SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: MERREM™

ACTIVE INGREDIENT: meropenem

Trial title (number): Multicenter Nonrandomized Trial of Intravenous MERREM™ (Meropenem, ICI 194,660) for the Treatment of Hospital-Acquired Pneumonia (3591US/0020)

Clinical phase: IIIb

First patient recruited: 24 June 1997
Last patient completed: 15 April 1999
AstraZeneca approval date: 14 August 2000

Principal investigator and location (center number):

Publications/Presentations: None at the time of report preparation

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OBJECTIVES

To acquire additional patients to evaluate the efficacy of intravenous meropenem for the treatment of hospital-acquired pneumonia

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METHODS

Design: The trial was a prospective, multicenter, nonrandomized, noncomparative evaluation of intravenous meropenem.

Population: Approximately 250 hospitalized male and female patients 13 years of age or older who had clinically, radiologically, and microbiologically confirmed hospital-acquired bacterial pneumonia were sought for enrollment in the trial, to provide 80 to 100 evaluable patients.
Key inclusion criteria: Hospitalized patients who had clinically, radiologically, and microbiologically confirmed hospital-acquired bacterial pneumonia; signed informed consent provided by the patient, parent, or legal guardian; isolation of pretreatment pathogen(s) susceptible to meropenem. Patients could either be hospitalized in an acute-care facility with development of pneumonia at least 72 hours after admission; be residents of an extended-care facility who had been transferred to an acute-care facility with pneumonia; or have multiple trauma or head trauma requiring intubation or assisted ventilation, with development of pneumonia less than 72 hours after admission. Patients who had received prior antimicrobial therapy for more than 24 hours could be entered only if a persistent positive culture was documented and the patient had not responded clinically.
Key exclusion criteria: Known bronchial obstruction or history of postobstructive pneumonia; primary lung cancer or another metastatic malignancy to the lungs; cystic fibrosis, human immunodeficiency virus (HIV), acquired immune deficiency syndrome, or active tuberculosis
Dosage: Eligible patients were assigned to receive meropenem 1g every 8 hours, with reduced dosages for patients with creatinine clearance less than 51 ml/min. Doses of meropenem were administered intravenously by infusion over a 15- to 30-minute period or by bolus injection over 3 to 5 minutes. The recommended treatment duration was 5 to 10 days depending on the patient's response. Based on the investigator's discretion, meropenem therapy could be changed to an oral antimicrobial agent after a minimum of 72 hours of intravenous meropenem according to a strict set of switching criteria.
Key assessments: Before treatment, patients were assessed for clinical, radiologic, and microbiologic (Gram stain) evidence of bacterial pneumonia. In addition, respiratory secretions and blood were cultured for pathogen isolation, identification, and susceptibility testing. During treatment, daily clinical signs and symptoms, and adverse events, withdrawals because of adverse events, and deaths were recorded. At the end of treatment, clinical laboratory, microbiologic, and follow-up radiologic assessments were performed. Overall clinical and microbiologic responses were assessed at the end of meropenem treatment and 7 to 14 days (up to 28 days was allowed) after completion of all antimicrobial treatment. At end of treatment, clinical response was judged as satisfactory (cure or improvement), unsatisfactory (failure), or indeterminate; at follow-up, clinical response was judged as satisfactory (cure), unsatisfactory (failure or relapse), or indeterminate. At end of treatment, microbiologic response was judged as satisfactory (eradication, presumed eradication, colonization), unsatisfactory (documented persistence, presumed persistence, or superinfection), or indeterminate. At follow-up, microbiologic response was judged as satisfactory (eradication, presumed eradication, colonization), unsatisfactory (recurrence, reinfection), or indeterminate.

Statistical considerations: The primary efficacy measure was clinical response at follow-up (7 to 14 days after completion of all antimicrobial treatment [up to 28 days was allowed]). Secondary measures were clinical and microbiologic responses at the end of meropenem therapy and microbiologic response at follow-up. The proportion of evaluable patients with satisfactory responses for each of these 4 end points was summarized. Adverse event and clinical laboratory data were summarized for all patients who received at least 1 dose of trial medication.

RESULTS

Demography: A total of 254 patients from 28 centers in the United States were given meropenem treatment. Of the 254 patients, 111 (44%) were considered fully evaluable for clinical and microbiological assessments of efficacy. Overall demographic (ie, sex, age, ethnic origin) and clinical (ie, general condition, infection characteristics) characteristics were generally similar between all patients and evaluable patients.

The mean duration of meropenem treatment among fully evaluable patients was 9.3 days (range 3 to 17 days). The duration of oral antimicrobial therapy for fully evaluable patients who switched to oral therapy at the end of meropenem treatment (n=15) ranged from 1 to 15 days (mean 7.0 days).

Efficacy: For fully evaluable patients, at end of treatment, the rates of satisfactory clinical and microbiologic responses were 74% and 79%, respectively. At follow-up, the rates of satisfactory clinical and microbiologic responses were 64% and 74%, respectively (follow-up clinical response was the primary measure of efficacy). For both time points (end of treatment and follow-up), the microbiologic success rates were slightly higher compared to the clinical success rates which may be due to the underlying clinical condition of some of the patients. Half (51%) of the patients were in poor clinical condition at the start of the trial and 54% of the patients had ventilator-associated pneumonia at the start of the trial. Table I summarizes clinical and microbiologic response rates.

Table I Clinical and microbiologic outcomes - fully evaluable patients

Response	End of treatment	Follow-up
Clinical response N=111		
Satisfactory		
Cured	52	71
Improved	30	NA
Satisfactory response rate, n (%)	82 (73.9)	71 (64.0)
Unsatisfactory		
Failure	29	31
Relapse	NA	9
Microbiologic response N=111		
Satisfactory		
Eradication	19	13
Presumed eradication	55	59
Colonization	14	10
Satisfactory response rate, n (%)	88 (79.3)	82 (73.9)
Unsatisfactory		
Documented persistence	1	1
Presumed persistence	10	10
Superinfection	12	12
Recurrence	NA	3
Relapse	NA	3

[a] Clinical failures at end of treatment did not require follow-up (clinical response remained failure at follow-up for these patients).
NA Not applicable.
N Number of patients in population.
n Number of patients with response.

Meropenem was effective in eradicating pathogens commonly associated with hospital-acquired bacterial pneumonia. As shown in Table II, the most common pretreatment pathogens were *S. aureus* (25 patients, 27 isolates), *H. influenzae* (21 patients), *P. aeruginosa* (17 patients), *S. pneumoniae* (14 patients, 16 isolates), and *K. pneumoniae* (13 patients). Satisfactory response rates (eradication or presumed eradication) for these pathogens were 80%, 95%, 65%, 86%, and 85%, respectively. A total of 10 patients had pathogens of the *Acinetobacter* genus cultured pretreatment (note: 2 patients each had 2 different species of *Acinetobacter* [thus n=12 in Table II], and 1 patient had *A. calcoaceticus* cultered in both blood and sputum, thus a total of 13 pathogens were isolated). In addition, a total of 11 patients had pathogens of the *Enterobacter* genus cultured pretreatment (note: 1 patient had 2 different species of *Enterobacter* cultured pretreatment, and 1 patient had *E. sakazakii* cultured, which was not listed in Table II, thus n=11 in Table II). Satifactory response rates for these genera were 80% (8 of 10 for *Acinetobacter*) and 100% (11 of 11 for *Enterobacter*).

Table II Satisfactory response rates for pretreatment pathogens - fully evaluable patients

Pathogen	Number of pretreatment pathogens[a]	Number of patients with pathogen (N=111)	Number (%) of patients with satisfactory response[b]
Gram-positive aerobes			
Staphylococcus aureus	27	25	20 (80.0)
Staphylococcus sp	2	2	2 (100)
S*treptococcus pneumoniae*	16	14	12 (85.7)
S. viridans grp, nos	3	3	3 (100)
S*treptococcus* sp	2	2	2 (100)
Gram-negative aerobes			
Acinetobacter baumanii	4	4	3 (75.0)
Acinetobacter calcoaceticus	9	8	6 (75.0)
Branhamella (Moraxella) catarrhalis	5	5	5 (100)
Enterobacter aerogenes	2	2	2 (100)
Enterobacter cloacae	7	7	7 (100)
Enterobacter sp	2	2	2 (100)
Escherichia coli	8	8	8 (100)
Haemophilus influenzae	21	21	20 (95.2)
Haemophilus parainfluenzae	4	4	4 (100)
Klebsiella oxytoca	3	3	3 (100)
Klebsiella pneumoniae	13	13	11 (84.6)
Pseudomonas aeruginosa	17	17	11 (64.7)
Proteus mirabilis	5	5	5 (100)
Serratia marcescens	4	4	3 (75.0)

[a] Pathogens listed are those that occurred in more than 1 patient. Pathogens were counted once per culture source; therefore, more than 1 pathogen per patient may be represented.

[b] Response was determined using pathogen and microbiologic results obtained from end of treatment through follow-up. Satisfactory response is defined as eradication, presumed eradication of the pretreatment pathogen. In cases of superinfection or reinfection, only the response of the pretreatment pathogen was assessed. Responses are based on the number of patients with each pathogen (ie, patients with more than 1 culture source per pathogen are counted only once).

N Total number of patients.

Table III shows clinical response by pathogen for patients with the most common pretreatment pathogens (*S. aureus*, *H. influenzae, P. aeruginosa*, *S. pneumoniae*, and *K. pneumoniae)* and for those with pathogens which belonged to a genus identified in 10 or more patients (*Acinetobacter* and *Enterobacter*, n=10 and n=11 patients, respectively*)*. For the 5 most common organisms, satisfactory clinical response (cured or improved) rates at end of treatment ranged from 71% (*P. aeruginosa*) to 81% (*H. influenzae*) and at follow-up ranged from 47% (*P. aeruginosa*) to 76% (*H. influenzae)*. Satisfactory clinical response rates for *Acinetobacter* and *Enterobacter*

genera were 80% (8 of 10) and 82% (9 of 11), respectively, at end of treatment and 70% (7 of 10) and 82% (9 of 11), respectively, at follow-up.

Table III Satisfactory clinical response rates by pretreatment pathogen - fully evaluable patients

Pathogen[a]	Number of patients with pathogen (N=111)	Number (%) of patients with satisfactory clinical response[b]	
		End of treatment	Follow-up
S. aureus	25	19 (76.0)	15 (60.0)
S. pneumoniae	14	11 (78.6)	10 (71.4)
H. influenzae	21	17 (81.0)	16 (76.2)
K. pneumoniae	13	10 (76.9)	9 (69.2)
P. aeruginosa	17	12 (70.6)	8 (47.1)
A. baumanii	4	4 (100)	3 (75.0)
A. calcoaceticus	8	6 (75.0)	5 (62.5)
E. aerogenes	2	2 (100)	2 (100)
E. cloacae	7	6 (85.7)	6 (85.7)
Enterobacter sp	2	2 (100)	2 (100)
E. sakazakii	1	0	0

[a] Pathogens listed are those that occurred in at least 10 patients, either individually or as a group (genus). A patient may have more than 1 organism.
[b] Clinical cure or improvement.
N Total number of patients.

Of the 111 fully evaluable patients, 60 (54%) patients had ventilator-associated pneumonia. A higher percentage of patients with ventilator-associated pneumonia were younger (33% were aged 18 to 44 years and only 17% were ≥75 years), were in critical condition (30%) at entry into the trial, and had a longer mean duration of dosing (9.8 days) compared to patients with non–ventilator-associated pneumonia (12% were aged 18 to 44 years and 45% were ≥75 years, 0% were in critical condition, and mean duration of dosing was 8.6 days). For patients with ventilator-associated pneumonia, the success rates for clinical and microbiologic responses were 68% and 75%, respectively, at end of treatment, and 63% and 72%, respectively, at follow-up. As expected, patients with non–ventilator-associated pneumonia had higher success rates for clinical and microbiologic responses at end of treatment (80% and 84%, respectively) compared to ventilated patients but response rates for the 2 groups were similar at follow-up (65% and 77%, respectively).

Of the 111 fully evaluable patients, 15 (14%) patients switched to oral therapy at the end of meropenem treatment. For these 15 patients, the success rates for clinical and microbiologic responses at end of treatment were 100% for each, and the success rates for clinical and microbiologic responses at follow-up were 80% and 100%, respectively. For 96 patients who did not switch to oral treatment at the end of meropenem treatment, the success rates for clinical and microbiologic responses at end of treatment were 70% and 76%, respectively, and the

success rates for clinical and microbiologic responses at follow-up were 62% and 70%, respectively.

A total of 127 patients were clinically evaluable, which includes 111 fully evaluable patients and 16 patients who were clinically evaluable only. These 16 patients were considered not fully evaluable microbiologically because of protocol deviations (although microbiologic responses were determined for 13 of the 16 patients). Clinical and microbiologic success rates for clinically evaluable patients (end of treatment, 76% and 80%, respectively, follow-up 65% and 75%, respectively) were slightly better than for fully evaluable patients (presented above); however, microbiologic assessments for the 16 clinically-evaluable-only patients did not meet all the protocol requirements for full evaluability.

Safety: Safety was evaluated in the 254 patients who were given meropenem treatment. Thirty-one patients (12%) had at least 1 adverse event that the investigator considered to be drug related. The most common drug-related adverse events were diarrhea (7 patients, 2.8%), liver function abnormality (4 patients, 1.6%), increased ALT (4 patients, 1.6%), and increased AST (4 patients, 1.6%). Although 4 patients (1.6%) had drug-related adverse events of liver function tests abnormal, 5 additional patients had drug-related adverse events of increased AST and/or ALT, for a total incidence of drug-related adverse events related to elevated liver enzymes of 3.5% (9 of 254 patients). Only 1 patient (0.4%) had anemia that was considered drug related. Eight patients (3.1%) had an adverse event that led to trial withdrawal. For only 1 of the 8 patients were the adverse events leading to withdrawal (rash and pruritus) considered related to meropenem treatment.

A total of 58 deaths (22.8%) were reported: 17 occurred during trial treatment, 22 occurred within 7 days after discontinuation of trial medication, and 19 occurred from 7 to 30 days after discontinuation of trial medication. None of the deaths was considered related to trial treatment by the investigators.

A total of 40 patients (15.7%) had nonfatal serious adverse events (33 patients had nonfatal serious adverse events only and 7 patients had both fatal and nonfatal serious adverse events). Of 53 nonfatal serious adverse events, the majority were respiratory (19) or cardiovascular events (16). Serious adverse events of seizure were reported in 2 patients; in neither case was the seizure considered drug related by the investigator. Worsening seizure activity led to death in 1 patient (seizures were present prior to trial entry) and the other patient died of cardiac arrest 3 days after worsening seizure activity was reported (24 days after meropenem treatment ended).

Thirty patients (11.8% of those who received meropenem) had an increase in ALT or AST to more than 3 times the baseline value. For the 13 patients who had follow-up values obtained after peak elevations, all follow-up values showed either a return to baseline values or a marked improvement from the peak elevations.

Thirty patients (11.8% of those who received meropenem) had a decrease in hemoglobin of at least ≥2.5 g/dl. The majority of these patients (22 of 30) were 65 years of age or older and many had severe active disease and were having frequent blood draws. Anemia is not uncommon in these hospitalized patients. Seven of the 30 patients had adverse events related to clinical bleeding, none of which was considered drug related by the investigator.