AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Not applicable. This was a non product related study.
ACTIVE INGREDIENT: Not applicable. This was a non product related study.

Study No: NIS-IEU-DUM-2010/1
Observational study to assess clinical management patterns in patients with hospitalised Community-Acquired Pneumonia (CAP) or complicated Skin and Soft Tissue Infections (cSSTI) – REACH Study

Developmental phase: Non-Interventional Study
Study Completion Date: 08 June 2011 (Last Subject In=Last Subject Last Visit)
Date of Report: 10-05-2012

OBJECTIVES:

Objectives: The primary objective was to provide accurate and reliable scientific data on the clinical management and burden of CAP and cSSTI across Europe; to evaluate and quantify unmet needs of these diseases by understanding the patient and disease characteristics, current practice, and clinical outcomes.

The secondary objectives were:

- To describe the population diagnosed with CAP and cSSTI requiring hospitalisation.
- To describe the current clinical management of hospitalised CAP and cSSTI infections.
- To evaluate the real-life effectiveness (time to infection resolution, hospital stays, relapses, etc.) of available treatments for hospitalised CAP and cSSTI infections.
- To calculate the use of resources (hospital stays, nursing, etc.) related to current CAP and cSSTI management.
- To describe the management patterns and related clinical outcomes of CAP and cSSTI patients attending recurrently to different health-related settings.
- To calculate the prevalence of MRSA / Multi-Drug Resistant *Streptococcus pneumoniae* (MDRSP) / Penicillin-Resistant *Streptococcus pneumoniae* (PRSP) among hospitalised

patients with CAP and cSSTI.

- To calculate the incidence of initial treatment modification due to resistances to treatment in the hospitalised MRSA/MDRSP/PRSP CAP and cSSTI infected populations.
- To assess clinical outcomes (mortality, morbidity, hospital stays) among the general and MRSA/MDRSP/PRSP CAP and cSSTI populations.

METHODS:

Methods: This was a multinational, multicentre, observational, retrospective cohort study of hospitalised patients with CAP or cSSTI.

Number of Subjects (planned and analyzed): Planned: It was estimated that approximately 4000 patients in approximately 330 sites across Europe would be analyzed in the study.

Actual: A total of 5249 patients were enrolled in the study, 2448 in the CAP disease group and 2801 in the cSSTI disease group.

Completed: 2050 patients (98.9%) in the CAP disease group and 2023 patients (97.9%) in the cSSTI disease group completed the study.

Analyzed: 2039 patients in the CAP disease group and 1996 patients in the cSSTI disease group were included in the analysis population.

Diagnosis and Main Criteria for Inclusion: Patients hospitalised for CAP or cSSTI were included.

Criteria for Evaluation

Efficacy**:** This was an observational, epidemiological study that was not designed to collect efficacy data. There was no single variable that directly supported the primary objective of the protocol; rather several descriptive summaries provided the data necessary to better understand the clinical management and burden of CAP and cSSTI and to evaluate the unmet needs of these diseases. A descriptive analysis approach (including frequency tables) was used to assess clinical management, clinical outcomes, and healthcare resources used and describe the effectiveness of the real world management approaches in CAP and cSSTI.

Safety: Safety was not assessed in this observational study.

Statistical Methods: The two-sided 95% confidence interval was obtained for the population estimation of the variables.

A descriptive analysis approach (including frequency tables) was used to assess clinical management, clinical outcomes and healthcare resources used. Multivariate analysis and survival analysis was performed for time-related events.

A comprehensive Statistical Analysis Plan (SAP) was prepared before database lock.

All of the study objectives and analyses were considered to provide descriptive evidence of any difference between the groups, and were analysed without any procedures to account for multiple comparisons.

Continuous or count variables were summarised by disease group and by country for each disease group using mean, standard deviation, 95% confidence interval for the mean, median, minimum and maximum values.

RESULTS:

Results

Subject Disposition

Of the 2448 patients enrolled in the CAP disease group, 2072 were deemed eligible, 22 were discontinued, 2050 completed the study, and 2039 were included in the analysis population.

Of the 2801 patients enrolled in the cSSTI disease group, 2066 were deemed eligible, 43 were discontinued, 2023 completed the study, and 1996 were included in the analysis population. Analysis population was defined as all enrolled and eligible patients as determined by inclusion/exclusion criteria who completed the study. Patients who were hospitalised prior to 01 March 2010 were excluded from the analysis population.

Efficacy Results:

This was an observational, epidemiological study that was not designed to collect efficacy data. Although many epidemiological and prognostic studies of CAP and cSSTI have been published, there is very little information about real-life management and initial treatment modification in these two diseases. A descriptive analysis approach (including frequency tables) was used to assess clinical management, clinical outcomes and healthcare resources used and describe the effectiveness of the real world management approaches in CAP and cSSTI. This study allowed us to compare the management of CAP and cSSTI across different European countries and to assess

the consequences of such management. These data address the relationship between a requirement for modification of initial antibiotic therapy, clinical response, and health care resource utilization.

CAP Disease Group

Of the 2448 patients enrolled in the CAP disease group, 2039 were included in the analysis population.

The results of this study indicate that there is a great degree of variability in the management of patients hospitalised with CAP infection across Europe. Fourty-eight different antimicrobial agents, alone or in combination, were used to treat CAP. The most commonly used initial line antibiotic regimens were: 1) amoxicillin-clavulanate (20.1%); 2) a penicillin (or penicillin combination) plus a macrolide (14.1%); and 3) a cephalosporine plus a macrolide (10.3%). Fluoroquinolone antibiotics either alone (13.8%) or in combination with other antibiotics (29.0%) were also frequently utilized as initial therapy. Of the 574 patients in the CAP disease group with microbiological diagnosis, causative agents for 298 patients (51.9%) were Gram positive cocci and causative agents for 97 patients (16.9%) were Gram negative bacilli. The most common Gram positive cocci were *Streptococcus pneumoniae*, found in 228 patients (39.7%). There were only 2 patients with MDRSP/PRSP in the CAP disease group. Twelve patients (2.1%) had MRSA. Bacteraemia developed in 116 patients (5.7%).

The mean (SD) duration of hospital stay was 12.1 (9.81) days and the mean time to clinical stability was 5.6 (5.11) days. The respective medians were 9.0 days and 4.0 days. Initial treatment modification or death (before treatment modification) was reported for 652 patients (32.0%). The reported reasons were insufficient response in 244 (12.0%) patients, adverse events in 41 (2.0%) patients, interaction with other treatments in 1 (0.0%) patients, other reasons in 149 (7.3%) patients and unknown reasons in 47 (2.3%) patients. A further 105 patients (5.1%) were reported to have initial treatment modification due to streamlining of therapy (de-escalation of treatment to narrower spectrum antibiotics upon patient improvement or confirmed microbiological diagnosis). These data show an unexpectedly high incidence of initial treatment modification or death while on initial therapy, suggesting that the current disease management does not achieve the desired treatment response in patients with moderate to severe infection. A requirement for initial treatment modification was more frequent in patients with a higher CURB-65 or PORT/PSI score, patients with comorbidities, immunocompromised patients, patients with MRSA (as

compared with MSSA) and patients hospitalized with recurrent infection. The comparison of resources used for patients requiring initial treatment modification with those who did not indicates that a change in the initial antibiotic regimen is associated with a higher use of healthcare resources, such as duration of hospitalisation (4 days longer), admission to the ICU (1.9 times higher), and duration of stay in the ICU (2.3 days longer). Among patients who required initial treatment modification, there was an increase in the proportion of patients with septic shock, renal failure necessitating renal replacement therapy, isolation, mechanical ventilation, blood pressure support, parenteral nutrition, and home-based care. The mortality rate was 7.2% (147 patients).

The population of CAP patients who experienced recurrences after initial discharge was characterized by high use of healthcare resources, including length of stay, admission to and time in ICU, septic shock, need for blood pressure support, etc. For example, the mean (SD) duration of hospitalisation for the CAP group was 25.1 (16.85) days for patients with recurrence compared to 11.5 (8.71) days for patients without recurrence.

Similarly, the population of CAP patients presenting with comorbidities, including respiratory disease, diabetes or cancer, had poorer outcomes than those without. For instance, they showed a higher rate of initial treatment modification, a longer length of stay and a higher mortality rate.

cSSTI Disease Group

Of the 2801 patients enrolled in the cSSTI disease group, 1996 were included in the analysis population.

There is a great degree of variability in the management of patients hospitalised with cSSTI infection across Europe. Over 54 different antimicrobial agents, alone or in combination, were used to treat cSSTI. The most commonly used initial line antibiotic agents were amoxicillin-clavulanate (18.3%), ampicillin-sulbactam (7.8%), and piperacillin-tazobactam (7.1%). Overall, 60.3% of patients received a penicillin or penicillin plus β-lactamase inhibitor combination, as monotherapy or in combination with any other agent/s, as their initial antibiotic coverage. Of the 1001 patients in the cSSTI group with microbiological diagnosis, causative agents for 702 patients (70.1%) were Gram positive cocci and causative agents for 341 (34.1%) were Gram negative bacteria. The most common Gram positive cocci were MSSA, found in 279 patients (27.9%) and coagulase-negative Staphylococci. MRSA was the causative agent in 102 patients (10.2%). Bacteremia developed in 124 patients (6.2%).

The mean (SD) duration of hospital stay was 18.0 (20.58) days and the mean time to clinical stability was 9.7 (11.24) days; The respective medians were 9.0 days and 4.0 days. Initial treatment modification or death (before treatment modification) was reported for 819 patients (41.0%). The reported reasons were insufficient response in 339 (17.0%) patients, adverse events in 55 (2.8%) patients, interaction with other treatments in 1 (0.1%) patients, other reasons in 246 (12.3%) patients and unknown reasons in 68 (3.4%) patients. A further 111 patients (5.6%) were reported to have initial treatment modification due to streamlining of therapy (de-escalation of treatment to narrower spectrum antibiotics upon patient improvement or confirmed microbiological diagnosis). These data show an unexpectedly high incidence of initial treatment modification or death while on initial therapy, suggesting that the current disease management does not achieve the desired treatment effect in patients with moderate to severe infection. A requirement for initial treatment modification was more frequent in patients with nosocomial infection, patients with comorbidities, immunocompromised patients, patients with MRSA (as compared with MSSA), patients with bacteraemia and patients hospitalized with recurrent infection. Evaluation of resources used for patients with initial treatment modification/death while on initial therapy compared to those without indicates that initial treatment modification is associated with a higher use of healthcare resources such as duration hospitalisation (10.6 days longer), admission to ICU (2.4 time higher), and duration of ICU stay (6.3 days longer). Initial treatment modification/death was also associated with an increase in the proportion of subjects with septic shock (9.8 times higher), surgical intervention (1.2 times higher), isolation (2.6 times higher), blood pressure support, parenteral nutrition, renal failure requiring renal replacement therapy, and home-based care. The mortality rate was 3.4% (68 patients).

The population of cSSTI patients who experienced recurrences after initial discharge was characterized by high use of healthcare resources, including length of stay, admission to ICU, need for surgery, septic shock, need for blood pressure support, home based care, etc. For example, the mean (SD) duration of hospitalisation for the cSSTI group was 36.1 (27.82) days for patients with recurrence compared to 17.3 (20.39) days for patients without recurrence. cSSTI patients with MRSA showed an initial treatment modification rate of 62.7% and presented a higher use of healthcare resources than the general population: ICU admissions were higher and their duration longer, a higher proportion of cases of septic shock were observed, isolation was more frequently required, etc.

cSSTI, patients presenting with comorbidities (including diabetes, peripheral vascular disease or

congestive heart disease) had poorer outcomes than those without, as shown by a higher rate of initial treatment modification, a longer length of stay and a higher mortality rate. Use of healthcare resources was also higher in cSSTI patients with comorbidites than in those without, including admission to ICU, rate of septic shock and requirement for isolation.

cSSTI patients in whom Methicillin-Resistant *S. aureus* (MRSA) was identified as the etiologic microorganism had poorer outcomes and used more healthcare resources than patients infected with Methicillin-Sensitive *S. aureus* (MSSA).

Safety Results: Safety was not assessed in this observational study.