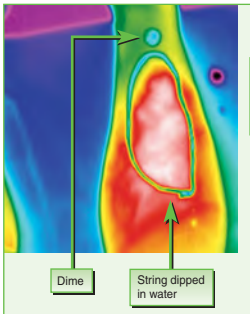
SD=standard deviation; ICC=Intraclass correlation coefficient; COV=Coefficient of variation.

Figure 1. Patient 103



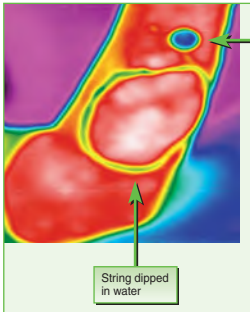
Right Upper Leg	Major Abscess
Surface Area	492.80 cm^2
Erythema	Severe
Heat/Localized Warmth	Severe
Tenderness to Palpation	Severe
Swelling	Severe
Induration	Present
Fluctuance	Absent
Discharge/Drainage	Present

Figure 2. Patient 504



Right Lower Leg	Cellulitis
Surface Area	81.60 cm^2
Erythema	Moderate
Heat/Localized Warmth	Moderate
Tenderness to Palpation	Severe
Swelling	Mild
Induration	Absent
Fluctuance	Absent
Discharge/Drainage	Absent

Figure 3. Patient 505



Left Lower Arm	Traumatic Wound
Surface Area	56.30 cm^2
Erythema	Moderate
Heat/Localized Warmth	Moderate
Tenderness to Palpation	Moderate
Swelling	Moderate
Induration	Present
Fluctuance	Absent
Discharge/Drainage	Present/Mild

Table 4. Measurements of Intra-observer Variability of Lesion Area by Imaging Technique

Enrolled Population (N=39)			
Lesion Size (cm^2)	**n**	**Mean (cm^2) (SD)**	**Difference (cm^2)**
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Transparent Dressing	32	360.17 (360.743)	−57.61

N=Number of patients in the enrolled population; SD=standard deviation.

n=Number of patients with a measurement obtained 1) using a ruler and other specified technique, or 2) using digital imaging and transparent dressing.

Note: Lesion size is defined as the average of the two ruler measurements conducted by the first observer.

Note: Paired difference is calculated 1) as ruler measurement minus other measurement within each patient paired by observer, or 2) as digital imaging measurement minus transparent dressing measurement within each patient.

Note: Mean area for the ruler measurements is based on the first ruler measurement taken by the observer with a paired measurement using either digital imaging or transparency grid.

CONCLUSIONS

- For all lesions without regard to size, the intra- and inter-observer ruler measurements showed almost perfect reliability with ICCs >0.9 for area (primary outcome).
- The percent differences in lesion measurements between different observers (17.4% for area) was larger than for repeated measurements by the same observer (4.1% for area). Results were similar for length and width.
- With ruler measurements of the abSSSI lesion area, there was a trend towards lower ICC scores with smaller lesions.
- Intra- and inter-observer reliability of ruler measurements (area, length, width) was almost perfect (ICC>0.9) regardless of infection type (abscess with or without incision/drainage, traumatic wound infection, cellulitis).
- As expected, in all comparisons the estimates of mean lesion area were nominally larger with the ruler (which measures a rectangle or square) compared to either digital imaging or transparency grid (which measure the actual lesion).
- Thermal imaging can identify involvement of infection beyond that defined by the surface representation of erythema.
- There was almost perfect intra-observer reliability (ICC>0.9) in the longest and shortest lesion measurements by ruler versus transparency grid.

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