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Published Ahead of Print 4 May 2009.

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Multicenter, Randomized Study of the Efficacy and Safety of Intravenous Iclaprim in Complicated Skin and Skin Structure Infections

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Received 15 October 2008/Returned for modification 29 December 2008/Accepted 29 April 2009

Iclaprim is a novel antibacterial agent that is currently in development for the treatment of complicated skin and skin structure infections (cSSSI). Iclaprim specifically and selectively inhibits bacterial dihydrofolate reductase, a critical enzyme in the bacterial folate pathway, and exhibits an extended spectrum of activity against various resistant pathogens, including methicillin (meticillin)-resistant Staphylococcus aureus (MRSA). The objective of this randomized, double-blind phase II study was to compare the efficacy and safety of iclaprim to those of vancomycin in patients with cSSSI. Patients were randomized to receive 0.8 mg iclaprim/kg of body weight, 1.6 mg/kg iclaprim, or 1 g vancomycin twice a day for 10 days. Clinical cure rates for the 0.8- and 1.6-mg/kg-iclaprim treatment groups were comparable to that for the vancomycin treatment group (28/28 patients [92.9%], 28/31 patients [90.3%], and 26/28 patients [92.9%], respectively). Iclaprim also showed high microbiological eradication rates. Iclaprim exhibited an eradication rate of 80% and 72% versus 59% observed with vancomycin for S. aureus, the pathogen most frequently isolated at baseline. Five MRSA cases were observed, four in the 0.8-mg/kg-iclaprim arm and one in the vancomycin arm, and all were both clinically and microbiologically cured. Iclaprim exhibited a safety profile similar to that of vancomycin, an established drug for the treatment of cSSSI. Results from this study indicate that iclaprim is a promising new therapy for the treatment of cSSSI, in particular those caused by S. aureus, including MRSA.
(6, 16). In addition, iclaprim in vitro is rapidly bactericidal to many pathogens at concentrations close to its MIC, achieving 99.9% reductions in bacterial loads of pathogens (such as MRSA and VISA) within 6 h, and demonstrates a postantibiotic effect lasting up to several hours (4, 7). Microbiological studies of a wide variety of pathogens from the United States and Europe have demonstrated that iclaprim has an extended spectrum of activity and is more potent than TMP against major gram-positive pathogens, particularly *S. aureus* and other streptococci, including strains resistant to TMP, methicillin and oxacillin, macrolides, quinolones, and glycopeptides, including VISA and vancomycin-resistant *S. aureus* (5, 16, 19).

This is the first report describing the clinical efficacy and safety of intravenous (i.v.) iclaprim in comparison to those of vancomycin for the treatment of patients with cSSSI.

(This work was presented in part at the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy [9].)

**MATERIALS AND METHODS**

**Study design.** This study was a randomized, double-blind, phase II study conducted at seven centers in three countries. Patients with cSSSI were randomized to receive either 0.8 mg i.v. iclaprim/kg of body weight, 1.6 mg/kg iclaprim, or 1 g vancomycin twice a day for 10 days. Patients received twice-daily 30-min i.v. infusions of iclaprim, followed by 30-min infusions of N-saline solution or a 60-min infusion of vancomycin. Iclaprim was administered i.v. to patients for 10 days (day 10 was the end of therapy [EOT]). The dosage of vancomycin was adjusted for patients with a protocol-acceptable degree of renal impairment. The final assessment was carried out at 20 ± 5 days after the EOT at the test of cure (TOC) visit.

This trial was conducted in accordance with the Declaration of Helsinki (26), with good clinical practices of the International Conference on Harmonisation, with the Food and Drug Administration (FDA) Code of Federal Regulations (25), and with all applicable local laws and regulations.

**Patient population.** Hospitalized patients between the ages of 18 and 65 years with clinical evidence of cSSSI were entered into the study. Eligibility criteria included infected ulcers, burns, or major abscesses; deep or extensive cellulitis; infected catheter sites (without a catheter); infected human or animal bites; and superficial infections of abscesses at high risk of infection due to MRSA. Eligible patients were required to have at least two of the following five signs or symptoms: drainage or discharge, erythema, swelling or induration, heat or localized warmth, and pain or tenderness to palpation. Patients with severe illness likely to lead to amputation of the infected site or death were not enrolled. Patients with abnormal electrocardiogram (ECG) values; necrotizing fasciitis; gangrene; other uncontrolled SSSI; fungal, parasitic, or viral infections; immune deficiency disease; recent cancer or renal disease; concurrent infection requiring a specific antibiotic; infected diabetic foot ulcer; chronic decubitus ulcer; infections associated with a permanent prosthetic device; and infections requiring more than 10 days of antibiotic therapy or treatable only by surgery were all excluded. Patients who had recently taken other investigative agents, oral steroids, other systemic or topical antibiotics or drugs that could interfere with the study medication, or drugs that could induce ECG changes were also excluded. Patients who had received concomitant medication for diabetes or the prevention of hyperglycemic: four in each group received insulin, one patient in each of the iclaprim

**RESULTS**

**Patient demographics and baseline characteristics.** Ninety-two patients were enrolled into the study at seven centers, and all were randomized to receive treatment (30 patients received iclaprim at 0.8 mg/kg, 32 patients received iclaprim at 1.6 mg/kg, and 30 patients received vancomycin). Eighty-six patients completed the treatment period, and 84 patients completed the study (eight patients discontinued the study prematurely; three of these were due to AEs, three were lost to follow-up, one withdrew consent, and one was eliminated due to temporary interruption of the study for implementation of the amendment of the study protocol). Withdrawal was not associated with any particular treatment group. Mean overall compliance with treatment in this study was 98.4%.

Eighty-seven patients were included in the ITT population, which included all patients with a postrandomization efficacy assessment, and 84 were clinically evaluable. There were no clinically significant differences between the groups with respect to demographics at baseline (Table 1). Approximately 50% of patients in each group had a physical abnormality at baseline, the most frequent being the lymph nodes proximal to the site of the infection and of the skin. Mean creatinine clearance levels were similar in all groups, with only seven patients falling into the category of mild renal dysfunction (50 to 80 ml/min).

All patients received adjunctive therapy (such as debride ment and dressing changes) for the infection during the study period, and there were no significant differences between the groups. Fourteen patients received concomitant medication for diabetes or the prevention of hyperglycemic: four in each group received insulin, one patient in each of the iclaprim
groups received metformin, and one of these also received glimepiride.

Patients in whom Gram staining of culturable material indicated the presence of gram-negative organisms were permitted to receive aztreonam. There were no differences between the groups with respect to aztreonam administration, with four patients in each group receiving aztreonam. Patients in whom anaerobic pathogens were isolated from their infection site received metronidazole as a concomitant medication. A total of four patients received metronidazole therapy, two in the 0.8-mg/kg-iclaprim group and two in the vancomycin group.

All patients except one of the ITT population presented at screening with all five sign or symptom categories of acute infection defined in the inclusion criteria (one patient in the 1.6-mg/kg-iclaprim arm had only four signs or symptoms); the protocol requested the presence of at least two of these. This is clear evidence that the patients included in this study had severe cSSSI. The eight individual signs and symptoms were balanced across each study arm, with over 89% of patients in all treatment groups experiencing each single sign and symptom. The only exception was with drainage, which was experienced by only approximately 30% of patients in each treatment group. Infection types recorded were ulcer (35%), burn (25%), cellulitis (22%), major abscess (15%), and animal bite (3%). There were no significant differences in the compositions of the treatment groups with respect to infection type.

In all treatment groups, there was a large variation in the extents of the infection sites at screening. Median length, width, and depth measurements were 160 by 100 by 6 mm for the 0.8-mg/kg-iclaprim group, 150 by 92.5 by 7 mm for the 1.6-mg/kg-iclaprim group, and 120 by 60 by 5 mm for the vancomycin group. Taken together, the median length, width, and depth were the smallest in the vancomycin group. Likewise, the proportions of patients with full-thickness tissue involvement were high in the 0.8-mg/kg and 1.6-mg/kg-iclaprim groups (57.1% and 64.5%) compared to that of the vancomycin group (42.9%).

Eighty-four gram-positive pathogens of 15 different species and 35 gram-negative pathogens of 12 different species were isolated at baseline. The most frequently isolated gram-positive pathogens are shown in Fig. 1; all other species were single cases only. There were no significant differences between the groups in terms of the distribution of isolated pathogens.

**Clinical response.** Clinical cure rates in the ITT population at the TOC visit were comparable for all groups: 92.9% for iclaprim at 0.8 mg/kg, 90.3% for iclaprim at 1.6 mg/kg, and 92.9% for vancomycin.

At the TOC visit, all signs or symptoms had resolved or improved, with no obvious differences between the treatment groups (Table 2). For most patients (>80%), drainage, erythema, swelling, heat, localized warmth, and pain completely resolved, whereas across all groups, induration, discharge, and tenderness on palpation improved for up to half of the patients. There were no differences between the treatment groups with respect to time to resolution of each sign or symptom.

The overall median extent of the infection site decreased to less than 2% of its original size at the TOC visit in all treatment groups. Similarly, the proportion of patients presenting with full-thickness tissue involvement at the TOC visit decreased to 0% (0/28 patients), 6.5% (2/31 patients), and 3.6% (1/28 patients) in the 0.8-mg/kg-iclaprim, 1.6-mg/kg-iclaprim, and vancomycin groups, respectively.

There were two treatment failures in the 0.8-mg/kg-iclaprim group; both were categorized as failures due to the clinical requirement to continue therapy beyond 10 days. One patient had a large infected gluteal abscess, and the other had an extensive infected lower-leg ulcer. The causative baseline *S. aureus* isolates were, in fact, in both cases highly susceptible to iclaprim (MIC ≤ 0.25 mg/liter), but the extents of the infection in both cases required antibiotic therapy beyond the allowed study medication period of 10 days. There were two failures, and one patient was lost to follow-up in the 1.6-mg/kg-iclaprim
group; one failure was so classified because of a diagnosis of osteomyelitis, and the other failure, which was due to large full-thickness cellulitis, required additional antibiotic therapy with penicillin. In the vancomycin group, one withdrawal occurred due to an AE (dermatitis medicamentosa), and one patient was lost to follow-up.

Microbiological efficacy. The high clinical cure rates achieved for each of the groups in this study were paralleled by high microbiological eradication rates for gram-positive pathogens (Fig. 2). The most frequently isolated pathogen at baseline was \textit{S. aureus} (50/87 patients [57%]), followed by \textit{S. pyogenes} (7/87 patients [8%]). Eradication rates for gram-positive pathogens at the TOC visit were 26/29 patients (90%) for iclaprim at 0.8 mg/kg, 24/30 (80%) for iclaprim at 1.6 mg/kg, and 18/25 (72%) for vancomycin. Eradication rates for \textit{S. aureus} were 12/15 patients (80%), 13/18 patients (72%), and 10/17 patients (59%), respectively. Five out of 50 \textit{S. aureus} isolates were methicillin resistant (four for which the MICs of oxacillin were \(\geq 16\) mg/liter and one for which the MIC of oxacillin was 4 mg/liter) (Fig. 3). Four of the MRSA isolates were present in the 0.8-mg/kg-iclaprim group, and one was present in vancomycin group. All patients with MRSA were clinically and microbiologically cured.

Only three patients in the 0.8-mg/kg-iclaprim group had \textit{S. aureus} present at the TOC visit; one of these was considered a clinical cure at the EOT and TOC, while the remaining two required further treatment with doxycycline and gentamicin, respectively, and were considered treatment failures. Five patients in the 1.6-mg/kg-iclaprim group had \textit{S. aureus} isolated at the TOC visit, of which three were clinically cured. Of the remaining two patients, one had osteomyelitis and the other had full-thickness cellulitis that required treatment with penicillin. The eradication rate of \textit{S. aureus} was lower in the vancomycin group, with 7/17 patients having \textit{S. aureus} present at the TOC visit. However, all patients were considered to be clinically cured except for one, who had to be withdrawn due to dermatitis medicamentosa.

MRSA was identified in five patients at baseline, four patients in the 0.8-mg/kg-iclaprim group, and one patient in the vancomycin group. All of these patients were considered to be clinically cured at the TOC visit, and in all cases, the baseline MRSA pathogen was eradicated.

Since gram-negative pathogens were not expected to be eradicated by vancomycin, comedication with aztreonam was permitted in this study in both the vancomycin and iclaprim arms, with a total of 12 patients receiving aztreonam treatment.

In summary, the clinical cure rates were comparable in all three treatment groups and were higher than 90%. The majority of cases were cured at day 10. There were no differences between the groups in terms of clinical cure by infection type or causative pathogen, although eradication rates of gram-positive pathogens were higher in the iclaprim groups than in

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### TABLE 2. Signs and symptoms of acute infection in the CE population at the TOC visit

<table>
<thead>
<tr>
<th>Sign or symptom</th>
<th>No. (%) of CE patients ((n = 84)) administered the following drug with the indicated result:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Iclaprim at 0.8 mg/kg ((n = 28))</td>
</tr>
<tr>
<td></td>
<td>Resolved</td>
</tr>
<tr>
<td>Drainage</td>
<td>8 (88.9)</td>
</tr>
<tr>
<td>Discharge</td>
<td>18 (66.7)</td>
</tr>
<tr>
<td>Erythema</td>
<td>25 (89.3)</td>
</tr>
<tr>
<td>Swelling</td>
<td>27 (96.4)</td>
</tr>
<tr>
<td>Induration</td>
<td>12 (48.0)</td>
</tr>
<tr>
<td>Heat</td>
<td>25 (96.2)</td>
</tr>
<tr>
<td>Localized warmth</td>
<td>28 (100)</td>
</tr>
<tr>
<td>Pain</td>
<td>27 (100)</td>
</tr>
<tr>
<td>Tenderness to palpation</td>
<td>17 (60.7)</td>
</tr>
</tbody>
</table>

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FIG. 2. Bacteriological response at the TOC (ITT population).

FIG. 3. MIC distributions of iclaprim, vancomycin, and oxacillin against \textit{S. aureus} isolates at baseline.
the vancomycin group. Approximately 10% of all S. aureus strains isolated at baseline were MRSA (four in the 0.8-mg/kg-iclaprim group and one in the vancomycin group); all were eradicated, and the patients were considered clinically cured.

Safety and tolerability. The safety population included all 92 randomized patients who took at least one dose of study medication. Overall, iclaprim was well tolerated in the study, with the 0.8-mg/kg group showing a slightly more favorable profile than the group on the higher dose.

AEs. Forty-five patients reported 66 treatment-emergent AEs, with the highest incidence occurring in the 1.6-mg/kg-iclaprim group: 19/32 patients (59.4%), compared to 14/30 patients (46.7%) in the vancomycin group and 12/30 patients (40.0%) in the 0.8-mg/kg-iclaprim group (Table 3). Numbers of AEs were low and comparable across all treatment groups. AEs were most frequent in cases of infections, infestations, and thermal burns, but they were considered to be related to the underlying type of infection that formed the basis for inclusion in this study. The second most frequently occurring AEs were laboratory findings (per the system organ classification of investigations) for 2/30 patients [6.7%] in the 0.8-mg/kg-iclaprim group, 6/32 patients [18.8%] in the 1.6-mg/kg-iclaprim group, and 2/30 patients [6.7%] in the vancomycin group.

Five patients experienced five nonserious AEs that were considered related to study drug: two patients (6.3%) with two events in the 1.6-mg/kg-iclaprim group (pruritus and erythema) and three patients (10.0%) with three events in the vancomycin group (tremor, pruritus, and dermatitis medicamentosa). No drug-related AEs were recorded in the 0.8-mg/kg-iclaprim group. All nonserious AEs were of mild or moderate intensity, and all patients recovered from their AEs, although the patient with dermatitis medicamentosa in the vancomycin group withdrew from the study as a result of the AE.

Serious AEs. One patient in the 0.8-mg/kg-iclaprim group was diagnosed with severe sepsis and died on day 3 of the treatment period due to multiorgan failure. The death was not considered to be related to the study drug. Six serious AEs were reported for this patient (face edema, pneumonia, sepsis, multiorgan failure, acute respiratory distress syndrome, and cavernous sinus thrombosis). Osteomyelitis was reported for one patient in the 1.6-mg/kg-iclaprim group, and pneumonia was reported for one vancomycin patient, both of which were considered unrelated to the study medication. Both patients were withdrawn from the study.

Shifts from normal baseline laboratory values were infrequent in all groups. There was a decrease in mean heart rate and temperature, within normal limits, which was probably due to resolution of the infection.

ECG monitoring. Only routine ECG monitoring was performed in this study until the introduction of a protocol amendment. This amendment was implemented when results from a phase I study suggested that iclaprim had mild QT-prolongation effects. The resulting amendment required more extensive ECG monitoring at various times throughout treatment (at pretreatment; on days 1, 3, and 10; and between 6 and 12 h following the last infusion of study medication) and was performed for a total of 48 patients.

The observed increases in QT measurements were mild and transient. No increases in QT intervals corrected for heart rate using Fridericia’s formula (QTcF intervals) of >60 ms from baseline were observed throughout the study. All QTcF intervals immediately following termination of the infusion were below 500 ms, and no cardiac-rhythm disturbances related to the prolongation of the QT interval were observed. Furthermore, no new cardiac rhythm disturbances were registered during the ECG monitoring period. AEs related to cardiac-rhythm disturbances were not reported in this study.

**DISCUSSION**

This is the first study exploring the safety and efficacy of the novel antibacterial agent iclaprim in patients with cSSTI. This phase II study was designed to compare 0.8 mg/kg and 1.6 mg/kg iclaprim with vancomycin, the current standard therapy for MRSA. A total of 92 patients were enrolled in this study at
seven centers, and all were randomized to receive treatment with either iclaprim or vancomycin. All patients enrolled in this study were diagnosed with severe cSSSI based upon the combination of local and systemic signs and symptoms of infection; all but one patient presented with all five sign and symptom categories evaluated at screening. Over 90% of these patients were clinically and microbiologically evaluable.

The overall results from this study suggest that both doses of iclaprim had efficacy profiles similar to those of vancomycin, with nearly all patients in the ITT population achieving clinical cure. Although no statistical conclusions can be drawn, results from this phase II study suggest that iclaprim is comparable to vancomycin with respect to clinical efficacy and safety. The clinical cure rates at the TOC visit were comparable across all treatment groups and were higher than 90% in the three study arms (92.9% in the 0.8-mg/kg-iclaprim group, 90.3% in the 1.6-mg/kg-iclaprim group, and 92.9% in the vancomycin group). There were no obvious differences between the treatment groups in terms of clinical cure by infection type or causative pathogen.

The clinical-cure rates for iclaprim were reflected by the high microbiological eradication rates. The most frequently isolated causative gram-positive pathogen in this study was S. aureus, followed by S. pyogenes. S. aureus was isolated in over half of the patients at baseline. Among these patients, five had MRSA (four for which the oxacillin MIC was >16 mg/liter and one for which the oxacillin MIC was 4 mg/liter). The majority of all baseline pathogens were eradicated in all groups by the time of the TOC visit, but eradication rates for gram-positive pathogens were slightly higher in both iclaprim groups than in the vancomycin group. All five cases with MRSA infection, four of which were in the 0.8-mg/kg-iclaprim group, resulted in clinical cure and eradication of the baseline pathogen. These results suggest that iclaprim is effective against gram-positive pathogens, including MRSA.

This study was not designed to assess the activity of iclaprim against gram-negative or anaerobic pathogens. As such, comedication with aztreonam and metronidazole was permitted. Previous in vitro data showed that iclaprim is also active against gram-negative pathogens but less active against anaerobes (10). Importantly, iclaprim exhibited neither antagonism nor synergy in combination with aztreonam or metronidazole in vitro checkerboard studies with gram-negative bacteria and anaerobes (10).

The data from this study raised no concerns regarding the safety of iclaprim; overall, both doses were well tolerated in this study. Fewer treatment-emergent AEs were observed in the 0.8-mg/kg-iclaprim group (in 40% of patients) than in the vancomycin (46.7%) and 1.6-mg/kg-iclaprim (59.4%) groups. Among the patients reporting AEs considered related to the study drug, two were from the 1.6-mg/kg-iclaprim group and three were from the vancomycin group. No drug-related AEs were reported in the 0.8-mg/kg-iclaprim group. No QTcF interval increases of >60 ms were recorded; likewise, no treatment-related cardiac-rhythm disturbances were observed. Comparison of the efficacy and safety results between the iclaprim treatment groups suggests that the 0.8-mg/kg-iclaprim dose confers the same efficacy as the higher dose, while minimizing AEs.

Until recently, vancomycin was one of the few agents available for the treatment of MRSA infections with multidrug resistance. However, the widespread use of vancomycin has triggered a rise in vancomycin-resistant bacterial strains, thus highlighting the need for the development of new antibiotic agents for the treatment of MRSA. The results from this study suggest that the DHFR inhibitor iclaprim is a safe and effective treatment for cSSSI caused by gram-positive pathogens, including MRSA. The use of iclaprim resulted in high eradication rates of gram-positive pathogens, including MRSA. Both doses of iclaprim achieved high clinical cure rates and were well tolerated in this study, and no serious AEs were related to the study drug.

ACKNOWLEDGMENT

This study was sponsored by Arpida Ltd., Reinach, Switzerland.

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