Background: The optimal duration of antibiotic therapy for soft-tissue infections of the diabetic foot remains unknown.

Objective: We determine if antibiotic therapy after debridement for a short (10 days), compared with a long (20 days), duration for soft-tissue infections of the diabetic foot results in similar rates of clinical remission and adverse events (AE).

Summary of Background Data: The optimal duration of systemic antibi- therapy, after successful debridement, for soft tissue infections of diabetic patients is unknown. Because of the high recurrence risk, over-use is commonplace.

Methods: This was a randomized, controlled, non-inferiority pilot trial of cases of diabetic foot infection (excluding osteomyelitis) with the primary outcome of “clinical remission at 2-months follow-up”.

Results: Among 66 enrolled episodes (17% females; median age 71 years), we randomized 35 to the 10-day arm and 31 to the 20-day arm. The median duration of the parenteral antibiotic therapy was 1 day, with the remainder given orally. In the intention-to-treat population, we achieved clinical remission in 27 (77%) patients in the 10-day arm compared to 22 (71%) in the 20-days arm (P = 0.57). There were a similar proportion in each arm of AE (14/35 versus 11/31; P = 0.71), and remission in the per-protocol population (25/32 vs 18/27; P = 0.32). Overall, 8 soft tissue DFIs in the 10-day arm and 5 cases in the 20-day arm recurred as a new osteomyelitis [8/35 (23%) versus 5/31 (16%); P = 0.53]. Overall, the number of recurrences limited to the soft tissues was 4 (6%). By multivariate analysis, rates of remission (intention-to-treat population, hazard ratio 0.6, 95%CI 0.3-1.1; per-protocol population 0.8, 95%CI 0.4-1.5) and AE were not significantly different with a 10-day compared to 20-day course.

Conclusions: In this randomized, controlled pilot trial, post-debridement antibiotic therapy for soft tissue DFI for 10 days gave similar (and non-inferior) rates of remission and AE to 20 days. A larger confirmatory trial is under way.

Trial registration: ClinicalTrials NCT03615807.

Keywords: adverse events; antibiotic duration; diabetic foot soft tissue infection; infection remission; randomized-controlled trial
was favorable. Another study of patients with various types of cellulitis found that clinical remission rates were similar for those treated with 7 days of systemic antibiotic therapy compared to those who received longer treatment durations.

Determining the most appropriate duration of antibiotic therapy for ST-DFIs is important, to avoid adverse outcomes both of under-treating these serious infections and overtreating them in violation of antibiotic stewardship principle. Thus, we need properly conducted randomized-controlled trials (RCT) to investigate this issue. Unfortunately, RCTs in this population are difficult to perform, due to various conceptual and practical problems. These include the confounding issues related to the: presence of limb ischemia; need for wound debridement; virulence of the pathogens; and, patient compliance. Furthermore, it is unclear if antibiotic can be discontinued when clinical signs or symptoms used to diagnose infection improve, or should be continued until they completely resolve. Moreover, recurrences of ST-DFI frequently appear with newly diagnosed bone involvement (DFO) or related to worsening ischemia. Our experience in performing antimicrobial RCTs in the DFI population, and our reviews on the antibiotic optimization in DFOs, make clear to us the need for a pilot RCT of a fixed duration of antibiotic therapy for ST-DFI. Of note, this RCT targets the therapy of ST-DFI. In contrast, it does not address the therapy of ischemia and/or the healing of diabetic foot ulcers, for which a broad literature is available.

METHODS

The enrollment for the study at Geneva University Hospitals upon which these data are based ran from 16 February 2017 to 1 October 2019. We closed the database on 31 March 2020. The Geneva Ethical Committee approved the project (BASEC 2016-01008), which we registered internationally (ClinicalTrials.gov NCT03615807). The overall study project encompassed 2 strata: 1) ST-DFIs; and, 2) DFOs. In this article we report only the results of the stratified ST-DFI trial (Fig. 1). We publish the results of the DFO trial separately.

Study Objectives, Criteria, and Definitions

We randomized all participants, in a ratio of 1:1, to a course of either short therapy (10 days ± 2 days), or long therapy (20 days ± 2 days). The study team generated the allocation sequence and sealed them in pre-fabricated envelopes. The primary aim of this study was to determine if the clinical outcome of short course therapy (remission or failure) was significantly different from that of long course therapy. The secondary objective was to compare the incidence of adverse events (AE) in each treatment arm. The choice for the fixed numbers of 10 versus 20 days was arbitrary and a practical compromise. In the literature, various reviews suggest antibiotic regimens for ST-DFI of relatively short (7–14 days) or relatively long durations (14–28 days). The IDSA guidance advocates 2–3 weeks for

FIGURE 1. Study flowchart.
moderate to severe DFIs; and the most recent International Working Group on the Diabetic Foot guidance recommends 1–2 weeks for moderate DFIs, but up to 3–4 weeks for severe, unusual, and predominantly ischemic cases. In Switzerland, surgeons often round up to 10 or 20 days. Hence, our choice of 10 and 20 days based on practical grounds and available literature.

Inclusion criteria for study enrollment were: age ≥18 years; manifestations of ST-DFI, based on definitions listed in the IDSA guidelines on diabetic foot infections; wound debrided by a qualified healthcare professional, with removal as much of the infected tissue as possible. Exclusion criteria were: presence of proven or suspected DFO by clinically, intraoperatively and per X-ray; treatment with effective antibiotic therapy for more than 96 hours immediately before enrollment; need to perform a total surgical amputation of all infected, necrotic or ischemic tissues; presence of necrotizing fasciitis involving the limb; or, presence of a remote infection requiring >10 days of therapy with a non-study antibiotic. The study details are supplied in the study protocol (Supplementary Digital Content File 1, http://links.lww.com/SLA/D429).

At the endpoint “Test-of-Cure”, we defined clinical remission as the absolute absence of clinical findings of infection and clinical failure as either a persistent, recurrent or newly acquired ST-DFI, or DFO at the original site. We defined microbiological failure as a culture-confirmed persistence or recurrence of infection at the same location with 1 or more of the same pathogens detected at enrollment. We renounced on superficial microbiological swabs for control and performed them only if there was clinical pus to swab. We accepted pressure off-loading of the affected foot as being correct if it appeared to result in avoidance of any mechanical stress on the affected extremity during most daytime activities (according to the patient’s history). To assess the wound size, we used a composite score sheet that we developed for a prior RCT. This scale (with a summed range of 4 to 30 points) was based on measured wound depth, and visual assessment of wound edges and redness (Supplemental Digital Content File 2, http://links.lww.com/SLA/D430). We defined an AE as any adverse medical occurrence during the conduct of the trial, with a serious adverse event (SAE) being 1 that that was life-threatening, or lead to substantial disability.

Study Conduct

Participation started at enrollment, which included a history, physical examination and a standard X-rays of the foot. If a given patient could be included as many times as he or she had a new ST-DFI episode in another location. The treatment period included the following (inpatient or outpatient) visits: visit 1 – Enrollment (Day 1); visit 2 – Day 10 (± 2 days); visit 3 – Day 20 (± 2 days; only if still receiving treatment after visit 2). The Test-of-Cure visit occurred at approximately 60 days (± 10 days) after the End-of-Treatment. Treating clinicians determined the frequency of wound debridement required, the method of pressure off-loading, whether or not to perform angioplasty, use negative-pressure vacuum therapy or use hyperbaric oxygen. To limit the number of antibiotic agents selected, we provided the treating clinicians a list of permitted regimens (Supplementary Digital Content File 3, http://links.lww.com/SLA/D431). We prohibited treatment with any topical antibiotics, silver dressings or antimicrobials would thus not be active against the majority of microorganisms.

We also required that any debridement be performed by healthcare workers with at least 2 years’ clinical and academic experience in diabetic foot care. Specialists in diabetology treated and monitored the glycemic control during hospitalization and most outpatient visits.

Statistical analyses

The primary outcome was the rate of clinical remission in patients with short course versus long course antibiotic therapy at a minimum follow-up of 2 months after End-of-Treatment. The secondary outcome was the incidence in these 2 groups of AEs. For the outcomes, we pre-estimated an incidence of 80% of remission, and an incidence of 20% of AE, respectively, based on prior publications. Using a binomial, categorical, non-inferiority design, with an alpha level of 5% and a statistical power of 80%, we needed 2x32 (64) episodes for each antibiotic duration group to achieve a non-inferiority margin of 25%. For the formal non-inferiority assessment, we used the t-test with a (unidirectional) confidence interval of 90%. To adjust for the case-mix, we planned a multivariate cluster-controlled Cox regression analysis with the outcome “clinical remission” (clustering on the individual patients’ level). As this was an RCT, the use of a propensity score or any other matching was unnecessary. The intention-to-treat (ITT) population consisted of all randomized and enrolled episodes. The per-protocol (PP) population included all participants who completed the study and whose treatment did not substantially deviate from the protocol. For statistical analysis we used STATA software (Version 15.0; College Station, TX).

RESULTS

Study Population

After excluding the 93 DFO patients enrolled in the overall project, there were 66 ST-DFI episodes for analysis (ITT population; Fig. 1). Overall, 11 episodes were in women (17%); the median patient age was 71 years; the median American Society of Anesthesiologists-Score was 3 points; the median transcutaneous oxygen tension was 30 mmHg (dorsal foot); the median serum C-reactive protein level at admission was 69 mg/L; and, the median body mass index was 28 kg/m². In 54 cases (82%), the patient was enrolled only once to the study. Ten patients were enrolled twice and 2 patients were enrolled 3 times during the study period. Overall, there were 49 different microbiology constellations, including Staphylococcus aureus (the most common pathogen, identified in 21 cases (32%)), streptococci (12 (18%)), gram-negative pathogens (17 (26%)) and polymicrobial infections (28 (42%)). These microbiological results based on a median of 1 deep tissue or pus sample (interquartile range (IQR), 0–3 samples) per patient. There were no positive blood cultures. The anatomic sites of ST-DFI were: a toe (n = 50); the midfoot (14); or, the hindfoot (5). Three episodes had multiple infection localizations. Overall, 42 ST-DFIs were complicated by a peripheral arterial disease (median ankle-brachial index 0.94) and 5 by Charcot arthropathy. The demographic characteristics of patients in the 2 study arms were not significantly different (Supplemental Digital Content File 4, http://links.lww.com/SLA/D432).

Treatment

In the ITT population, we randomized 35 subjects to the 10-day arm and 31 to the 20-day arm. Among all patients, thirteen (20%) underwent successful angioplasty and ten (15%)
completed a course of hyperbaric oxygen therapy (30 seances to 2 hours). The median number of surgical debridement per infection episode was 1 (IQR, 0–1 interventions), among which 31 included a partial resection of necrosis. For pressure offloading we used one or more of the following devices: Darco shoe (n = 48); specialized shoes (7); immovable plaster casts (2); axillary crutches (1); and, new insoles (1). In 8 cases, we re-emphasized to the patient the importance of adherence to using a previously provided, but underused, insole. Based on nurses’ notes and other medical information, we assessed the patient’s compliance as sufficient in 57 cases (86%), but we had limited information on patient adherence with our off-loading recommendations when they were at home. Treating clinicians prescribed 28 different antibiotic regimens, either concomitantly or sequentially, of which the most frequent agents were co-amoxiclav (n = 45); levo-fl oxacin (13), and clindamycin (1). The following allowed drugs were less often used: piperacillin/tazobactam (2), metronidazole (1), line-zolid (1), and aztreonam (never). In one case each, 3 scheduled antibiotics were replaced with co-trimoxazol, imipenem and cipro-fl oxacin due to intolerance or suspected intolerances. The median duration of the initial parenteral therapy was 1 day and the median length of hospital stay was 11 days (IQR, 3–25 d). We never prescribed levofloxacin, metronidazole or clindamycin intravenously.

**Outcomes**

After an active median follow-up period of 11 months (IQR, 5–18 mts) the outcome was clinical remission in 27 of 35 (77%) episodes in the 10-day treatment arm compared to 22 of 31 (71%) in the 20-day treatment arm (P = 0.57). Thus, there was no significant difference in the incidence of clinical remission between the 2 study arms (Supplementary Digital Content File 4, http://links.lww.com/SLA/D432 and Table 1). There were an additional ten, non-infectious failures related to progressive limb ischemia, bringing the overall number of clinical failures to 27 (41%) that occurred after a median of 39 days after the end-of-treatment. Among the 17 episodes of clinical failures that were related to infection; in 8 there was a documented microbiological recurrence (at least 1 of the same pathogens as cultured in the index episodes; 8/66; 12%), while in the other 9 the new infection was with new (not previously isolated) pathogens. Importantly, 8 ST-DFIs in the short course arm and 5 cases in the long course arm recurred as DFO (8/35 (22%) vs 5/31 (16%); P = 0.53). Hence, 76% (13/17) of all infectious recurrences presented either as a contiguous propagation of the soft tissue infection into bone or recognition of a previously missed diagnosis of DFO from the start. Only 4 recurrences (6% of the entire ST-DFI population) were limited to the soft tissues. The median Wound Score regressed from 12 to 4 points; corresponding to a median decrease of 75%. Only one patient, who was treated for newly diagnosed pyelonephritis and was excluded from the ITT population, required non-study antibiotic therapy during treatment for ST-DFI (Fig. 1).

**Adverse Events**

We noted 19 different AE that occurred in 25 separate treatment episodes (25/66; 38%), of which we classified 12 as serious (SAE). The incidence of AE was not significantly different in the 2 study arms (Supplementary Digital Content File 4, http://links.lww.com/SLA/D432). While the most serious AE were unrelated to infection (6 were due to acute ischemia, 3 to postoperative bronchial aspiration, 2 to acute gout crisis), we attributed 6 to the study-related antibiotic therapy (1 fungal intertrigo requiring topical antymycotic treatment; 1 skin rash related to clindamycin; 1 toxic skin reaction due to either co-amoxiclav or levofloxacin; 1 cardiac decompensation due to an salt load from therapy with piperacillin-tazobactam; and, 2 episodes of nausea to co-amoxiclav).

**Per-protocol Analysis**

Among the 66 ST-DFI episodes composing the ITT population, we removed 7 (11%) when constituting the PP population (Fig. 1). In the PP population, the rate of clinical remission was similar to that in the ITT population: 25 of 32 episodes in the 10-day arm versus 18 of 27 episodes in the 20-day arm (78% vs 67%; P = 0.32). The rate of AE was also similar to the ITT population and for the 2 arms: 13/32 in the short course versus 10/27 in the long course (P = 0.78). Specifically looking at antibiotic-related AEs, rates were similar in the short versus long treatment arms (2/32 versus 3/24 cases, P = 0.50).

**Multivariate Adjustment**

To further adjust for non-randomized variables, we added a cluster-controlled Cox regression analysis (Supplementary Digital Content File 5, http://links.lww.com/SLA/D433; left part). As in previous analyses, treatment with the 10-day compared to the 20-day antibiotic course did not influence the rate of clinical remission [ITT population: hazard ratio 0.6, 95% confidence interval (CI) 0.3–1.1]. The respective multivariate result in the PP population was hazard ratio 0.8, 95% CI 0.4–1.5 (Supplementary Digital Content File 5, http://links.lww.com/SLA/D433; right part). Of note, the patients’ demographics,

**TABLE 1. Characteristics of Episodes With an Outcome of Clinical Remission Versus Clinical Failure (Intention-To-Treat Population)**

| Characteristic (n = 66) | Failure n = 17 | Remission n = 49 | P-value* |
|-------------------------|---------------|-----------------|---------|
| Female sex              | 2 (12%)       | 9 (18%)         | 0.53    |
| Median age              | 68 years      | 71 years        | 0.32    |
| Median body mass index  | 28 kg/m²      | 27 kg/m²        | 0.59    |
| Clinical peripheral arterial disease | 10 (59%) | 32 (65%) | 0.63 |
| Infection due to Gram-negative pathogens | 4 (24%) | 13 (27%) | 0.81 |
| Wound Score at admission (median) | 15 points | 12 points | 0.82 |
| Number of surgical debridement (median) | 1 intervention | 1 intervention | 0.62 |
| Partial resections of necrosis | 8 (47%) | 23 (47%) | 0.99 |
| Successful angioplasty   | 4 (24%)       | 9 (18%)         | 0.65    |
| Hyperbaric O₂ therapy   | 2 (12%)       | 8 (16%)         | 0.65    |
| Median duration of initial parenteral antibiotic course | 4 days | 1 day | 0.62 |
| Adequate off-loading as assessed by nurses/clinicians | 14 (82%) | 43 (88%) | 0.58 |

*Pearson χ²-test or Wilcoxon-ranksum-tests.
pathogen groups, the degree of ischemia and the amount of inflammation failed to influence the outcome in our trial.

Non-inferiority

We analyzed a sufficient number of episodes of ST-DFI to achieve the pre-scheduled statistical non-inferiority in the ITT population. For clinical remission, the calculated confidence intervals excluded the 25% non-inferiority-margin (6.2 difference points [90% CI -24% to +12%] (ITT population). Similarly, there was statistical non-inferiority for antibiotic-related AE (7.2 difference points [90% CI -7% to +21%]) (ITT population). The corresponding results in the PP population were 11.5 difference points [90% CI -31% to +8%] (clinical remission) and 7.3 difference points [90% CI -10% to +19%] (antibiotic-related AE). Hence, we formally failed to achieve non-inferiority for clinical remission in the PP population.

DISCUSSION

The results of this single-center pilot study in adult patients with ST-DFI demonstrated that a relatively short course of antibiotic therapy (10 days) was non-inferior to a relatively long course (20 days) in terms of the likelihood of clinical remission and the incidence of AE, albeit with a fairly wide statistical margin of 25%. Overall, the rate of clinical remission for the entire study population at 2 months after treatment was 74%, which is similar to rates for treatment of ST-DFI reported in the literature, independently of the pathogen(s). AE occurred in 38%, with no significant difference between the 2 arms, which is again a rate similar to those reported in the literature, including in our own previous publication.

Unlike many other types of infections, there is no well-established duration of antibiotic therapy for soft tissue infections. Thus, therapy must be tailored according to the clinical evaluation including physical examination, inflammatory markers and sometimes imaging tests. As a general rule for all orthopedic implant-free infections, and as expected, the bacterial pathogen does not determine the duration of systemic antibiotic administration. However, these evaluations, particularly physical examination, are subjective and not strongly evidence based. Thus, clinicians are prone to extend the antibiotic duration, especially those who are in-experienced or not committed to antimicrobial stewardship principles. We thus believe that the results of RCTs like this one can help to establish reasonable a minimum and/or maximal duration of treatment. Our results, combined with the limited available data from the literature, suggest that the treatment for ST-DFI for more than 10 days is probably unnecessary.

Our RCT has many strengths, but also has 5 important limitations. First, being a pilot study with relatively few cases, we avoided separate analyses based on potential different patient strata, such as the presence of limb ischemia, or by the causative pathogen(s). Such stratification of an RCT would require a larger sample size, making it unlikely to be funded without a prior pilot study. Evidence suggests that soft tissue infections caused by b-hemolytic streptococci may be associated with more severe clinical manifestations than those caused by the staphylococci. However, this initial virulence does not appear to influence the final outcome. Similarly, in diabetic foot infections, isolation of virulent organisms such as methicillin-resistant Staphylococcus aureus, or less virulent pathogens such an anaerobes, does not appear to influence the likelihood of clinical remission, in contrast to the patient’s adherence to treatment or the presence of limb ischemia. We also noted that infection with a streptococcal pathogen was not associated with the outcomes in our RCT.

Second, while our pre-study estimated clinical remission rate of 80% matched well with the observed rate of 74%, our non-inferiority margin of 25% may appear to be too large. We suggest justifying acceptance of this large margin by: 1) the non-lethal nature of most ST-DFIs; 2) the fact that this was a pilot study; and, 3) that antibiotic agents are only one part in the multifaceted treatment of DFI.

Third, we found a strikingly high proportion of infection “recurrences” (13; 20%) that appeared to be an extension of the former soft tissue infection into the underlying bone; the rate of these treatment failures was similar for the 2 antibiotic duration arms. Of note, the proportion of true soft tissue DFI recurrences was only 6% in our ST-DFI study population. Indeed, only one ST-DFI recurrence was limited to just the soft tissues. This case was caused by S. aureus and occurred in the 20-day treatment arm. It is difficult to know in these situations if a ST-DFI evolves into DFO despite correct antibiotic therapy, or if we missed diagnosing a DFO that was present from the start. In the absence of a chronic, deep ulcer, a DFO might be missed in the early stages by both clinical evaluation and plain X-rays. It is likely that treatment of bone infection for only 10-days is likely to be too short. We recommend that any future trial aimed at confirming our findings include more decisive MRI studies at enrollment, to better exclude osteomyelitis.

Fourth, while we arbitrarily fixed the duration of antibiotic therapy in our trial, we did not ordain the route of administration. We purposely decided to leave this choice to the treating clinician, since the route of antibiotic administration does not appear to influence the outcome of therapy of localized DFIs or perhaps even for DFOs outcomes. The results of the recent landmark OVIVA trial demonstrated that there was no benefit for administering parenteral (as opposed to oral) antibiotic therapy for more than 1 week for most or thopedic infections, including DFIs. We decided against a double randomization for therapy duration and for the administration route in a patient population that is genuinely inhomogeneous, as it would have unnecessarily complicated our pilot study.

Fifth, we enrolled ST-DFI among who were hospitalized, who needed professional wound care, off-loading and bed rest, and the majority of which were moderate or severe DFI. Mild DFIs are likely to be treated by general practitioners in the ambulatory settings. This selection bias is likely to favor a short duration of antibiotic courses. Likewise, our trial targeted the infection, and not the underlying ulcer (which may or not become infected). A trial targeting ulcer healing would be much different in design and follow-up visits.

CONCLUSION

Our pilot trial suggests that a relatively short duration of post-debridement systemic antibiotic therapy (no more than 10 days) might be sufficient for treating most ST-DFI. Clearly, to increase the certainty of these preliminary results we need a larger confirmatory RCT. We started such a trial at our medical center in Zurich, using a non-inferiority margin of 10% and a pre-treatment radiological assessment with magnetic resonance imaging (MRI). This confirmatory trial will also include a higher proportion of patients treated in an outpatient setting than we enrolled in our pilot study and will assess nutritional parameters and the utility of laboratory parameters and scores and promising classifications, e.g. the Wfii classification (Wound, Ischemia, and Foot Infection) for ischemia and imminent amputation, before and during therapy. We hope this study, which we can support undertaking based...
on the findings of our pilot trial, will provide a more definitive answer to the question of the required duration of antibiotic therapy for ST-DFI.8

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