Efficacy of Tulathromycin Injectable Solution for the Treatment of Naturally Occurring Swine Respiratory Disease*

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CLINICAL RELEVANCE

Tulathromycin, a novel triamilide antimicrobial, was evaluated for treatment of swine respiratory disease (SRD) in field efficacy studies involving 720 pigs in six North American swine herds. In each study, feeder pigs with clinical SRD were randomly assigned in equal numbers to a group treated with tulathromycin given as a single injection at 2.5 mg/kg of body weight or to a saline-treated control group. Four of the studies included a third group treated with ceftiofur sodium for 3 consecutive days at 3 mg/kg of body weight. Pigs were treated on day 0 and evaluated for treatment response on day 7. In each study, 10 or more nontreated pigs and saline-treated pigs that did not respond to treatment underwent necropsies to obtain lung samples, which were evaluated for SRD pathogens. The overall cure rate was 46.4% for saline-treated pigs, 71.1% for tulathromycin-treated pigs, and 63.1% for ceftiofur-treated pigs. The cure rate for tulathromycin-treated pigs was significantly higher than for saline-treated pigs \(P = 0.0116\). Mortality from SRD occurred in 24 control pigs, seven tulathromycin-treated pigs, and one ceftiofur-treated pig. The mortality rate was significantly lower for both the tulathromycin- and ceftiofur-treated pigs compared with those treated with saline \(P = 0.0148\) and \(P = 0.0195\), respectively). Actinobacillus pleuropneumoniae, Pasteurella multocida, Haemophilus parasuis, and Mycoplasma hyopneumoniae, bacteria commonly associated with SRD, were isolated from SRD-affected pigs. Under field conditions, tulathromycin injectable solution given as a single IM dose of 2.5 mg/kg of body weight was safe and effective in the treatment of SRD.

INTRODUCTION

It would be difficult to overstate the impact of swine respiratory disease (SRD) on swine herd health. Virtually every herd is affected to some degree, and it is generally recognized that SRD is the most important disease problem affecting the swine industry. SRD is usual-
ly a complex caused by multiple bacterial and viral infectious agents in combination with various contributing factors.\textsuperscript{1,3–5} The latter include stress, environmental conditions that lead to exposure or immunologic compromise, genetic predisposition, nutritional deficiencies, and management influences such as poor climate control, large herd size, and high stocking density. Good production methods that include vaccination and prudent use of antimicrobials may make SRD more manageable, but outbreaks and subclinical forms of this multifactorial disease occur even in high-health herds.\textsuperscript{2}

A striking feature of SRD is the frequency with which the infectious causative agents appear in the swine population, including herds with subclinical infection. For example, the percentage of midwestern US herds positive for \textit{Actinobacillus pleuropneumoniae} has been estimated to be 70% to 80%; for \textit{Mycoplasma hyopneumoniae}, more than 90%;\textsuperscript{1,5} and for \textit{Pasturella multocida}, more than 85%.\textsuperscript{2} More recently, \textit{Haemophilus parasuis} has become known as an important contributor to SRD, being associated with high morbidity and mortality in high-health status herds.\textsuperscript{6} These and other common bacterial and mycoplasmal pathogens, often in combination with such viruses as swine influenza and porcine reproductive and respiratory syndrome (PRRS), are commonly associated with the porcine respiratory disease complex.\textsuperscript{5,7} More often, they are a cause of subclinical infection, even in production facilities where sound management procedures have reduced the incidence of clinical disease.\textsuperscript{7,8}

Antimicrobial agents continue to be the primary treatment for acute SRD. Macrolides have a history of success in treating SRD caused by gram-negative bacteria, including disease caused by \textit{P. multocida}, \textit{A. pleuropneumoniae}, \textit{H. parasuis}, and \textit{M. hyopneumoniae}.\textsuperscript{6,9–14} Macrolide concentrations are consistently higher in tissue than in plasma, including high levels in lung, lung epithelial lining fluid, and phagocytic cells in both human and animal models.\textsuperscript{15–17} Macrolide efficacy also derives in part from drug accumulation in neutrophils, alveolar macrophages, and fibroblasts with subsequent efflux of drug at the site of infection.\textsuperscript{17–20}

Tulathromycin is a triamilide, a macrolide subclass specifically developed for swine and bovine respiratory disease for use as a single-dose administration.\textsuperscript{21} Structurally related to azithromycin, a macrolide antimicrobial used extensively in human medicine,\textsuperscript{22} tulathromycin IM injection is highly bioavailable. After IM administration at 2.5 mg/kg of body weight, maximum concentration ($C_{\text{max}}$) in plasma is approximately 0.6 µg/ml, with mean time of maximum plasma concentration ($T_{\text{max}}$) achieved within 15 minutes after dosing.\textsuperscript{23} High concentrations in lung tissue occur within 12 hours after dose administration with a $C_{\text{max}}$ of approximately 3.5 µg/g.\textsuperscript{23} The lung:plasma ratio of area under the curve (AUC) values for tulathromycin in swine has been shown to be 61.4, with a mean half-life in porcine lung tissue of 142 hours (5.9 days).\textsuperscript{23} In vitro, tulathromycin has been shown to accumulate in swine neutrophils and alveolar macrophages.\textsuperscript{24} Persistence in respiratory tissues and recruitment of drug-loaded neu-

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\textbf{A striking feature of SRD is the frequency with which the infectious causative agents appear in the swine population.}
trophils and alveolar macrophages in the lung are pharmacokinetic properties that could potentially contribute to clinical efficacy against key bacterial respiratory pathogens.\(^{18}\)

Tulathromycin also shows in vitro bactericidal activity against several important gram-negative pathogens, including *P. multocida*,\(^ {21}\) and has a broader antibacterial spectrum than tilmicosin.\(^ {25}\) Additionally, in vitro analysis has shown that, compared with tilmicosin, tulathromycin is more potent against *P. multocida* and *A. pleuropneumoniae*.\(^ {25}\)

This report describes six controlled studies conducted in North America to evaluate the field efficacy of tulathromycin against naturally occurring SRD. The primary assessment of efficacy for these studies was cure rate, a derived variable of treatment success through the final day of the study that included assessments of mortality, attitude and respiratory scores, and rectal temperature. Based on these efficacy assessments, in the United States, tulathromycin injectable solution is indicated for the treatment of SRD associated with *P. multocida*, *A. pleuropneumoniae*, *H. parasuis*, and *Bordetella bronchiseptica*.\(^ {26}\)

In two of the studies, response of pigs to tulathromycin administered as a single IM dose at 2.5 mg/kg of body weight was compared with the response of control pigs given a similar saline injection. In the remaining four studies, response of tulathromycin-treated pigs was compared with a saline-treated control group and a group treated with ceftiofur sodium administered in three daily parenteral doses of 3.0 mg/kg. The ceftiofur-treated groups were included to confirm the antimicrobial responsiveness of the SRD being treated. Each study included females and castrated males. All pigs enrolled in the efficacy studies were identified with uniquely numbered ear tags.

Exclusion criteria consisted of a known history of receiving antimicrobials within 5 days before enrollment, clinical signs of SRD on arrival, preexisting medical conditions, moribund attitude, clinical signs of disease other than SRD, intractable behavior, and significant trauma. Clinical evidence of SRD was characterized by respiratory scores, attitude scores, and rectal temperature.

Respiratory scores were assigned as:

0 = Normal

1 = Mild increase in respiratory effort and/or occasional cough

2 = Moderate increase in respiratory effort and/or obvious cough (e.g., multiple coughing episodes within several minutes)

3 = Dyspnea (i.e., gasping or open-mouth breathing) and/or cyanosis

**Tulathromycin shows in vitro bactericidal activity against several important gram-negative pathogens.**
Attitude scores were assigned as:

0 = Normal
1 = Mild depression, lethargy but responsive to stimulation
2 = Moderate depression, lethargy, recumbent but ambulatory when stimulated
3 = Severe depression or moribund, unable to rise, resistant to stimulation but capable of rising

Pigs were eligible for enrollment if they had a respiratory score above 1 and/or an attitude score above 1 and a rectal temperature of 40°C (104°F) or higher on day 0.

Treatments

Tulathromycin injectable solution (Draxxin Injectable Solution, Pfizer Animal Health) was administered as a single IM injection in the neck at a dose of 2.5 mg/kg (1.1 ml/100 lb) of body weight. Dose volume of tulathromycin did not exceed 2.5 ml/injection site. Physiologic saline was used as a control and given as a single IM injection in the neck at a dose volume of 0.025 ml/kg. In the latter four of the six studies, commercial ceftiofur sodium (Naxcel, Pfizer) was given as a daily IM injection in the neck for 3 consecutive days at a dosage of 3.0 mg/kg (1 ml/22 lb) of body weight.

Study Design

Six field efficacy studies were conducted according to a common protocol at contract research or commercial grow–finish facilities. The studies were conducted at five geographically separate sites in the United States and Canada. Husbandry at each study location was typical for swine production systems. Pigs were offered nonmedicated pelleted rations and ad libitum water via nipple waterers. Building ventilation was mechanical, natural, or a combination of both. Commercial-type feeders provided adequate feeder space for each pig, and floor space ranged from about 4 to 9.7 sq ft/pig.

In each study, candidate animals were observed for clinical disease twice daily during a preenrollment period lasting at least 5 days. At the beginning of each outbreak, the first pigs at each site that exhibited clinical signs of SRD (respiratory or attitude scores >1) were classified as nontreated animals, euthanized, and necropsied to obtain pneumonic lung samples, which were tested at regional diagnostic laboratories for bacterial and mycoplasmal pathogens commonly associated with SRD.

After adequate numbers of lung samples were collected from the nontreated animals, animals meeting the enrollment criteria were randomly assigned in equal numbers to respective treatment groups and pens according to a randomized complete block design with sexes balanced across treatment groups. Pigs were blocked by order of enrollment and gender. Blocks consisted of one pig from each treatment group, and enrollment in any block was completed within 1 day. Pens contained complete blocks only, with each pen housing six animals. Treated pigs were observed for adverse local or systemic effects at 1 and 4 hours after treatment. The enrollment and treatment process continued until the allotted number of test animals for the study was reached. In five of the studies, full enrollment ranged from 1 to 5 days. At the Iowa study location, enrollment occurred over a 21-day period. Except for Ontario, Canada, where only 30 pigs were enrolled in each treatment group because acute diarrhea excluded the remaining study candidate pigs from enrollment, 44 to 48 pigs were enrolled in each treatment group.

In California and Ontario, Canada, enrolled pigs were assigned to one of two treatment groups, saline or tulathromycin. At these locations, each pen contained three pigs from each treatment group. In the subsequent four studies, animals were assigned to one of three treat-
ments: saline, tulathromycin, or ceftiofur sodium. Each pen in these study locations housed two pigs from each treatment group. All treatments were based on day 0 body weights. Site investigators and all other personnel making clinical assessments were masked to the identity of the treatment group to which study animals were assigned.

The primary endpoint of each study was cure rate, which was based on assessments of clinical scores, rectal temperatures, and mortality. On day 7 following treatment, surviving animals (in addition to mortalities, some animals may have been removed from the study because of disease other than SRD or injury) were considered cured if they did not have a respiratory or attitude score above 1 or a rectal temperature of 40°C (104°F) or higher. Animals not cured by day 7 were considered nonresponders. Saline-treated nonresponders were euthanized on the day they were identified as such and necropsied for identification of SRD pathogens. The SRD pathogens identified from the saline-treated nonresponding animals at each site were used to determine which bacterial pathogens were present. Bacterial isolation and identification were performed at regional laboratories. Minimum inhibitory concentrations (MICs) of bacterial pathogens were determined by Colorado Animal Research Enterprise, Fort Collins, CO. MICs were determined according to applicable National Committee for Clinical Laboratory Standards (NCCLS; now Clinical and Laboratory Standards Institute [CLSI]) methods. Mycoplasmal identification and MIC determinations were performed at the Animal Disease and Diagnostic Laboratory, Purdue University, following methods previously described.

Statistical Analysis

Each pig was considered an experimental unit. Frequencies of mortality and cure rates were analyzed in each study using the Cochran-Mantel-Haenszel row means score test. Following a significant overall test of treatment differences within studies with three treatment groups, pairwise comparisons of cure rates were tested with Fisher’s exact test with a bootstrap adjusted P value. The GLIMMIX macro in the SAS (SAS Version 8.1, SAS Institute, Cary, NC) system was used to conduct a multistudy analysis of cure rate and mortality with a model that included terms for study, treatment, and treatment by study interaction. A 5% probability level (P ≤ .05) was used to determine statistically significant differences. Cure rate (%) in a treatment group was defined as:

\[
100 \times \left( \frac{\text{No. of animals classified as cures}}{\text{No. of animals in the group} - \text{No. of animals removed for non-SRD reasons}} \right)
\]

These studies were designed for 40 animals in each of the two or three treatment groups. The sample size was chosen to provide 80% power of detecting a 30% difference in cure rates between treatment groups.

RESULTS

A total of 720 pigs were assigned to the three treatment groups across the six individual studies, as noted in Table 1. Mortality and cure rates were calculated for 267 saline-, 266 tulathromycin-, and 187 ceftiofur-treated pigs. The overall cure rate was 46.4% for the saline-treated pigs, 71.1% for the tulathromycin-treated pigs, and 63.1% for the ceftiofur-treated pigs. The overall cure rate for tulathromycin-treated animals was significantly (P = .0116) higher versus that for the control group and not statistically different (P = .4556) compared with that of the ceftiofur-treated pigs. In three of the six individual studies, cure rates were significantly (P < .05) higher for tulathromycin-treated pigs compared with the saline group (Table
TABLE 1. Therapeutic Efficacy of Tulathromycin against Naturally Occurring SRD

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>California</th>
<th>Ontario, Canada</th>
<th>Nebraska 1</th>
<th>Iowa</th>
<th>Ohio</th>
<th>Nebraska 2</th>
<th>All Studies (Total [Least Squares Means])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline (n = 267)</td>
<td>34 (70.8%)</td>
<td>13 (43.3%)</td>
<td>14 (28.6%)</td>
<td>21 (47.7%)</td>
<td>23 (47.9%)</td>
<td>19 (39.6%)</td>
<td>124 (46.1%)</td>
</tr>
<tr>
<td>Tulathromycin (n = 266)</td>
<td>38 (79.2%)</td>
<td>12 (40.0%)</td>
<td>31 (64.6%)</td>
<td>30 (68.2%)</td>
<td>39 (81.3%)</td>
<td>39 (81.3%)</td>
<td>189 (70.6%)</td>
</tr>
<tr>
<td>Ceftiofur (n = 187)</td>
<td>NA</td>
<td>NA</td>
<td>18 (38.3%)</td>
<td>35 (79.5%)</td>
<td>28 (58.3%)</td>
<td>37 (77.1%)</td>
<td>118 (64.4%)</td>
</tr>
</tbody>
</table>

P Values

- Saline vs tulathromycin: .3460
- Saline vs ceftiofur: N/A
- Tulathromycin vs ceftiofur: N/A

Treatment differences for cure rates are statistically significant if P ≤ .05.

Cochran-Mantel-Haenszel test followed by Fisher’s exact test with bootstrap adjustment for pairwise comparisons.

Generalized linear mixed model (GLIMMIX macro). Least squares means backtransformed from logit scale to percentages.

TABLE 2. SRD Mortality by Study

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>California</th>
<th>Ontario, Canada</th>
<th>Nebraska 1</th>
<th>Iowa</th>
<th>Ohio</th>
<th>Nebraska 2</th>
<th>All Studies (Total [Least Squares Means])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>2</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Tulathromycin</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Ceftiofur</td>
<td>N/A</td>
<td>N/A</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

P Values

- Saline vs tulathromycin: .0530
- Saline vs ceftiofur: N/A
- Tulathromycin vs ceftiofur: N/A

Treatment differences for mortality rates are statistically significant if P ≤ .05.

Cochran-Mantel-Haenszel test followed by Fisher’s exact test with bootstrap adjustment for pairwise comparisons.

Generalized linear mixed model (GLIMMIX macro). Least squares means backtransformed from logit scale to percentages.

Overall tests not significant; therefore, contract P values not reported.
In two of the four studies in which ceftiofur was compared with tulathromycin, cure rates were significantly \( P = .0276 \) and \( P = .0406 \) higher for pigs treated with tulathromycin. In the other two studies, there were no differences between the two antimicrobial treatments. During these studies, no pigs were removed for non-SRD reasons following enrollment, and no adverse drug experiences were observed in any pigs treated with saline, tulathromycin, or ceftiofur.

Mortality from SRD occurred in three studies, with overall death loss totaling 24 saline-treated pigs (9.0%), seven tulathromycin-treated pigs (2.6%), and one ceftiofur-treated pig (0.5%) (Table 2). The difference in mortality rates between the saline and tulathromycin groups was not significant in any of the individual studies, although it approached significance in the California study \( P = .0530 \). In the Iowa study, differences in mortality between the saline and ceftiofur groups were significant \( P = .0001 \). The overall mortality rate was significantly lower for both the tulathromycin and ceftiofur treatment groups compared with saline-treated pigs \( P = .0148 \) and \( P = .0195 \), respectively). The mortality rates were not significantly \( P = .1710 \) different between the tulathromycin and ceftiofur treatment groups.

Table 3 presents the bacterial and mycoplasmal pathogens isolated from lung tissue of nontreated (i.e., nonenrolled pigs with SRD) and enrolled saline-treated nonresponders, in order of pathogen frequency. The most commonly isolated primary pathogens associated with SRD were \textit{M. hyopneumoniae} and \textit{A. pleuropneumoniae} followed by \textit{B. bronchiseptica}, \textit{P. multocida}, and \textit{H. parasuis}. Five of the studies had substantial \textit{M. hyopneumoniae} and \textit{Mycoplasma hyorhinis} involvement. In two of the three studies (Nebraska 1 and Ohio) in which tulathromycin-treated pigs experienced a statistically significant improvement in cure rate, the predominant pathogens were \textit{M. hyopneumoniae}, \textit{M. hyorhinis}, \textit{M. hyopneumoniae}, and \textit{P. multocida}.

In one study (Ontario, Canada), PRRS and swine influenza viruses were isolated. The PRRS virus was determined to be the primary etiologic agent in affected pigs at this particular site. Concurrent presence of \textit{M. hyopneumoniae} in these study pigs was consistent with the etiology of porcine respiratory disease complex (PRDC), a syndrome of multifactorial origin but typically involving primary infection with PRRS virus or \textit{M. hyopneumoniae} in combination with secondary bacterial pathogens.

In vitro tulathromycin susceptibility testing was conducted in separate studies for the bacterial and mycoplasmal organisms. Isolates were obtained from untreated animals at the beginning of respiratory disease outbreaks or from euthanized saline-treated pigs determined to be nonresponders (Table 4). Animals sampled were participants of the studies described herein and three exploratory (nonpivotal) studies conducted under a different protocol. The MIC\(_{90}\) values (the lowest concentrations that completely inhibited visible growth of 90% of isolates) were determined to be 32 µg/ml for \textit{A. pleuropneumoniae} incubated in carbon dioxide, 8 µg/ml for \textit{B. bronchiseptica}, 2 µg/ml for \textit{H. parasuis} incubated in carbon dioxide, 2 µg/ml for \textit{P. multocida}, and more than 64 µg/ml for \textit{Streptococcus suis} and \textit{Arcanobacterium pyogenes}. For \textit{M. hyopneumoniae} and \textit{M. hyorhinis}, the MIC\(_{50}\) was 8 and 0.063 µg/ml or less, respectively, and the MIC\(_{90}\) was more than 32 µg/ml for both organisms.

**DISCUSSION**

Based on the overall analysis of cure rate, the primary assessment of efficacy, these results indicated that pigs with acute SRD given a single dose of tulathromycin at 2.5 mg/kg of body weight had a significantly improved therapeutic response compared with saline-treated pigs. Variable responses to antimicrobial treatment
### TABLE 3. Target SRD Pathogens Cultured from Nontreated and Nonresponding Saline-Treated Pigs

<table>
<thead>
<tr>
<th>Targeted Pathogen</th>
<th>No. of Pigs with Positive Lung Culture by Study</th>
<th>No. (%) of Culture-Positive Pigs</th>
<th>Total Pigs Sampled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>California Ontario, Canada Nebraska 1 Iowa Ohio Nebraska 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>M. hyorhinis</em></td>
<td>0 29 27 30 36 23</td>
<td>145 (66.5%)</td>
<td>218</td>
</tr>
<tr>
<td><em>M. hyopneumoniae</em></td>
<td>0 20 14 24 30 18</td>
<td>106 (49.5%)</td>
<td>214</td>
</tr>
<tr>
<td><em>A. pleuropneumoniae</em></td>
<td>0 0 2 47 2 42</td>
<td>93 (37.2%)</td>
<td>250</td>
</tr>
<tr>
<td><em>B. bronchiseptica</em></td>
<td>12 5 0 17 9 0</td>
<td>43 (17.2%)</td>
<td>250</td>
</tr>
<tr>
<td><em>P. multocida</em></td>
<td>4 1 10 10 12 3</td>
<td>40 (16.0%)</td>
<td>250</td>
</tr>
<tr>
<td><em>H. parasuis</em></td>
<td>8 18 0 0 9 0</td>
<td>35 (14.0%)</td>
<td>250</td>
</tr>
<tr>
<td><em>S. suis</em></td>
<td>2 11 0 0 6 1</td>
<td>23 (9.2%)</td>
<td>250</td>
</tr>
<tr>
<td><em>A. pyogenes</em></td>
<td>2 2 0 3 2 0</td>
<td>9 (3.6%)</td>
<td>250</td>
</tr>
<tr>
<td><em>Actinobacillus suis</em></td>
<td>0 0 0 0 0 6</td>
<td>6 (2.4%)</td>
<td>250</td>
</tr>
</tbody>
</table>

More than one bacterial species may have been isolated from a pig.

### TABLE 4. MICs of Tulathromycin against Bacteria Isolated from Pigs with Naturally Occurring SRD

<table>
<thead>
<tr>
<th>Bacterial and Mycoplasmal Isolates</th>
<th>App in Air (n = 135)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>App in CO&lt;sub&gt;2&lt;/sub&gt; (n = 135)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Pm (n = 55)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Bb (n = 42)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Hp in Air (n = 34)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Hp in CO&lt;sub&gt;2&lt;/sub&gt; (n = 30)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Mhp (n = 30)</th>
<th>Mhr (n = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>1 16 0.5 2 ≤0.063 0.25 ≤0.063 ≤0.063</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode</td>
<td>4 16 0.5 4 0.25 1 ≤0.063 ≤0.063</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>4 32 &gt;64 8 &gt;64 &gt;64 &gt;32 &gt;32</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>4 16 1 4 0.25 1 8 ≤0.063</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>4 32 2 8 0.5 2 &gt;32 &gt;32</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<sup>a</sup>Of the total *A. pleuropneumoniae* (App) isolates, 45 were obtained from nonpivotal studies.

<sup>b</sup>Of the total *P. multocida* (Pm) isolates, 19 were obtained from nonpivotal studies.

<sup>c</sup>Of the total *B. bronchiseptica* (Bb) isolates, three were obtained from nonpivotal studies.

<sup>d</sup>Of the total *H. parasuis* (Hp) isolates, three were obtained from nonpivotal studies.

CO<sub>2</sub> = carbon dioxide; Mhp = *M. hyopneumoniae; Mhr = M. hyorhinis.*
in some studies suggest that clinical signs present at enrollment and/or on day 7 were not related to antimicrobial-responsive disease. In the California study, eight deaths were observed in the saline control pigs versus two deaths in the tulathromycin-treated pigs. While this result tends to indicate that some pigs had severe bacterial disease, a higher-than-expected response rate in the saline groups (70.8%) indicates that a high proportion of pigs were minimally affected. In the Ontario study, microbiologic testing in treated animals confirmed involvement of PRRS and swine influenza virus, a primary viral etiology that would have been refractory to antimicrobial therapy. In contrast, in the other four studies, the therapeutic responses of tulathromycin or ceftiofur confirmed respiratory disease associated with a primary bacterial etiology. Tulathromycin had superior cure rates compared with saline in three studies. In the Iowa study, in which there were no significant differences in cure rates between tulathromycin- and saline-treated pigs, there was a high incidence of mortalities in the tulathromycin and saline treatment groups, but none in the ceftiofur-treated pigs. Additionally, a high frequency of _A. pleuropneumoniae_ was cultured from saline-treated nonresponders and nontreated pigs. Furthermore, cure rates of ceftiofur-treated pigs were superior to those of saline-treated pigs. These findings suggest that the respiratory disease in this study may have been more severe than in the other studies.

Although tulathromycin had superior cure rates compared with ceftiofur in two of the four comparisons, the overall cure rate for the pigs treated with ceftiofur compared favorably with that for tulathromycin-treated pigs. An explanation for the individual location efficacy differences between these antimicrobials may be the multifactorial bacterial etiology of respiratory disease in swine. _M. hyopneumoniae_ was present in lung samples obtained at each of the four sites. _M. hyopneumoniae_ and bacterial infections, especially _P. multocida_, commonly result in enzootic pneumonia. Furthermore, the presence of _M. hyopneumoniae_ and secondary bacteria, such as _P. multocida_, often results in an increased severity of pneumonia. Because of the lack of a cell wall, mycoplasmas are resistant to cephalosporin-class antimicrobials, such as ceftiofur. In contrast, tulathromycin has been shown to be effective in the treatment of SRD associated with _M. hyopneumoniae_ in the European Union. Also, it was interesting to note that at the two locations where tulathromycin had superior cure rates compared to ceftiofur, few _A. pleuropneumoniae_ were cultured from the lungs of saline and nontreated pigs. Conversely, at the other two sites, there were no differences in cure rates between the two antimicrobials, but a much higher frequency of _A. pleuropneumoniae_ was cultured from the lungs of saline and nontreated pigs. However, the prolonged elimination of tulathromycin provides for a single-dose regimen, which is a distinct advantage compared with three daily doses of ceftiofur. Additionally, single-dose administration will minimize animal handling and ensure proper dose frequency compliance.

The in vitro susceptibility testing of the clinical field isolates provides interesting data relative to correlation of clinical response and in vitro potency. Relatively high MICs were observed for several pathogens for which clinical response has been observed. The apparently high MIC$_{90}$ for _A. pleuropneumoniae_, the causative agent of porcine pleuropneumonia, is perhaps the most relevant because standardized microdilution methods have been described for this organism. Some fastidious bacteria, such as _A. pleuropneumoniae_ and _H. parasuis_, can sometimes require carbon dioxide supplementation to achieve proper growth for testing conditions. Comparison of MICs with and without carbon dioxide supplementation
Table 4) shows MIC results four to eight times higher with supplemented carbon dioxide than without. The most likely explanation is an acid pH shift outside of normal range under incubation.\(^{30,31}\) Tulathromycin, like some other macrolides, produces higher MICs under acidic conditions. Another culture condition known to reduce the MIC of \(A.\) pleuropneumoniae and other pathogens is media supplementation with heat-treated serum, even in the absence of carbon dioxide.\(^{32}\)

Test methods for \(Mycoplasma\) spp are not yet standardized across laboratories. Although carbon dioxide supplementation was not used in the tests described herein, growth of the organism was detected through phenol red color change produced by acid fermentation of media substrate over several days. MICs have not been determined under conditions controlling pH during organism growth.

Although pharmacokinetic data are successfully used to predict efficacy in the presence of low MICs and the absence of clinical data, controlled clinical efficacy studies are necessary to determine the significance of MIC values that are high because of laboratory testing conditions. In addition to the clinical results outlined in this report, clinical efficacy of tulathromycin at 2.5 mg/kg against \(A.\) pleuropneumoniae was clearly demonstrated in a controlled study in which the MIC of the challenge agent was 16 µg/ml.\(^{35}\)

CONCLUSION

In this field efficacy study conducted at five geographically separate sites, tulathromycin was both safe and effective in the treatment of SRD, particularly in herds in which \(A.\) pleuropneumoniae, \(P.\) multocida, and \(M.\) hyopneumoniae were present.

ACKNOWLEDGMENTS

The authors thank the following investigators and their staffs for conducting the studies: John J. Brennan, PhD, Shur-Gain Agresearch, Burford, ON, Canada; Gary W. Davis, DVM, PhD, Greenbriar Veterinary Services, Inc., Delaware, OH; Lyle Kesl, DVM, PhD, Veterinary Resources, Inc., Ames, IA; Kelly F. Lechtenberg, DVM, PhD, Midwest Veterinary Services, Oakland, NE; and Terry N. Terhune, DVM, PhD, HMS Veterinary Development, Tulare, CA; and thank Donald J. Bade, BS, Colorado Animal Research Enterprises, Fort Collins, CO, and Ching Ching Wu, DVM, PhD, Purdue University, West Lafayette, IN, for the microdilution susceptibility testing. We also thank Mark Dana for assistance in preparing the manuscript.

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