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Sponsor/company: sanofi-aventis Generic drug name: teicoplanin		Clinicaltrials.gov Identifier: NCT00454272 Study Code: M000507_6004 Date: 05/Mar/2009	
Title of the study:		Comparison of Teicoplanin and Vancomycin in terms of efficacy and side effect profile during initial antibiotic treatment of febrile neutropenic patients at high risk for gram-positive infection: multi-center, prospective, randomized study. <i>Study code: M000507_6004</i>	
Investigator(s):		Hamdi Akan, Dr. Ankara University, Faculty of Medicine, Ibn-i Sina Hospital, Department of Hematology	
Study center(s):		28 centers (planned), 21 centers (actualized)	
Publications (reference):		NA	
Study period: Date first patient enrolled: 18-Jan-2005 Date last patient completed: 09-Aug-2007		Phase of development: IV	
Objectives:		<ol style="list-style-type: none"> To evaluate whether or not the use of Teicoplanin containing regimens during initial empirical antibiotic treatment of febrile neutropenic patients at high risk for gram-positive infection was at least equivalent to Vancomycin containing regimens, in terms of fever remission or eradication of isolated gram-positive bacteria. To evaluate whether or not there is any difference between the two regimens in terms of side effect profiles. 	
Methodology:		<i>National, multi-center, prospective, two-armed, randomized, phase IV clinical study.</i>	
Number of patients:		Planned: 212	Randomized: 190
Evaluated:		190	Safety: 190
Diagnosis and criteria for inclusion:		<ol style="list-style-type: none"> In neutropenic and febrile patients with hematological or solid tumors: <ul style="list-style-type: none"> Absolute neutrophil counts (ANC) of less than or equal to 500/mm³ in peripheral blood, were considered as neutropenia. Patients with absolute neutrophil counts between 500 and 1000/mm³, that was expected to fall below 500/mm³ in the next 24 hours due to chemotherapy, were also considered as neutropenic. In order for a patient to be considered febrile, body temperature measured by oral or axillary method should be over 38.3°C once or over 38.0°C twice in at least half an hour intervals in a 12 hour period. Patients were included in the study in their first fever attack of febrile neutropenic episodes. Therefore patients who were afebrile for at least 3 days after the empirical treatment of previous febrile attack have been included in the study. 	

<p>Investigational product:</p> <p>Dose:</p> <p>Administration:</p>	<p>Teicoplanin</p> <p>Loading dose in adults was 400 mg intravenous injection every 12 hours for first 3 doses, and maintenance dose was 400 mg once daily. Loading dose in children aged 2-16 years was 10 mg/kg intravenous injection every 12 doses for first 3 doses, and maintenance dose was 10 mg/kg/day.</p> <p>Diluted teicoplanin was administered intravenously by rapid injection within 3-5 minutes or by slow infusion within 30 minutes.</p>	
<p>Criteria to stop Teicoplanin or Vancomycin containing regimens</p>	<p>a) Treatment was stopped when the absolute neutrophil count was over 500/mm³, the patient's fever had remitted and there were no more signs of infection.</p> <p>b) When there was ongoing neutropenia, when the etiological microorganism of infection was not determined and the patient's general condition was stable, duration of the treatment was 5 feverless days following the remission of fever (In case of severe mucositis, unstable patient condition and severe neutropenia (<100/mm³), early cessation was not appropriate before remission of these signs).</p> <p>c) In patients whom clinical or microbiological infection focus/agent had been demonstrated, treatment duration was at least 10 days or until remission of neutropenia and complete disappearance of infection-associated symptoms and signs.</p>	
<p>Duration of treatment: 5-21 days</p>		<p>Duration of observation: 21 days</p>
<p>Reference therapy:</p> <p>Dose:</p> <p>Administration:</p>	<p>Vancomycin</p> <p>The dose for children over 2 years of age was 10 mg/kg every 6 hours.</p> <p>Vancomycin was administered as 1 gr. every 12 hours by slow infusion (at least in one hour) intravenously.</p>	
<p>Criteria for evaluation:</p>	<p>Highest fever, blood pressure, heart rate, ECOG performance status, infection signs and symptoms, clinical focus, microbiological findings, infection classification and absolute neutrophil counts were recorded daily during treatment period for 21 days. Laboratory examinations were performed at basal level, on 3rd, 5th, 7th, 10-12th, 14-16th and 18-20th days of the treatment. Following the end of study treatment, routine laboratory tests were repeated at 24 hours (visit for end of treatment assessment), 5-7 days after the treatment was stopped (test of cure visit) and in the last day of neutropenia. The primary criteria were assessed 5 days after completion of treatment.</p>	
<p>Efficacy:</p>	<ol style="list-style-type: none"> 1. Microbiologically proven infections: <ul style="list-style-type: none"> • Success: Remission of all pre-treatment disease symptoms and signs without any need for additional antibiotics, eradication of etiological microorganisms, no recurrence of symptoms for at least 5 days after completion of treatment and inability to isolate etiological microorganisms. • Success by treatment modification: Addition of antifungal, antiviral or antiparasitic medications for infections that were due to microorganisms other than the etiological infection agent which was eradicated by initial treatment and were not in the antibiotic effect spectrum or addition of anti-gram negative antibacterial medications to treatment, in the case of isolation of gram-negative bacteria as the etiological agent. • Failure: Addition of another anti-gram positive antibacterial medication to treatment in order to eradicate the primary infection agent (gram-positive), resistance of the isolated microorganism to Vancomycin or Teicoplanin or infection-associated death of the patient. 2. Clinically detected infections that could not be documented microbiologically: <ul style="list-style-type: none"> • Success: Remission of all pre-treatment disease symptoms and signs without any need for additional antibiotics, eradication of etiological microorganisms and no recurrence of symptoms for at least 5 days after completion of treatment. 	

	<ul style="list-style-type: none"> • Success by treatment modification: Control of fever, which has initially remitted but re-occurred within 5 days after cessation of therapy, by antimicrobials that have antibiotic effect spectrum other than the initial (i.e. antifungal, antiviral, antiparasitic). • Failure: Addition of another antibacterial agent due to unremitting fever or infection-associated death of the patient. Treatment protocol was not considered as a failure in patients with relapsing fever within first 5 days following end-of-treatment visit unless a new anti-gram-positive agent was added to the therapy regime. <p>3. Fever of unknown origin:</p> <ul style="list-style-type: none"> • Success: Remission of fever and neutropenia by initial treatment or no recurrence of fever after completion of treatment and for at least 5 days after cessation of therapy. • Success by treatment modification: Relapsing of the initially remitted fever and then its control by antimicrobials that had antibiotic effect spectrum other than the initial (i.e. antifungal, antiviral, antiparasitic). • Failure: Addition of another antibacterial agent due to unremitting or relapsing fever or infection-associated death of the patient. Use of antifungal, antiviral or antiparasitic medications in patients with unremitting fever by initial treatment or use of anti-gram-positive antibacterial agents other than initial treatment for a new bacterial infection was considered as failure. Treatment protocol was not considered as a failure in patients with relapsing fever within first 5 days following end-of-treatment visit unless a new anti-gram-positive agent was added to the therapy regimen.
Safety:	Adverse events reported by the patient or noted by the investigator.
Statistical methods:	<ul style="list-style-type: none"> • Study Populations <ul style="list-style-type: none"> • Analysis of all patients included (<i>Intention to treat: ITT</i>): All patients who had satisfied the inclusion criteria and been randomized for the study were included in ITT analysis. Major protocol violation or not to have received any study medications after randomization did not necessitate exclusion from ITT efficacy analysis. • Analysis of patients who followed the protocol (<i>Per-protocol: PP</i>): Patients who have violated the protocol in a way to influence the evaluation of efficacy and therefore have been withdrawn from the study were not included in PP analysis. Also, patients whose fever have been shown not to be due to infection and those who have been discharged from the hospital before fever remission were not included in this analysis. • Safety population: Patients who have received at least one dose of study medication were included in safety analysis. • End points: <ul style="list-style-type: none"> • Success of empirical treatment was the primary end-point of the study. Secondary end-points were time until fever remission, time until protocol modification and survival at 30 days. The primary end-points were assessed 5 days after completion of treatment. • Interim Analysis: <ul style="list-style-type: none"> • Preliminary results of the study were evaluated by an interim analysis when 100 patients were included. • Analysis: <ul style="list-style-type: none"> • Ceftazidime+Amikacin+Teicoplanin (Teicoplanin arm) and Ceftazidime +Amikacin +Vancomycin (Vancomycin arm) were compared using Chi-Square statistics (Chi-Square test or Fisher test for 2X2 tables and Mantel-Haenzsel test for ordinal variants). Mann-Whitney <i>U</i> test was used for digital data with abnormal distribution. Kaplan Meier test was used for survival analyses. Survival comparisons were performed via Log Rank test and survival curves were presented. The level of statistical significance was

	determined as $p < 0.05$.
Summary:	In the present study, 190 patients were enrolled. There were two randomization arms, 97 of 190 patients were using Ceftazidime+Amikacin+Teicoplanin (Teicoplanin arm) and 93 of them were using Ceftazidime +Amikacin +Vancomycin (Vancomycin arm). In Teicoplanin and arm Vancomycin arms, the mean ages were 36.4 ± 20.2 and 37.5 ± 19.9 , respectively.
Efficacy results:	<ul style="list-style-type: none"> Demography and evolution of blood cells: A total of 190 patients (106 male, mean age 36.9 ± 20.0 years) from 21 centers were randomized to teicoplanin (97 patients) and vancomycin (93 patients) arms. These patients were receiving at least 1 g/m² ARA-C on the last regimen (67.0%), having grade II-IV mucositis (26.9%), or both (6.0%). Of the included patients, 94.9% (n=166) had hematological malignancies and 5.1% (n=9) had solid tumors. Of the patients who had hematological malignancies; 57.8% were in remission, 24.1% were in relapse and 18.1% were in progression ($p=0.747$, for treatment arms); 36.3% received antimicrobial prophylaxis before and 11.7% during the study. There was no significant difference between treatment arms in terms of antimicrobial prophylaxis. Microbiological data were evaluated before the treatment, at the first 3 days of the treatment and after 3rd day. A total of 43 pathogens were identified in the beginning (22.6% of all patients). As expected, Gram-positive microorganisms (64.2%) were isolated more than the Gram-negative isolates (35.8%) and coagulase-negative staphylococci were the main pathogens. There were only 6 isolates identified after the 3rd day. <p>At baseline, there was no significant difference between teicoplanin and vancomycin groups according to the highest body temperature ($p=0.868$), presence of high fever, leukocyte count ($p=0.730$) and absolute neutrophil count ($p=0.267$).</p> <p>In the follow up which was planned day after day for 21 days period, there was not any statistically significant difference between the randomization arms in respect to leukocyte counts, the mean absolute neutrophil counts, and performance status (ECOG). At the last day of the protocol treatment, during 24 hours, no significant difference was observed in the evaluations between the randomization arms in respect to the mean leukocyte counts [Teicoplanin ($5718/\text{mm}^3 \pm 8450$) and Vancomycin ($5994/\text{mm}^3 \pm 10500$, $p=0.611$)], the mean neutrophil counts [Teicoplanin ($3727.6 \text{ ANC}/\text{mm}^3 \pm 7019.6$) and Vancomycin ($3098.7 \text{ ANC}/\text{mm}^3 \pm 7489.6$, $p=0.744$)], the mean ECOG scores ($p=0.218$). At the 5th day after the completion of the treatment, there was no significant difference between the randomization arms in respect to leukocyte counts ($p=0.394$), the mean absolute neutrophil counts ($p=0.280$), and performance status (ECOG, $p=0.561$). Moreover, in the evaluation performed on the day neutropenia ended, no significant difference was observed between the randomization arms in respect to leukocyte counts in Teicoplanin ($3609/\text{mm}^3 \pm 2813$) and Vancomycin ($3836/\text{mm}^3 \pm 3609$, $p=0.976$) arms.</p> <p>Only at the 10th day of follow up, the rate of presence of a clinical focus in Teicoplanin arm (18.4%) was significantly higher than Vancomycin arm (2.3%, $p=0.014$). Considering the other follow up days, no significant difference was observed in respect to the rate of presence of a clinical focus. In the follow up, no significant difference was observed between the randomization arms according to the ratios of unknown fever, microbiologically diagnosed infection, clinically diagnosed infection, and fever without infection.</p> <ul style="list-style-type: none"> Primary Efficacy Analyses: According to the evaluation of patients' last condition, 36.2% of the patients were still hospitalized, 54.8% of them were discharged and 5.9% of them were dead. Overall, 7.2% of patients in Teicoplanin group and 4.4% of patients in Vancomycin group died. No

	<p>significant difference was observed between Teicoplanin and Vancomycin arms according to the patients' last condition ($p=0.832$). Disease status after treatment was evaluated in 54 patients and 74.1% of them were in remission, 14.8% were refractory and 11.1% could not be evaluated due to death. There was no difference between teicoplanin and vancomycin groups according to these data.</p> <p>It was determined that administered treatment was successful in 55.7% and 53.3%, failed in 18.6% and 24.4% and was successful with modification in 21.6% and 17.8% in teicoplanin and vancomycin groups, respectively. Response could not be evaluated in 4.3% of the patients. There was no significant difference between treatment arms according to treatment responses. Most common causes of treatment failure were persistence of fever and clinical deterioration under therapy (45%), breakthrough bacteremia (15%), and death due to infection (12.5%).</p> <p>While protocol treatment was not changed in 58.2% of the patients, the treatment was either switched or other medications were added in the remainder. Protocol treatment modification (adding drug) and alteration (ceasing the treatment, and /or initiation of new drugs) ratios were not significantly different between the two groups ($p=0.711$, 0.857, respectively).</p> <p>A new infection was present in 22.1% of patients and the remainder did not have any new infection under treatment or 5 days after the completion of treatment. When Teicoplanin and Vancomycin groups were compared, a new infection was present in 22.6% and 21.6% of patients, respectively. No significant difference was observed between two groups ($p=0.873$).</p> <p>There was no statistically significant difference between teicoplanin and vancomycin groups according to body temperature at the last day of the protocol treatment ($37.2 \pm 1.1^\circ\text{C}$ vs. $37.3 \pm 1.1^\circ\text{C}$, respectively, $p=0.220$).</p> <p>The duration of neutropenia defined as $\text{ANC} < 500/\mu^3$ was similar in both groups (7.9 ± 5.1 days vs. 6.4 ± 4.6 days, $p=0.081$) but duration of $\text{ANC} < 100/\mu^3$ was significantly longer in vancomycin group (4.3 ± 3.6 days vs. 6.4 ± 4.7 days, $p=0.001$).</p> <ul style="list-style-type: none"> • Secondary Efficacy Analyses: In the follow up, 84% of the patients survived without infection, 7.4% survived in the presence of infection, 7.4% died and 1.1% of them decided to quit the study. In regards to the patients' survival conditions, there was no significant difference between the randomization arms. <p>The mean follow-up time of Teicoplanin randomization arm was 351.85 (SD=40.69 95% CI 272.10; 431.61) days, and the mean follow up time of Vancomycin randomization arm was 175.60 (SD=5.65 95% CI 164.52; 186.68) days. There was not any significant difference between Teicoplanin (92.55%) and Vancomycin randomization arms (92.56%) with regards to the survival conditions (Log Rank $p=0.872$).</p>
Safety results:	<p>Adverse events observed during the study were bone pain grade 1-2, allergic rhinitis, anuria, bronchospasm, nausea, nose bleeding, diarrhea, eruption, flashing, hepatotoxicity, Herpes zoster, hypokalemia, stomach ache, coagulation defect, constipation, difficulty in breathing, nephrotoxicity, change in prothrombin time, respiratory distress, hematoma due to the thrombocytopenia, and rash on face.</p> <p>Forty-four of 89 adverse events were mild, 32 of them were moderate and 13 of them were severe adverse events. There was not any significant difference between the randomization arms regarding the adverse events.</p> <p>Seventy-one of 84 adverse events were not serious adverse events, though initially five of them were reported as life-threatening, and 5 of them as death, finally 13 of the cases died during and after the study.</p> <p>Overall, 11 deaths were observed during the study. Two additional deaths occurred</p>

	after the patients were discharged. (lymphoma progression and metastasis of cancer). The reasons of the deaths during the study were; infection (4 patients), bleeding (3 patients), bleeding and infection (2 patients), metastasis of cancer and infection (1 patient), sepsis and disseminated intravascular coagulation (1 patient). No significant difference was observed between the randomization arms according to the death reasons of the patients.
Date of report:	21-Jan-2009