Contemporary Clinical Trials 50 (2016) 265–272

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Clinician-reported lesion measurements in skin infection trials: Definitions, reliability, and association with patient-reported pain

John H. Powers III MD [a,*], Anita F. Das PhD [b], Carisa De Anda PharmD [c], Philippe Prokocimer MD [c]

[a] George Washington University School of Medicine, Washington, DC, USA
[b] InClin, San Mateo, CA, USA
[c] Merck & Co, Inc., Kenilworth, NJ, USA

ARTICLE INFO

Article history:
Received 13 May 2016
Received in revised form 4 August 2016
Accepted 9 August 2016
Available online 13 August 2016

Keywords:
Acute bacterial skin and skin structure infections
Trial design
Outcome assessments
Endpoints
Patient-reported outcomes
Clinician-reported outcomes

ABSTRACT

Objectives: Outcome assessments as clinical trial endpoints should be well-defined, reliable, and reflect meaningful treatment benefits. For acute bacterial skin and skin structure infections (ABSSSI) trials, recent recommendations suggest a primary endpoint of reduction in skin lesion area. Objectives were: evaluate ABSSSI lesion area measurement reliability, evaluate impact of various lesion area definitions on treatment effect size, and explore relationships between lesion area and pain.
Methods: Data from two randomized, double-blinded Phase 3 trials comparing tedizolid to linezolid in ABSSSI and one open-label, non-comparative Phase 2 study of tedizolid in cellulitis/erysipelas and skin abscess were analyzed. Repeated lesion area measurements were prospectively obtained in all studies. In the open-label study, lesion area was measured by two investigators, using four different definitions. Repeated pain assessments using two patient-reported outcome instruments (Visual Analog Scale [VAS] and Faces Rating Scale [FRS]) were elicited in the randomized trials.
Results: At baseline, lesion size did not correlate with pain intensity: $r = 0.02$ for VAS and $r < 0.01$ for FRS pain scores. However, decreasing lesion size and decreasing pain were strongly associated over time, regardless of initial lesion size or pain intensity ($r = 0.20$ for VAS and $r = 0.21$ for FRS scores at Day 10–13). Each lesion area definition demonstrated high inter-observer reliability (intra-class correlation coefficient > 0.95).
Conclusions: Decreasing lesion area (indirect clinician-reported measure of benefit) and pain (direct patient-reported measure of benefit) were strongly associated over time, and lesion area measurements were reliable, regardless of their definition. These findings support both measures as outcome assessments in ABSSSI clinical trials.
Registration: Clinicaltrials.gov NCT01519778, NCT01170221, and NCT01421511.

1. Introduction

Understanding treatment benefits of medical interventions for patients requires clearly defined outcome assessments (OAs) [1]. OAs are the measurements used to evaluate treatment outcomes in clinical trials [2] while 'endpoints' are constructed using these OAs in order to demonstrate treatment benefit (i.e., improvements in how patients feel, function, or survive). A particular OA can be used in various ways to define endpoints. Endpoint definitions include timing (i.e., when to measure) and analysis method (e.g., difference in proportions, time to event), considerations that are not inherent in the OA itself. Numerous stakeholders have expressed increasing interest in patient-centered outcomes and patient-reported health-related quality of life. Payers have indicated such information is needed to justify reimbursement [3]. Well-defined and reliable OAs specify a) the variables measured, b) the method by which measurements are obtained, and c) how the outcomes are analyzed [4,5].

Many new antibiotics, including three in the past 2 years, are initially evaluated for treatment of acute bacterial skin and skin-structure infections (ABSSSI) [6–8,9–11]. Therefore, it is crucial to base efficacy endpoints in ABSSSI clinical trials on well-defined and reliable outcome measures, and also to understand how these measures may reflect direct patient benefit. Similar to clinical trials for other infectious diseases, OAs in ABSSSI trials have traditionally been clinician-reported outcomes (ClinROs). ClinROs in infectious disease trials often are evaluating global impressions of changes in signs, symptoms, laboratory values, and radiology. These OAs are often not well-defined, both in terms of specific variables assessed and the amount of change representing treatment "success" or "failure" (i.e., clinician-judged need for non-study antimicrobial therapy). Global ClinROs may also lack reliability [12], and clinicians may not accurately capture patients' symptoms [13,14], which are most accurately reported by patients themselves.

* Corresponding author at: Penfield House, 15915 Emory Lane, Rockville, MD 20853, USA.
E-mail address: jpowers3@aol.com (J.H. Powers).

http://dx.doi.org/10.1016/j.cct.2016.08.010
1551-7144/

Given these issues, recent initiatives have begun re-evaluating OAs used to define endpoints for ABSSSI trials. Recent recommendations suggest basing efficacy evaluations on the ClinRO of skin lesion area, with the primary endpoint (particularly for non-inferiority trials) defined as >20% reduction in lesion area at 48–72 h after randomization [15,16]. This recommendation is based upon controlled trials in erysipelas, where cessation of lesion spread at 48 h was the endpoint with the largest treatment effect [17,18]. Those historical observations were used to justify non-inferiority hypotheses and non-inferiority margins as defined in international guidance [19]. Several recent ABSSSI trials have subsequently used the ClinRO of lesion area to define primary or secondary endpoints [6,7,9–11].

While lesion measurements meet the criteria for "well-defined", they are indirect measures of patients' symptoms and function in their daily lives. The relationship of lesion size to patient-reported symptoms (direct measures of treatment benefit), impact of different lesion area definitions on measurements, and lesion measurement reliability have not been prospectively evaluated. Therefore, we performed an exploratory analysis to evaluate relationships between changes in lesion size and changes in patients' pain scores, using prospectively collected data from two previously published randomized ABSSSI trials [6–8]. For a rigorous evaluation of potential associations between pain and lesion size, it was critical to ensure reliability of lesion area measurements. We therefore also conducted a non-comparative study prospectively evaluating (a) the impact of different lesion definitions on outcomes and (b) the reliability of lesion measurements using a plastic ruler.

2. Methods

2.1. Assessment of association between pain and lesion area

Relationships between patient-reported pain and clinician-reported lesion area were evaluated retrospectively using data from two previously published randomized, double-blind, non-inferiority trials comparing tedizolid phosphate 200 mg once daily for 6 days to linezolid 600 mg twice daily for 10 days in treatment of ABSSSI (cellulitis/erysipelas, cutaneous abscesses, and wound infections) due to gram-positive pathogens [6,7]. ESTABLISH-1 (clinicaltrials.gov NCT01170221) evaluated oral therapy [6] and ESTABLISH-2 (clinicaltrials.gov NCT01421511) intravenous therapy followed by optional oral switch [7]. Adult patients with ABSSSIs and lesion area ≥ 75 cm^2 were eligible; exclusion criteria were described previously [6,7]. We examined associations between lesion area and pain intensity at baseline; changes in lesion area and patient-reported pain were also evaluated, comparing baseline to day 2, 48 to 72 h, days 4 to 6, days 7 to 9, days 10 to 13, and day >14 in the intent-to-treat (ITT) population. Data were pooled across both studies.

Lesion area was defined as the longest head-to-toe length multiplied by the widest perpendicular width of the lesion, measured using flexible plastic rulers. The endpoint in ESTABLISH-2 defined lesion length and width using erythema, induration, or edema (EIE), whichever was largest; ESTABLISH-1 used erythema only (Fig. 1). Patient-reported pain was assessed using the Visual Analog Scale (VAS) administered twice within 5 min, with the mean of the two scores used for analysis, and the Faces Rating Scale (FRS) administered once after the VAS. Both scales are utilized in many research settings [20]. The VAS is a 100-mm line, with 0 mm indicating "no pain" and 100 mm "worst pain ever". VAS ratings of 0–4 mm are considered no pain; 5–44 mm, mild; 45–74 mm, moderate; and 75–100 mm, severe pain [21]. The FRS is a 10-point scale, with 0 considered no pain, 1–3 mild, 4–6 moderate, and 7–10 severe pain [22].

2.2. Assessment of reliability of lesion area measurements

ABSSSI lesion area measurement reliability was evaluated in a Phase 2, open-label, multicenter, non-comparative, exploratory study conducted at 10 US sites (clinicaltrials.gov NCT01519778). Inclusion criteria were age ≥ 18 years and presence of cellulitis/erysipelas (i.e., rapidly spreading areas of EIE without apparent pus collection) or major cutaneous abscess, with lesion surface area of ≥75 cm^2 and suspected/documented as due to gram-positive pathogens. Local infection symptoms must have had started ≤7 days before screening. Key exclusion criteria were postsurgical or open wound infections; uncomplicated skin and skin structure infections (e.g., furuncles, minor abscesses, or impetigo); infections associated with/in close proximity to prosthetic devices; suspected/documented gram-negative infections; necrotizing processes; concomitant infection at another site; severe sepsis or septic shock; known bacteremia; presumed/confirmed osteomyelitis; diabetic foot infection; gangrene; infected burns/bites; decubitus ulcers; ischemic ulcers due to vascular disease; and/or infections at vascular catheter sites. Lesions were categorized as small (75 to <150 cm^2), medium (150 to <300 cm^2), or large (≥300 cm^2); at least 15 patients each for cellulitis/erysipelas and abscess were to be enrolled per size category. This study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies; patients provided written informed consent before enrollment.

The primary study objective was to evaluate adverse effects associated with open-label tedizolid 200 mg once daily for 6 days in the study population. All investigative team members (i.e., site investigators and/or site study coordinators) received standardized training on conducting lesion area measurements before enrolling patients. Lesions were measured at the screening and 48 to 72 h visits, and two measurement aspects were varied: [1] lesion length, measured as either (a) head-to-toe length or (b) longest measurement within the lesion regardless of orientation and [2] lesion extent, defined as either (a) erythema only or (b) EIE; lesion width was always measured perpendicularly to length. This resulted in four different lesion area definitions (Fig. 1). At all visits, two different investigative team members measured lesions, both using all four definitions once each.

Prospective analyses comprised: comparison of clinical response rates (i.e., ≥20% decrease in lesion area from baseline at 48 to 72 h) using different lesion area definitions (determined separately by observer), comparison of lesion area measurements obtained using different lesion area definitions (determined separately by observer), and assessment of inter-observer reliability of lesion area measurements. The study's sample size was set at 200 patients, based on anticipated ability to adequately assess adverse events.

2.3. Statistical analysis

2.3.1. Association between pain and lesion area

The associations between [1] lesion area and pain at baseline and [2] changes in lesion area and changes in pain over time were explored graphically. The data were modeled using a mixed linear model with a compound symmetry covariance matrix, where each lesion area and pain measurement within a patient were the repeated measures; the pain score (FRS or VAS) was modeled with the following three variables: percent change in lesion size, day of assessment, and the interaction of percent change in lesion size and day of visit. The purpose of this model was two-fold, to determine if there was a significant time effect and also whether there was a significant association between pain and lesion measurements across time. All statistical analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

2.3.2. Reliability of lesion area measurements

There were no pre-stated hypotheses in these analyses, which were exploratory and descriptive only. In the non-comparative Phase 2 study, we compared the four possible lesion area definitions by determining intra-class correlation coefficients (ICCs) and 95% confidence intervals