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A randomized trial to compare the efficacy of tildipirosin and tulathromycin for initial treatment of bovine respiratory disease in naturally exposed commercial feedlot heifers

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Abstract

This clinical trial compared health and performance outcomes between commercial feeder heifers that received either tulathromycin (TUL) or tildipirosin (TLD) for initial treatment of bovine respiratory disease (BRD). Study heifers, predominately Angus-cross (503.44 lb [228.36 kg] mean body weight), were recently received at a west Texas feedlot from Kentucky, Alabama, and Arkansas, and did not receive metaphylaxis. An experienced pen rider, blinded to treatment groups throughout the study, observed heifers daily for clinical signs of BRD. Six hundred heifers, with either mild BRD and a rectal temperature ≥ 104°F (40°C), or moderate to severe BRD regardless of rectal temperature, were randomly allocated to receive either TUL (100 mg/mL, 1.13 mg/lb [2.5 mg/kg] body weight) or TLD (180 mg/mL, 1.81 mg/lb [4 mg/kg] body weight). Heifers were randomly allocated to 12 commingled pens, each holding 25 hd of each treatment group (50 hd total/pen). Data were analyzed with linear mixed models for a randomized complete block design. There were no significant differences among treatment groups for baseline allocation data or for measures of body weight (P=0.52) or average daily gain (deads-out) at re-implant (P=0.20) or close-out (P=0.85). However, first treatment success was significantly better (P=0.05) for TUL (67.17%; 95% confidence interval 60.08 - 73.56%) than for TLD cattle (59.26; 51.91 - 66.23%). Second and third treatment success, and the percent designated as BRD chronics, did not differ significantly between groups (P-values > 0.10). The TUL treated heifers had significantly (P-values = 0.02) less BRD mortality (4.95%; 2.89 - 8.35) and overall mortality (5.94%; 3.61 - 9.61) as compared to TLD treated heifers (10.25%; 6.88 - 15.02, and 11.56%; 7.90 - 16.62, respectively). Overall, TUL as initial BRD treatment resulted in significantly better health outcomes as compared to TLD treatment in this study population.

Key words: bovine, respiratory disease, BRD, tildipirosin, tulathromycin, feedlot

Résumé

Cet essai clinique a été mené afin de comparer la santé et la performance chez des génisses de parcs d'engraissement recevant soit de la tulathromycine (TUL) ou soit de la tildipirosine (TLD) pour le traitement initial du complexe respiratoire bovin (CRB). Les génisses à l'étude, principalement de race Angus (503.44 lb [228.36 kg] poids corporel moyen), venaient d'arriver récemment à un parc d'engraissement de l'ouest du Texas en provenance du Kentucky, de l'Alabama et de l'Arkansas et n'avaient pas reçu de médicaments en métaphylaxie. Un employé du parc à l'insu des groupes de traitement a observé les génisses chaque jour pour des signes cliniques associés au CRB. Un total de 600 génisses, avec soit un CRB léger et une température rectale ≥ 104°F ou soit un CRB modéré ou sévère sans égard à la température, ont été alloués aléatoirement au groupe TUL (100 mg/mL, 1.13 mg/lb [2.5 mg/kg] poids corporel) ou au groupe TLD (180 mg/mL, 1.81 mg/lb [4 mg/kg] poids corporel). Les génisses étaient placées aléatoirement dans 12 enclos regroupant chacun 25 têtes de chaque groupe de traitement (50 têtes au total/enclos). Les données ont été analysées avec des modèles linéaires mixtes selon un plan pour blocs aléatoires complets. Il n'y avait pas de différence significatives entre les deux groupes pour les données d'allocation de base, pour les mesures de poids corporel (P=0.52) ou pour le gain quotidien moyen (excluant les morts) à la réimplantation (P=0.20) ou à la sortie (P=0.85). Le succès du premier traitement était significativement plus

élevé (P=0.05) dans le groupe TUL (67.17%; intervalle de confiance à 95% 60.08 - 73.56%) que dans le groupe TLD (59.26; 51.91 - 66.23%). Le succès du second ou troisième traitement et le pourcentage de cas considérés comme chroniques n'étaient pas différents dans les deux groupes (les valeurs de P>0.10). La mortalité reliée au CRB (4.95%; 2.89 - 8.35) et la mortalité en général (5.94%; 3.61 - 9.61) étaient moindres chez les génisses traitées du groupe TUL (valeurs de P=0.02) que chez les génisses du groupe TLB (10.25%; 6.88 - 15.02, et 11.56%; 7.90 - 16.62, respectivement). Dans son ensemble, le traitement initial du CRB avec TUL a permis une amélioration significative de la guérison par rapport au traitement avec TLD dans cette population d'étude.

Introduction

The bovine respiratory disease (BRD) complex is a multi-causal disease syndrome that has a significant negative impact on the health and performance of feedlot cattle. In a cattle health and management survey of US feedlots in 2011, BRD was the most common cause of mortality and morbidity with 16.2.% of feedlot cattle diagnosed with BRD, and an average cost for each treatment of $23.60.[15] Furthermore, economic losses due to BRD extend beyond direct treatment costs to the effects of reduced average daily gain (ADG), reduced feed conversion, increased lung lesions, and reduced weight and quality of carcasses at harvest.[4,7,13] Irsik et al estimated additional production costs per hundred lb body weight gain ranged from $0 (no cattle in pen treated) to $35.52 (all cattle in pen treated),[8] while another study estimated reduced carcass values of $23.23, $30.15, and $54.02 for commercial feedlot cattle with 1, 2, or 3 or more BRD treatments, respectively.[12] In addition, Cernicchiaro et al demonstrated that net economic returns for feedlot cattle were significantly associated with the number of BRD treatments, and that these effects varied based on season, even after accounting for the variability in arrival weight and gender of feedlot cattle populations.[4]

Effective prevention, control, and treatment of BRD remains of paramount importance to the feedlot industry. Prevention and control methods for BRD often target a combination of environmental, host, and management factors.[6] Antimicrobial administration, as metaphylaxis and/or as treatment for BRD, is a specific control method that remains critical to improving health and welfare in feeder cattle.[10] There is tremendous diversity in the types of cattle fed in feedlot production systems, as well as in the types of antimicrobials available for use in control and treatment of BRD. Antimicrobial use strategies for treatment of BRD are often implemented based on effectiveness, duration of effect, and cost. Macrolide antimicrobials are often a preferred choice for initial treatment for BRD based on relative efficacy and the fact they only require a single dose, which reduces handling stress.

Several macrolide antibiotics, including gamithromycin, tildipirosin, tilmicosin, and tulathromycin, are approved for use in feedlot cattle for the treatment of BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and/or *Histophilus somni*. Meta-analyses and randomized treatment trials have been used to compare the efficacy of tulathromycin and tildipirosin when used as metaphylaxis for BRD control in feedlot cattle.[1,11] To the authors' knowledge, there are no randomized clinical trials published that directly compare the effectiveness of tulathromycin and tildipirosin as first-line therapy for BRD in commercial feeder cattle. Therefore, the objective of this study was to compare health and performance outcomes between commercial feeder heifers that received tulathromycin or tildipirosin for initial treatment of bovine respiratory disease.

Materials and Methods

Cattle

Predominantly Angus-cross, commercial feedlot heifers were purchased from Kentucky, Alabama, and northwestern Arkansas through order-buying firms and shipped to a cattle feedlot research facility in the Texas Panhandle, arriving November 2 thru 12, 2016. The heifers were processed within 24 hours of arrival and placed in outdoor, dirt-floor, holding pens with not less than 100 sq ft (9.3 sq m)/animal. During processing, all heifers were assigned individual, duplicate visual identification ear tags in each ear, administered modified-live bovine rhinotracheitis (IBR) virus, bovine viral diarrhea (BVD) virus types 1 and 2, parainfluenza3 (PI3) virus, and bovine respiratory syncytial virus (BRSV) vaccine[a] (2 mL subcutaneously (SQ), *Clostridium chauvoei-septicum-novyi-sordellii-perfringens Type B, C & D* bacterin-toxoid[b] (2 mL SQ), doramectin[c] for internal and external parasites (10 mg/mL, 4.5 mL SQ), implanted with 100 mg progesterone and 10 mg estradiol benzoate[d] SQ), and administered dinoprost tromethamine[e] (5 mg/mL, 5 mL SQ) to abort pregnancies. Immediately following processing, heifers were returned to the holding pens. All heifers were re-implanted with 200 mg testosterone and 28 mg estradiol benzoate[f] on January 11, 2017.

Health observations and study allocation

Heifers that exhibited signs of BRD between arrival and processing were ineligible for study enrollment. Beginning the day after arrival processing, an experienced pen rider observed the heifers daily in their holding pens for clinical signs of BRD. The pen rider was blinded to treatments throughout the study, and was not present during treatment administration. Throughout the study, the same pen rider observed the heifers and assigned Clinical Appearance Scores (CAS). To assess eligibility for study entry (BRD treatment), heifers that exhibited clinical signs of BRD were assigned a CAS according to the following schedule:

0 = No clinical signs of BRD.

1 = Mild BRD clinical signs; heifer appears mildly depressed and/or has nasal and/or ocular discharge. Heifer usually alert and moves away when approached.

2 = Moderate BRD; heifer appears moderately depressed and moves slowly, even when approached. May exhibit nasal and/or ocular discharge, coughing, and dyspnea.

3 = Severe BRD; heifer appears severely depressed, anorexic, and stumbles or resists prodding. Heifer may have frequent coughing and copious nasal and/or ocular discharge.

4 = Moribund; heifer is recumbent and unwilling to rise. Heifer may be unable to move to the water tank or feed bunk.

The criteria for initial BRD treatment (i.e. study enrollment) included a CAS of 1 and pyrexia (rectal temperature[g] ≥ 104°F [40°C]) or a CAS ≥ 2 regardless of rectal temperature. Heifers that had a CAS ≥ 1 on d 0 were removed from the holding pen and processed for collection of rectal temperature. Heifers with a CAS = 1 and a rectal temperature ≥ 104°F (40°C) or a CAS ≥ 2, regardless of rectal temperature, were weighed, allocated to a treatment group, and administered appropriate treatment as follows. Heifers allocated to receive tulathromycin were administered 100 mg/mL tulathromycin[h] injectable solution (TUL) at a dosage of 1.13 mg/lb (2.5 mg/kg) body weight subcutaneously in the left lateral neck. Similarly, heifers allocated to receive tildipirosin were administered 180 mg/mL tildipirosin[i] (TLD) at a dosage of 1.81 mg/lb (4 mg/kg) body weight subcutaneously in the left lateral neck. Injections were administered using proper skin-tenting technique with a 12 mL syringe and a 16-gauge 1-inch hypodermic needle. A new needle was used on each heifer. All treatments were administered by 1 of 2 study treatment administrators; the blinded pen rider was not present for treatments. Based on pharmacokinetics and pharmacodynamics of macrolides, as well as industry practices, a 10-day post treatment interval (PTI) was observed on all initial treatments.

Pairs of heifers eligible for initial BRD treatment/study enrollment on the same day were allocated to treatment using a randomized treatment plan that was developed by using a Microsoft® Excel® random number generator that assigned a random number to 600 sequence numbers. The lowest random number within each pair of sequence numbers was assigned to the tulathromycin group, while the remaining random number was assigned to the tildipirosin group. The first heifer entering the treatment chute was randomly assigned to 1 of 2 treatments, and the second heifer entering the chute was assigned to the remaining treatment. This procedure continued for each pair of calves on a given allocation day. Heifers corresponding to the first 50 sequence numbers were assigned to 1 study pen, while heifers corresponding to the next 50 sequence numbers were assigned to a study pen, and so on until all 600 heifers were assigned to the 12 study pens. Allocation of 50 animals per pen (25 animals per treatment group) was based upon optimal pen density.

Following the initial treatment PTI, heifers meeting the aforementioned treatment criteria were administered ceftiofur crystalline free acid[j] (3.0 mg/lb [6.6 mg/kg] body weight) SC at the base of the ear, with a 7-day PTI before additional intervention. Heifers that completed the second BRD treatment PTI and were observed to have a CAS = 1 and a rectal temperature ≥ 104°F (≥ 40°C), or a CAS ≥ 2 regardless of rectal temperature, were pulled for re-treatment and administered oxytetracycline[k] (200 mg/mL, 9 mg/lb [20 mg/kg] body weight) SC in the neck, with a 3-day PTI before additional intervention.

Heifers were returned to their study pens following each treatment. Heifers requiring a fourth BRD treatment ("chronics") or assessed with a CAS of 3 during any BRD PTI period, regardless of rectal temperature ("rescues"), were moved from their study pen, weighed, administered enrofloxacin[l] (100 mg/mL, 5 mg/lb [11 mg/kg] body weight), and housed in a holding pen until being moved to a pasture. At any time during the study heifers with a CAS = 4, regardless of rectal temperature, were weighed, removed from study, and humanely euthanized. Prior to study initiation, standards of cattle care and welfare were defined in the protocol, and the owner of the cattle provided consent subject to protocol adherence.

Housing and feeding

Study cattle were housed in outdoor, dirt-floor pens constructed of pipe and cable. The pens measured 50 ft (15.24 m) wide and 100 ft (30.5 m) long, allowing 100 sq ft (9.3 sq m) of area per animal. All pens faced north on the same alley. The concrete feedbunk for each pen extended the entire width of the pen, with an 8 ft (2.4 m) concrete bunk apron. Heifers were fed standard feedlot rations comprised of steam flaked corn, chopped alfalfa hay, dried distillers grain (DDG), molasses blend, fat, micro-ingredients, and trace mineral supplement. Beginning on day of arrival, heifers were fed hay top-dressed with a starter ration (Ration #1) containing monensin[m] (Table 1); heifers were fed the starter ration (Ration #1) through December 19, 2016 (Table 1). Heifers were then fed the intermediate ration (Ration #2), containing monensin and tylosin[n] (Table 1), every other day for 4 days in order to accustom the heifers to eating a higher concentrate diet. Heifers were then only fed the intermediate ration (Ration #2) from December 24, 2016 through January 29, 2017. Heifers were then fed the finish ration (Ration #3) containing monensin and tylosin (Table 1) every other day for 4 days. The heifers were then fed the finish ration (Ration #3) exclusively from February 3, 2017 through June 6, 2017, after which the heifers were fed the finish ration (Ration #4) containing monensin, tylosin, and ractopamine hydrochloride[o] (Table 1) until the conclusion of the study on July 12, 2017.

Body weight measurements

Individual body weights were collected on all heifers on d 0, at re-implant, and at study conclusion (close-out) using a hydraulic chute with load cells.[p] Heifers also were weighed prior to administration of treatment therapy or study re-

Table 1. Ration composition and supplements fed (100% dry matter basis) to heifers from arrival to close-out.

Ingredient	Ration #1	Ration #2	Ration #3	Ration #4
Flaked corn, %	40.00	60.00	74.50	74.50
Alfalfa hay, %	38.50	23.00	8.50	8.50
Dried distillers grain, %	6.00	5.50	5.50	5.50
Molasses blend, %	10.00	5.00	4.00	4.00
Fat, %	0.00	1.00	2.00	2.00
Micro ingredient, %	1.00	1.00	1.00	1.00
Mineral supplement, %	4.50	4.50	4.50	4.50
Calculated Nutrients, 100% Dry Matter Basis				
Actual dry matter	80.24	80.87	80.56	80.56
Net energy main. Kcal/100 lb	80.95	91.30	100.58	100.58
Net energy prod. Kcal/100 lb	50.01	60.20	69.24	69.24
Crude protein	16.05	14.62	13.62	13.62
Non-protein nitrogen	2.08	1.98	1.96	1.96
Crude fat	3.35	4.88	6.33	6.33
Crude fiber	13.90	9.76	5.92	5.92
Calcium	0.81	0.70	0.62	0.62
Phosphorus	0.40	0.38	0.39	0.39
Potassium	1.94	1.31	0.81	0.81

All rations were formulated to also include a total of 40,000, 400, and 40 IU/head of vitamins A, D, and E, respectively, as well as targeted doses of 150-350 mg/head of monensin and 350 mg/head of ractopamine hydrochloride, and 8-10 g/ton of tylosin (on a 90% dry matter basis as per the Veterinary Feed Directive [VFD]).

moval. At close-out, all heifers were individually weighed prior to transport, and all harvested on the same day at a commercial beef processing facility in the Texas Panhandle.

Statistical analysis

Individual cattle, which were randomly allocated to treatment and then commingled within 12 pens, represented the experimental unit. Primary outcomes were the following binary variables: first treatment success, second treatment success, third treatment success, pen removal, chronic and mortality (within study pen mortality and post-pen removal mortality). Treatment success was defined as not requiring further treatment for BRD and not removed or died due to BRD. Treatment failures included heifers that: 1) were re-treated for BRD following completion of PTI, 2) were treated for BRD during PTI (rescue therapy) and removed from their study pen, and 3) died due to BRD. Animals removed from their study pen prior to eligibility for a subsequent BRD treatment (i.e. before the end of the corresponding PTI) for non-BRD reasons were considered neither a failure nor a success; instead, they were considered missing data for that specific analysis. Allocation and performance data included number allocated, initial source, initial body weight, re-implant body weight, final body weight, and ADG at re-implant and close-out. Average daily gain was calculated on a deads-out basis; only animals that were re-implanted or finished the study were included in the ADG analysis.

General and generalized linear mixed models (for performance and health variables, respectively) were used for all analyses using SAS Proc Glimmix.[9] Treatment was a fixed effect in the model, while pen was used as a random effect to account for the lack of independence among cattle within pens. Model adjusted means, standard errors of the means (SEM) or 95% confidence intervals (CI) were reported for all outcomes. A $P \leq 0.05$ level was used to define statistically significant differences between treatment groups.

Results

Heifers enrolled into the study arrived over an 11-day span from 3 origins. From 1 origin, heifers averaged 511.06 lb (231.82 kg) at purchase with an average off-truck weight of 482.68 lb (218.94 kg) for an in-transit shrink of 5.55% on the approximately 18-hour haul (n=382). For the second origin, heifers averaged 522.69 lb (237.09 kg) at purchase with an average off-truck weight of 492.21 lb (223.26 kg) for an in-transit shrink of 5.83% on the approximately 18-hour haul (n=283). Heifers from the third origin averaged 516.35 lb (234.21 kg) at purchase with an average off-truck weight of 492.94 lb (223.60 kg) for an in-transit shrink of 4.53% on the approximately 9-hour haul (n=126).

A total of 600 clinically ill heifers were pulled from holding pens and allocated to treatment between November 4 and November 14, 2016. Each study pen was filled within a 3-day period or less: 6 pens were filled within a 1-day period, 4 pens were filled within a 2-day period, and 2 pens were filled within a 3-day period. The distribution of heifers allocated from the 3 different cattle sources was not significantly different between treatment groups (P=0.39). In addition, mean body weights at allocation were not significantly different

among treatment groups (Table 2). Similarly, at re-implant and at close-out, neither mean body weights nor ADG (deads-out) differed significantly among treatment groups (Table 2). At study enrollment, 262 and 38 heifers in the tulathromycin group were assigned CAS of 1 and 2, respectively, while 261 and 39 heifers in the tildipirosin group were assigned CAS of 1 and 2, respectively.

Only 6 animals died while still in study pens, but there were also 105 total removals, 47 of which eventually died (46 attributed to BRD). Thus, overall mortality (all causes) was 8.83% (53/600). Over 70% (70.27%; 78/111) of removals and deaths occurred during the first 30 days-on-feed (DOF), with an additional 25 removals and deaths occurring by 60 DOF (92.79% 103/111). All 6 animals that died while still in study pens died after 60 DOF; these mortalities were attributed to bloat (3), musculoskeletal trauma (2), or calving difficulty (1). Cause of death was determined via necropsy performed by an on-site veterinarian who was blinded to treatment groups. Of the 105 heifers removed from the study pens, the majority were removed due to chronic BRD (as defined above; n=54) or severe BRD requiring emergency therapy (CAS = 3, as designated by blinded observer; n=46). The remaining removals were due to encephalitis (1), congestive heart failure (1), protocol deviation/wrong drug administered (1), or lameness (2). Of the BRD-related mortalities in the TUL group, 86.0% (13/15) and 14% (2/15) had been enrolled with a CAS of 1 and 2, respectively. In the TLD group, 83.9% (26/31) and 16.1% (5/31) of the BRD-related mortalities had been enrolled with a CAS of 1 and 2, respectively.

Treatment means, confidence intervals, and *P*-values for comparisons of health outcomes among treatment groups are provided in Table 3. The first treatment success was significantly better for TUL treated heifers than for TLD treated heifers (Table 3). The second and third treatment success, and the percent of heifers designated as BRD chronics or removed from their study pen for any reason, did not differ significantly among treatment groups (Table 3). Overall, 5 heifers in the TLD group and 5 heifers in the TUL group became missing values for the first treatment success analysis because they were removed from their study pens (during

Table 2. Allocation and performance data. Model-adjusted means* (and standard errors of the means) by treatment group, and *P*-values for the overall effect of treatment (i.e. testing the null hypothesis that treatment group means are equal).

	Tulathromycin†	Tildipirosin‡	*P*-value
No. allocated	300§	300§	-
Allocation body weight, lb	502.52 (2.63)	504.37 (2.63)	0.52
Re-implant§ body weight, lb	702.00 (5.66)	699.51 (5.75)	0.66
Final§ body weight, lb	1281.88 (9.56)	1282.64 (9.70)	0.94
Re-implant§ ADG, lb	3.18 (0.06)	3.09 (0.06)	0.20
Final§ ADG, lb	3.20 (0.03)	3.19 (0.03)	0.85

*From statistical analyses that account for the lack of independence among animals within pens.
†Draxxin®, Zoetis, Parsippany, NJ
‡Zuprevo®, Merck Animal Health, Madison, NJ
§Head counts were 256 and 241 at re-implant, 251 and 238 at close-out, for tulathromycin and tildipirosin groups, respectively.

Table 3. Health outcomes: model-adjusted means* and 95% confidence intervals (CI) by treatment group, and *P*-values for the overall effect of treatment.

	Tulathromycin†		Tildipirosin‡		*P*-value
	Mean	95% CI	Mean	95% CI	
First treatment success, %	67.17	60.08 - 73.56	59.26	51.91 - 66.23	0.05
Second treatment success, %	55.26	41.38 - 68.37	53.28	39.93 - 66.18	0.79
Third treatment success, %	38.46	24.51 - 54.61	33.33	21.04 - 48.40	0.62
Percent chronic, %	12.04	7.44 - 18.91	13.97	8.79 - 21.50	0.47
Total study pen removals (all causes), %	14.88	10.27 - 21.08	19.19	13.68 - 26.25	0.16
Died in study pens§ (all non-BRD), %	1.00	0.32 - 3.06	1.00	0.32 - 3.06	1.00
BRD mortality (all post pen-removal), %	4.95	2.89 - 8.35	10.25	6.88 - 15.02	0.02
Total mortality¶, %	5.94	3.61 - 9.61	11.56	7.90 - 16.62	0.02

*From generalized linear mixed statistical models that account for the lack of independence among animals within pens.
†Draxxin®, Zoetis, Parsippany, NJ
‡Zuprevo®, Merck Animal Health, Madison, NJ
§Mortality diagnosis for tulathromycin group was 1 each bloat, calving complications, and back injury; for tildipirosin group was 2 bloat and 1 back injury.
¶Total mortality includes those died on study (all were non-BRD) and those died following removal (all BRD except 1 that was returned to home herd as a cripple and subsequently died).

the PTI) for non-BRD reasons. No heifers were considered missing values for any of the other analyses. Of the heifers that required a second BRD treatment in the TUL group, 88.8% (87/98) and 11.2% (11/98) had been enrolled with a CAS of 1 and 2, respectively. In the TLD group, 87.6% (106/121) and 12.4% (15/121) were enrolled with a CAS of 1 and 2, respectively. Three cattle in each treatment group died prior to removal from their study pen (Table 3). All mortalities attributed to BRD (n=46) occurred following removal from study pens, and the TUL-treated heifers had significantly less BRD mortality and overall mortality as compared to TLD-treated heifers (Table 3).

Discussion

This is the first published randomized clinical trial to directly compare the efficacy of tulathromycin and tildipirosin for initial treatment of BRD in commercial feeder cattle. The study population of Angus-cross heifers was transported from 3 sources in the southeastern US to a research feedlot in the Texas Panhandle during November. Although the overall health of the heifers was good at arrival, shipping stress and commingling contributed to a high risk of BRD. The 600 study heifers, randomly assigned to 2 treatment groups, were diagnosed with clinical BRD over the first 10 days following arrival processing. In this study population, tulathromycin was significantly more effective than tildipirosin in first treatment success (P=0.05), total BRD mortality (P=0.02), and overall mortality (P=0.02).

Although to our knowledge there are no other published studies that directly compare the efficacy of tulathromycin and tildipirosin when administered for initial treatment of naturally acquired BRD in commercial feedlot cattle, there are published experimental challenge studies with BRD-related pathogens, metaphylaxis studies, and meta-analyses with indirect comparisons of tulathromycin and tildipirosin. Confer compared health and lung lesions in calves that were experimentally infected with *Histophilus somni* 5 days after receiving tulathromycin or tildipirosin.[5] Calves that had received tildipirosin had lower BRD clinical scores and less lung consolidation than calves that had received tulathromycin metaphylaxis or a saline control treatment. This study population was comprised of twenty-four (n=8 per treatment group) 3-month-old Holstein steers, and thus the external validity of this experimental challenge study, relative to the feedlot industry, was limited. Another experimental challenge study compared tildipirosin and tulathromycin metaphylaxis followed by inoculation of calves with *Mannheimia haemolytica*.[2] Calves in this study that received tildipirosin pre-challenge had fewer lung lesions and lower clinical scores than calves that had received tulathromycin or saline. In contrast, Bartram showed that calves treated with tulathromycin had fewer lung lesions, lower clinical scores, and lower mortality than calves that had received tildipirosin. However, this experimental study used a *Mycoplasma bovis* challenge model.[3]

A randomized trial in commercial feedlot steers that were naturally exposed to BRD, with BRD morbidity measured throughout the feeding period, compared the efficacy of tulathromycin, tildipirosin, and tilmicosin metaphylaxis.[14] Calves that had received tulathromycin had lower BRD morbidity, BRD chronics, BRD mortality, and overall mortality than calves that had received tilmicosin or tildipirosin metaphylaxis.

Meta-analyses that describe the efficacy of tildipirosin and tulathromycin in feedlot cattle have been conducted; these studies analyzed BRD metaphylaxis rather than first-line BRD therapy,[1] general treatment for BRD,[11] or both metaphylaxis and post-diagnosis treatment for BRD.[9] Abell showed that metaphylactic administration of tulathromycin was more effective at preventing BRD than tildipirosin in feedlot cattle; however, these results were based on comparisons using data from multiple studies that did not directly compare tulathromycin and tildipirosin (i.e. indirect comparisons based on studies that compared tulathromycin or tildipirosin to other treatments). Their meta-analysis estimated that the odds of BRD morbidity (OR=2.27, 95% CI 1.10 – 4.06) and mortality (OR=5.39, 95% CI 1.03 – 14.73) in feedlot cattle was higher with tildipirosin metaphylaxis as compared to tulathromycin.[1] O'Connor also conducted a meta-analysis with comparisons of antimicrobial efficacy, in this case, for BRD treatment. They showed a higher risk of BRD re-treatment after tildipirosin treatment as compared with tulathromycin treatment, but this was not significantly different and again was based only on indirect comparisons of BRD treatment efficacy.[11] Nautrup restricted their meta-analysis only to studies comparing tulathromycin with other antimicrobials. They estimated that tildipirosin treatment for BRD was associated with more re-treatments than tulathromycin, but there was not a strong association.[9]

Although heifers in both treatment groups were managed identically, the comparative results of our study may have been influenced by a high burden of BRD-related illness within study pens. In these BRD cases, overall mortality, which was mostly comprised of heifers that died after study pen removal due to severe or chronic BRD, was 8.83% (53/600), and over 70% (70.27%; 78/111) of removals and deaths occurred during the first 30 DOF. The removal and rescue therapy of heifers with CAS = 3 contributed to a high-study pen removal rate and low within-study pen mortality. These removed heifers were not allowed the opportunity to reveal future health outcomes in the study pen. Hence, we reported the final disposition of all animals that were enrolled in the study in order to provide comprehensive information on all enrolled cattle. There were twice as many BRD mortalities after removal from study pens in the tildipirosin group versus the tulathromycin group (Table 3), which may be an important economic consideration. There was no difference in ADG between treatment groups, but ADG data were based on "deads-out" calculations (i.e. data did not include dead or removed cattle) at re-implant or close-out times. This distinction is important in this case, given that total mortalities, primarily occurring post-removal from study pens, differed among groups (Table 3). There were no significant

differences in second and third treatment successes between treatment groups. This may have been because all study heifers requiring re-treatment were administered identical therapy.

The external validity of this study should be assessed with regards to the unique characteristics of the study population, including source, season of placement, and overall stress. In addition, high-risk feeder cattle are often administered metaphylaxis and/or a *Mannheimia haemolytica* bacterin-toxoid, which could have potentially lowered the BRD incidence in the study population. Study pens were entirely comprised of heifers that were diagnosed and treated for BRD (i.e. were not treated and returned to home pens that included cattle without BRD). Thus, each study pen may have had a high BRD pathogen burden. Specific causes of BRD in this population were not investigated, nor is this typically done in commercial settings. It is possible that overall treatment efficacy may have been affected by the type of causative pathogens, whether bacterial or viral. Bacterial pathogen susceptibility to tildipirosin and tulathromycin, or macrolides in general, was not evaluated. Although clinical scores and body temperatures have inherent limitations in diagnostic sensitivity and specificity for BRD, the pen rider was blinded to treatment group assignment, and thus the same level of diagnostic performance would have been applied equally to both treatment populations.

Conclusions

This is the first published study directly comparing tulathromycin and tildipirosin for initial treatment of BRD in commercial feedlot heifers. In this study population, treatment with tulathromycin was associated with significantly lower BRD mortality and overall mortality, and significantly better first treatment success compared with tildipirosin treatment. To further determine the impacts of these BRD therapeutic options in the feedlot industry, future studies should include different feeder cattle populations managed in different production settings.

Endnotes

[a]Bovi-Shield Gold® 5, Zoetis, Parsippany, NJ
[b]Ultra Choice® 7, Zoetis, Parsippany, NJ
[c]Dectomax®, Zoetis, Parsippany, NJ
[d]Synovex® C, Zoetis, Parsippany, NJ
[e]Lutalyse®, Zoetis, Parsippany, NJ
[f]Synovex® One Feedlot, Zoetis, Parsippany, NJ
[g]M700 digital veterinary thermometer, GLA Agricultural Electronics, San Luis Obispo, CA
[h]Draxxin®, Zoetis, Parsippany, NJ
[i]Zuprevo®, Merck Animal Health, Madison, NJ
[j]Excede®, Zoetis, Parsippany, NJ
[k]Liquamycin® LA-200®, Zoetis, Parsippany, NJ
[l]Baytril®, Bayer, Shawnee Mission, KS
[m]Rumensin®, Elanco Animal Health, Greenfield, IN
[n]Tylan®, Elanco Animal Health, Greenfield, IN
[o]Actogain®, Zoetis, Parsippany, NJ
[p]GSE Model 350, GSE Scale Systems, Novi, MI
[q]SAS 9.4, SAS Institute, Cary, NC

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