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Therapy of *Rhodococcus equi* Disseminated Infections in Nude Mice

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***Rhodococcus equi* is a facultative, intracellular, gram-positive coccobacillus increasingly reported as an opportunistic pathogen in human immunodeficiency virus-positive patients. However, the optimal drug regimen for treating *R. equi* pulmonary or systemic infections is not yet known. Therefore, a model of intravenously infected nude mice with disseminated infection was created to study the efficacy of antibiotics alone or in combination as determined by the reduction of bacterial CFU per gram in the lungs and spleen after 4 and 11 days of treatment. The studied antibiotics possessing low MICs against *R. equi* strains were amikacin, ciprofloxacin, erythromycin, imipenem, minocycline, rifampin, and vancomycin. Vancomycin, imipenem, and rifampin were the most effective agents in monotherapy. On the other hand, amikacin, ciprofloxacin, erythromycin, and minocycline alone were not active in this model. The most active drug combinations were those including vancomycin. No antibiotic-resistant mutants were selected in vivo with treatment involving any drugs used alone or in combination. Although the treatment recommended until now for *R. equi* infections is rifampin plus erythromycin, this study suggests that antibiotic combinations which include vancomycin may be the most effective in vivo.**

Rhodococcus equi is a gram-positive coccobacillus which is well known by veterinary microbiologists because it causes pneumonia in foals (24). In humans, pneumonia and lung abscesses are the most frequent infections due to this facultative intracellular organism (8, 12, 14). However, nonpulmonary infections such as endophthalmitis, osteomyelitis, and brain, kidney, and pelvis abscesses are also reported (5, 10, 11, 14, 23, 27, 29). All except two described cases of *R. equi* infection have been in immunocompromised patients (14). Since the AIDS epidemic, *R. equi* infections are increasingly reported (8, 14, 26). On the basis of the results of treatment of *R. equi* pneumonia in foals, rifampin combined with erythromycin is known to be effective in vivo (15). However, in humans, the optimal antimicrobial regimen is not yet known, since frequent relapses occur during the course of the disease, especially in AIDS cases (8). Therefore, the aim of this work was to assess the abilities of several antibiotics and antibiotic combinations to clear an *R. equi* inoculum in experimentally infected mice. Since *R. equi* infections are of a chronic mode in immunocompromised humans, intravenously (i.v.) infected nude mice in which *R. equi* persisted in the lungs and spleen for at least 3 weeks were used as the experimental model of infection. The idea to use such an animal model was provided by the results of testing the antibacterial activities of in *Listeria monocytogenes*-infected nude mice and by the persistence of *R. equi* in infected normal mice treated with cyclophosphamide (16, 17, 19). The choice of antibiotics was guided by the results of previous susceptibility studies in vitro (2, 4, 22, 30). The following seven compounds were studied because they possessed relatively low MICs: amikacin, ciprofloxacin, erythromycin, imipenem, minocycline, rifampin, and vancomycin. Therapeutic trials with these drugs in monotherapy as well as in combination were performed. Seven combinations of antibiotics were studied. Four of them were studied because they were synergistic according to previous in vitro determinations of fractional inhibitory concentration indices (22), namely, imipenem plus amikacin, erythromycin plus minocycline, rifampin plus erythromycin, and rifampin plus minocycline. The efficacy of the combination imipenem plus vancomycin was studied because imipenem combined with glycopeptides has been shown recently to have successfully treated two cases of human *R. equi* infection (1a, 25). The combination ciprofloxacin plus rifampin was studied because both of these antibiotics possess high intramacrophagic uptake (28) and are known to treat several other intracellular infections. The last drug combination, rifampin plus vancomycin, was studied because both rifampin and vancomycin alone were particularly active in a preliminary in vivo therapeutic trial. Finally, since in vivo selection of antibiotic-resistant mutants in patients under treatment has been described previously (2, 12, 21), selection of such mutants in mice treated with antibiotics alone or in combination were also evaluated.

MATERIALS AND METHODS

Drugs used. The antimicrobial agents used in this study were obtained from laboratory standard powders and were used immediately after being diluted. The agents and their sources were amikacin (Bristol), vancomycin (Eli Lilly), erythromycin lactobionate (Abbott), imipenem/cilastatin at a fixed ratio of 1:1 (Merck Sharp & Dohme), ciprofloxacin (Bayer), rifampin (Gruppo Lepetit), and minocycline (Lederle). All of the antibiotics were dissolved in sterile distilled water at the appropriate dilutions before being used.

Challenge organism. The strain *R. equi* PN 1002, which had been simultaneously isolated from sputum and blood cultures of a human immunodeficiency virus-positive patient who died of pneumonia, was used (20). Its identification (gram-positive coccobacillus, salmon-pink colonies, catalase

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positive, oxidase negative, urease positive, nitrate reduction negative, sugar nonfermenting) was assessed by the API Corynebacteria test (Biomerieux S.A., Marcy l'Etoile, France) and the identification center of the Institut Pasteur (Paris, France). Virulence of the organisms was maintained by repeated passages through Swiss mice. Overnight cultures of the strain in Trypticase soy broth (Diagnostics Pasteur, Paris, France) were frozen in 5% glycerol-containing samples at −70°C in order to obtain reproducible amounts of bacteria once the samples thawed. This strain was susceptible to low concentrations of the antibiotics studied, as shown by the following MICs (in micrograms per milliliter), determined for the strain in broth by a macrodilution technique (18): amikacin, 1; vancomycin, 0.12; minocycline, 0.12; rifampin, 0.06; erythromycin, 0.25; ciprofloxacin, 0.25; imipenem, 0.25. Only amikacin, vancomycin, and ciprofloxacin were bactericidal. Their MBCs as determined by a macrodilution technique (18) were 8, 1, and 2 μg/ml, respectively.

Animals. Six- to eight-week-old female normal and congenitally athymic nude (*nu/nu*) Swiss mice were purchased from Iffa-Credo (L'Arbresle, France). The animals were caged in groups of six, and food and water were given ad libitum.

Infection of animals. Prior to therapeutic trials, comparisons of the clearance of *R. equi* CFU from the lungs and spleen of normal and immunodeficient nude infected mice were established over a 3-week period. Fifteen animals of each type were inoculated i.v. with 5×10^7 to 6×10^7 CFU of *R. equi* to obtain reproducible amounts of the inoculated organisms. Moreover, the route of the i.v. inoculation resulted not only in lung infection but also in spleen infection. Therefore, pulmonary as well as nonpulmonary infections occurring in animals were comparable to those described for humans. For therapeutic trials, nude mice were also inoculated i.v. with 5×10^7 to 6×10^7 CFU of *R. equi*.

Administration of drugs. Therapeutic trials with nude mice were initiated 4 days after the animals were inoculated in order to let the infection peak in both the lungs and spleen. Adjustments were made in the dosing schedule and in the dosages of the antibiotics to account for mouse pharmacokinetics in an effort to parallel the pharmacokinetics of these agents in humans. The original antibiotic solutions were appropriately diluted in sterile water to obtain the requisite dose, which was injected subcutaneously in a volume of 0.1 to 0.2 ml for each mouse. Rifampin (10 mg/kg of body weight) was given once a day, and minocycline (15 mg/kg) was given twice a day. Erythromycin (50 mg/kg), imipenem-cilastatin (60 mg of each per kg), amikacin (20 mg/kg), vancomycin (25 mg/kg), and ciprofloxacin (20 mg/kg) were given every 6 h. Therapeutic trials were performed with these antibiotics alone and with the following seven antibiotic combinations: amikacin plus imipenem-cilastatin, erythromycin plus minocycline, rifampin plus erythromycin, rifampin plus minocycline, rifampin plus ciprofloxacin, rifampin plus vancomycin, and vancomycin plus imipenem-cilastatin. The total number of animals in each group of treated mice was six. All mice except the controls were treated daily from day 4 to day 15 after i.v. inoculation. Controls consisted of infected but untreated animals.

Levels of agents in serum. Pooled sera were obtained from groups of three noninfected Swiss mice, sacrificed at 0.25, 0.50, 1, 2, 4, or 8 h after a single subcutaneous dose of the antibiotic. Animals were briefly anesthetized with ether and exsanguinated by intracardiac puncture. Blood samples were centrifuged, and serum was collected. Serum concentrations of ciprofloxacin, erythromycin, imipenem, minocycline, and rifampin were determined by an agar well diffusion method of bioassay (6). The indicator strains were *Escherichia coli* ATCC 25922 for determination of ciprofloxacin and imipenem levels in serum and *Staphylococcus aureus* ATCC 25923 for determination of minocycline, erythromycin, and rifampin levels in serum. Concentrations in serum of amikacin and vancomycin were measured by using the fluorescence polarization immunoassay developed by Abbott Laboratories, North Chicago, Ill. (1). Pharmacokinetic analyses were performed by routine graphical methods, and parameters were evaluated by standard methods (13). C_{max} was the maximal concentration observed, T_{max} was the time to C_{max}, $t_{1/2}$ was the elimination half-life calculated by using linear least-squares regression, and the inhibitor quotient (IQ) was calculated as follows: IQ = C_{max}/MIC (7). The MICs retained for the IQ calculations were those of the *R. equi* strain used in the experimental infections.

Quantities of *R. equi* in lungs and spleen. In the experiment which established the comparison between clearance of *R. equi* CFU counts from the lungs and spleen in Swiss mice and that in nude Swiss mice, a group of three mice was sacrificed on days 2, 4, 8, 15, and 21 after the infectious i.v. challenge. For therapeutic trials, three mice in each group were sacrificed on days 8 and 15 after the infectious challenge. Day 8 was chosen because it represented a short (4-day) therapy, and day 15 permitted an evaluation of the effectiveness of treatment for a longer period. In all experiments, lungs and spleen were removed aseptically, weighed, and placed in 2 ml of sterile buffered water. Organs were homogenized with a hand-held glass homogenizer, and serial 10-fold dilutions were plated on Trypticase soy agar. After 48 h of incubation at 30°C (the temperature for *R. equi* optimal growth [24]), colonies were of sufficient size to be counted, and the number of bacterial CFU per gram of tissue was determined. Titers were expressed as $\log_{10}$ CFU per gram of organ. The titers for the infected mice were compared with those for the control mice, and the difference was expressed as follows: variation in $\log_{10}$ CFU per gram of tissue compared with the control = [$\log_{10}$ CFU per gram of tissue in control mice] − [$\log_{10}$ CFU per gram of tissue in treated mice].

In vivo selection of antibiotic-resistant mutants. The in vivo emergence of mutants that were resistant to the drug with which the mice were treated was determined by inoculating nondiluted tissue extract at each time of sacrifice on Trypticase soy agar impregnated with antibiotics. The antibiotic concentrations (in micrograms per milliliter) in the plates, which were 10-fold higher than the MICs, were as follows: amikacin, 10; ciprofloxacin, 2.5; erythromycin, 0.25; imipenem, 2.5; minocycline, 1.2; rifampin, 0.6; vancomycin, 1.2.

Statistics. Standard randomization procedures were employed in selecting animals to be killed at scheduled intervals. CFU counts of each treated group were compared with those of the control group and with those of each of the other groups by variance analysis. This was performed on the basis of the results of the parametric Tukey's studentized range test (SAS/stat; SAS Institute Inc., Cary, N.C. 1989) for a fixed value of $P = 0.05$.

RESULTS

Pharmacokinetic data. Following a single subcutaneous dose of each antibiotic in Swiss mice, pharmacokinetic data were obtained (Table 1). The C_{max} was highest for vanco-

TABLE 1. Serum pharmacokinetic parameters of various antibiotics in mice following a subcutaneous injection[a]

Drug	Dosage (mg/kg)	C_{max} (μg/ml)[b]	T_{max} (h)	$t_{1/2}$ (h)	IQ[c]
Amikacin	20	31.5 ± 2	0.25	0.4	31
Ciprofloxacin	20	5.0 ± 0.4	0.25	0.75	20
Erythromycin	50	7.0 ± 0.3	0.5	0.75	28
Imipenem	60	80.2 ± 9.4	0.25	0.2	320
Minocycline	15	1.5 ± 0.2	0.5	2	12
Rifampin	10	11.0 ± 0.8	0.5	5	183
Vancomycin	25	35.6 ± 8.4	0.25	0.3	296

[a] Values are calculated from the mean concentrations in serum taken at 0.2, 0.5, 1, 2, 4, and 8 h after dosing.
[b] Values are means ± standard deviations for three samples.
[c] IQs (= C_{max}/MIC) were calculated with the MICs of the *R. equi* strain used in experimental infections.

mycin and imipenem/cilastatin. The $t_{1/2}$ was longest for rifampin and minocycline. The IQ calculated at peak concentrations in serum was highest for imipenem, vancomycin, and rifampin.

Comparison of clearance of *R. equi* CFU counts from lungs and spleen of normal and nude mice. Normal mice and T-lymphocyte-deficient nude mice were infected with the same challenge inoculum of 5×10^7 to 6×10^7 CFU of *R. equi*. The kinetics of clearance of bacterial counts from lungs and spleen in both groups of mice over a 3-week period are given in Fig. 1. In both groups of mice, bacterial counts were greater in the spleen than in the lungs and peaked at day 4 postinoculation. However, the kinetics of CFU counts over time followed the same trend in lungs and spleen. In immunocompetent mice, the bacterial CFU counts progressively decreased in lungs and spleen over 3 weeks and reached the limits of detectability (i.e., 1.0 $\log_{10}$ CFU) within 21 days. On the other hand, in nude mice, the bacterial CFU counts remained the same for a given organ from day 4 to day 21 after the infectious i.v. challenge. Nude mice were unable to clear the bacterial inoculum. Even though the inoculum of 5 $\times 10^7$ to 6 $\times 10^7$ CFU of *R. equi* was high, no mice died during the 3-week experiment.

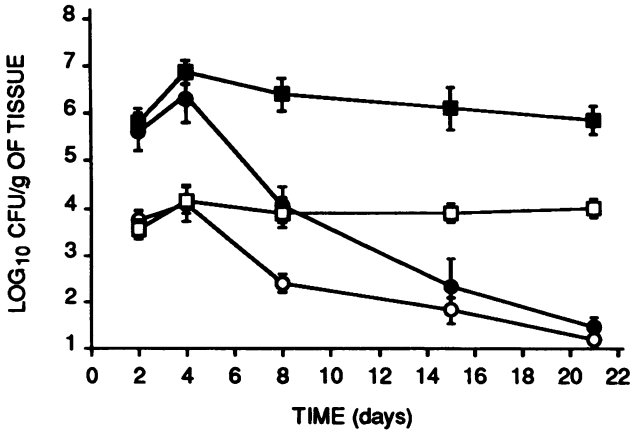

FIG. 1. Mean $\log_{10}$ CFU of *R. equi* per gram of tissue recovered from lungs and spleen of normal and nude mice after a single i.v. inoculation of 5×10^7 to 6×10^7 CFU. Symbols represent CFU counts per gram of the following: spleen of normal mice (●), spleen of nude mice (■), lungs of normal mice (○), and lungs of nude mice (□). Each point represents the mean value for three animals. Bars represent standard deviations. $1 \times \log_{10}$ CFU per gram of tissue was the bacterial detection limit.

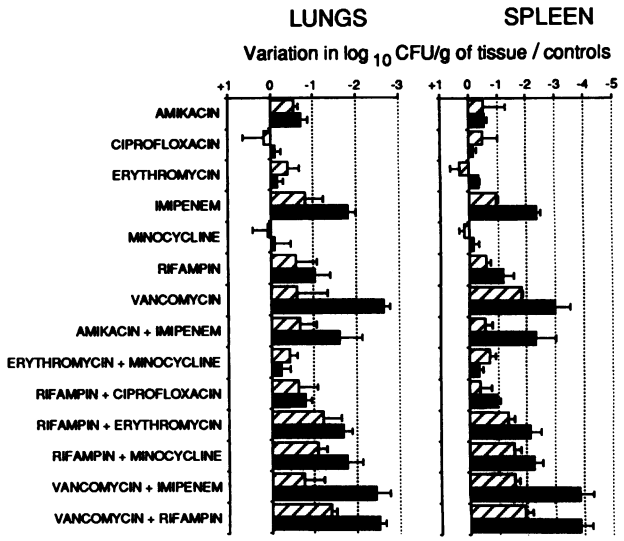

FIG. 2. Effects of various therapeutic regimens on bacterial CFU counts, expressed as mean $\log_{10}$ change in CFU per gram of lungs (left) and of spleen (right). Bacterial counts in nude mice infected with 5×10^7 CFU of *R. equi* over an 11-day treatment period were compared with those in untreated control mice. Hatched bars show the results obtained after 4 days of treatment, and black bars show the results after 11 days of treatment. Each bar is the mean value for three animals. One-directional error bars indicate the standard deviations of the means. Therapy with antibiotics alone or with drug combinations are indicated on the vertical axis.

Therapeutic trials. Treatment of nude mice began on day 4 after the inoculum challenge and was continued daily until day 15. A comparison of the mean variation (± standard deviation) in bacterial $\log_{10}$ CFU counts in the lungs and spleen of treated mice and control mice at day 8 and day 15 after the infectious challenge are given in Fig. 2. A similar trend in decrease of bacterial CFU counts was obtained for a given drug regimen in the lungs and spleen from day 8 to day 15. The following treatments did not lead to a statistically significant decrease in bacterial CFU compared with that of the controls in either the lungs or spleen at day 8 and day 15: amikacin, erythromycin, ciprofloxacin, minocycline, and erythromycin combined with minocycline. For the other treatments, the antibacterial effect was more marked at day 15 than at day 4. Vancomycin monotherapy led to a statistically significant difference in reducing the bacterial CFU compared with any other monotherapy. At day 15, vancomycin monotherapy lead to a greater decrease in bacterial CFU than did rifampin combined with erythromycin. However, vancomycin combined with another drug was not statistically different from vancomycin monotherapy. Among therapeutic regimens including drugs in combination, the most effective were those including vancomycin. Moreover, only two antibiotic combinations led to a statistically significant greater decrease in CFU counts than was observed with the relevant antibiotic alone: rifampin combined with minocycline and rifampin combined with erythromycin as compared with rifampin alone.

Selection of antibiotic-resistant mutants in vivo. The frequencies of selection of antibiotic-resistant mutants in the spleen after drug monotherapy were as follows: amikacin, 6×10^{-4}; imipenem, 9×10^{-6}; ciprofloxacin, $<1 \times 10^{-7}$;

erythromycin, $<1 \times 10^{-7}$; minocycline, $<1 \times 10^{-7}$; rifampin, 1×10^{-7}; vancomycin, $<1 \times 10^{-7}$. For a given antibiotic, frequencies of selection of antibiotic-resistant mutants were identical when the mice were treated with the drug alone or in combination. In the lungs, the frequencies of selection of antibiotic-resistant mutants were not detectable, since there was a lower number of bacterial CFU counts than in the spleen. The same frequencies of selection of antibiotic-resistant mutants were obtained with the untreated control. Therefore, no selection of antibiotic-resistant mutants occurred in vivo. The antibiotic-resistant mutants obtained resulted from selection in vitro rather than selection in vivo.

DISCUSSION

Several interesting observations emerged from this study. (i) Nude mice, as opposed to immunocompetent mice, could not clear an *R. equi* challenge i.v. from the lungs and spleen for at least 3 weeks, thus providing an animal model of chronic infection which resembled the course of the human infection. Moreover, the persistence of the *R. equi* challenge in nude mice which are congenitally T-lymphocyte deficient may suggest that T-lymphocyte subsets are critical for the clearing *R. equi* infection in immunocompetent patients. (ii) Even though *R. equi* is a facultative intracellular organism persisting in macrophages (24), the efficacy of drugs in monotherapy was not related to their intracellular uptake. Ciprofloxacin, erythromycin, and minocycline alone, despite their low MICs and their high intramacrophagic uptake, showed a surprising lack of activity against *R. equi*-infected animals. On the other hand, therapy with vancomycin or imipenem, which are antibiotics not known to concentrate in macrophages, led to a significant reduction in the CFU counts in the lungs and spleen after 4 or 11 days of treatment. Furthermore, monotherapy efficacy may be more related to the serum IQ than to the known intracellular uptake of the antibiotics. The efficacy of vancomycin was noteworthy and may be related to its high IQ, 296, as well as to its bactericidal properties against *R. equi*. Therefore, one may suggest that extramacrophagic development is of significant importance in the growth in vivo of *R. equi*, as it is known to be for *L. monocytogenes* (3). Moreover, as suggested for *L. monocytogenes*, the inefficacy in vivo of minocycline and erythromycin despite their low MICs may have resulted from their inactivation due to the effect of a low pH in the phagolysosomes where *R. equi* may persist (16, 24). (iii) The low therapeutic effect of ciprofloxacin for *R. equi* infections may be due to its low antibacterial effect. *R. equi* is much less susceptible in vitro to ciprofloxacin than gram-negative bacteria are. This lack of ciprofloxacin efficacy may explain the previous selection of a rifampin-resistant strain from a patient treated with ciprofloxacin plus rifampin resulting, in fact, in a rifampin monotherapy (21). (iv) Our results confirm the efficacy of the rifampin-erythromycin combination, as indicated by the results of treatment of infected foals (15). However, the present study may indicate that vancomycin is the most effective antibiotic in vivo. This was also recently suggested by the efficacy of the imipenem-glycopeptide combination in the treatment of two human cases of *R. equi* infection (1a, 25). Consequently, if it is valid to deduce the most effective human therapy from results obtained with an animal model, one may propose an initial therapy including vancomycin. Since vancomycin is as effective alone as with any other antibiotic in combination, a combination of antibiotics including vancomycin, such as vancomycin-imipenem, may act by limiting the emergence in vivo of antibiotic-resistant mutants rather than by further decreasing the bacterial inoculum. Actually, the lack of selection of antibiotic-resistant mutants in the animal model should be carefully considered. These mutants can probably be selected in vivo under other experimental conditions, such as a longer treatment period, a lower antibiotic concentration in the selection plates, or a greater number of treated mice. (v) Since *R. equi* infections may be mistaken for tuberculosis and mistreated with antituberculosis drugs, the initial treatment given before the results of the in vitro susceptibility of the isolated *R. equi* strain are known should not include rifampin in case the strain is rifampin resistant. After initial treatment with a vancomycin-containing drug combination, a more convenient therapy of oral dosages of antibiotics such as a combination of rifampin plus minocycline or rifampin plus erythromycin may be recommended. (vi) Finally, this nude mouse model of chronic infection may permit an evaluation of the antibacterial activity of other drugs. Trimethoprim-sulfamethoxazole and new macrolides such as clarithromycin that possess low MICs against *R. equi* strains may be interesting to study, as they show high antimicrobial activity against other pulmonary opportunistic pathogens (*Pneumocystis carinii* and atypical mycobacteria [9]) with which *R. equi* may be combined in AIDS cases (14).

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