Randomized Non-inferiority Clinical Trial Evaluating Three Commercial Dry-Cow Mastitis Preparations

Based on Publications:


Overview

A large clinical trial was conducted to compare the treatment efficacy of three dry-cow formulations: ToMORROW® (cephapirin benzathine), Spectramast® DC (500mg ceftiofur HCL) and Quartermaster® (1 x 10⁶ units penicillin G and 1g dihydrostreptomycin). The study was conducted across multiple states: WI (2), MN (1), IA (1) and CA (2), with 363 cows (1,452 quarters) randomly allocated per treatment. All quarters were also infused with Orbeseal®.

There was no difference among the preparations in the following quarter-level outcomes:

- The prevalence of intramammary infections (IMI) post calving
- Ability to cure preexisting IMI during the dry period
- Ability to prevent new IMI during the dry period
- Risk for a clinical mastitis event between calving and 100 days in milk (DIM)

There was also no difference in the following cow-level outcomes up to 100 DIM.

- Milk production (305ME)
- Linear score
- Risk for a clinical mastitis event
- Risk for leaving the herd
- Risk for getting pregnant

Introduction

Dry-cow mastitis treatment is a well-established management practice, intended to cure existing IMI acquired during lactation and to prevent new IMI in the dry period. The prevalence of subclinical IMI at dry-off can vary between 13 and 35%, and the incidence of new IMI during the dry period can vary from 8 to 25% (Godden, et al. 2003). The majority (50 to 60%) of all new infections, caused by environmental pathogens, occur during the dry period (Bradley and Green 2000).
Materials and Methods

The study was designed to detect a 10% difference in treatment effects at the quarter level. To qualify for the study, cows had to have four functional quarters, be in good general health, be in a herd undergoing regular Dairy Herd Improvement Association (DHIA) testing, no clinical mastitis at dry-off, and no history of having been treated with antibiotics or anti-inflammatory drugs within 30 days prior to enrollment. All study enrollment and sampling activities were conducted by university technicians who visited the herd on dry-off day each week.

Milk culture and pathogen identification techniques were in accordance with National Mastitis Council guidelines. The definitions for intramammary infection status were as follows:

- Presence of an IMI:
  - Most pathogens: ≥ 1 colony isolated in 10 μL of milk
  - Coagulase-negative staphylococci ≥ 2 colonies
  - Bacillus spp. ≥ 5 colonies
- Bacteriologic cure of an IMI:
  - Disappearance of one or two pathogens that were previously isolated at the dry-off milk sample from both post-calving samples
- New IMI:
  - Growth of one or two pathogens that had not been previously isolated at dry-off in either the 0–6 DIM or 7–13 DIM sample

Results

The IMI pathogens isolated during the study are displayed in Chart 1:

**Chart 1**

AER (Aerococcus spp.), BAC (Bacillus spp.), CNS (Coagulase-negative staphylococcus), COR (Corynebacterium spp.), ENT (Enterococcus spp.), GPO (Other Gram-positive), SDY (Streptococcus dysgalactiae), STA (Staphylococcus aureus), STR (Other streptococci), SUB (Streptococcus uberis), ECO (Escherichia coli), ENB (Enterobacter spp.), KLE (Klebsiella spp.), OGN (Other Gram-negative), SER (Serratia spp.)
At dry-off, 94.4% of the IMI were Gram-positive and 4.9% Gram-negative. After calving (0–6 DIM), 89.7% of the IMI were Gram-positive and 7% Gram-negative. The culture results were consistent with the pathogen profiles from dry-off and freshening cows in the modern dairy industry; the majority of isolates were environmental Gram-positives, with CNS spp. predominating. Contagious pathogens, which traditionally have been the major target for dry-cow therapy, were either totally absent (Streptococcus agalactiae) or were a very small percentage of isolated IMI (Staphylococcus aureus, 2.5% and 1.3% at dry-off and 0–6 DIM).

Statistical analysis of the results was performed with SAS 9.2. A logistic regression model was used for risk of IMI prevalence and cure. A mixed linear model was used for milk production and linear score to 100 DIM. Survival analysis was used for risk of clinical mastitis, risk of leaving herd and risk of becoming pregnant by 100 DIM.

A comparison of prevalence of IMI at dry-off, cure and new IMI among the three dry-cow therapies are shown in Table 1:

<table>
<thead>
<tr>
<th></th>
<th>ToMORROW® (cephapirin benzathine)</th>
<th>Quartermaster® (penicillin-dihydrostreptomycin in oil)</th>
<th>Spectramast® DC (ceftiofur hydrochloride)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMI present at Dry-off</td>
<td>20.7%</td>
<td>18.8%</td>
<td>18.2%</td>
<td>0.58</td>
</tr>
<tr>
<td>IMI present at 0–6 DIM</td>
<td>15.3%</td>
<td>15.4%</td>
<td>13.2%</td>
<td>0.3</td>
</tr>
<tr>
<td>IMI present at 7–13 DIM</td>
<td>13.7%</td>
<td>15.4%</td>
<td>14.9%</td>
<td>0.41</td>
</tr>
<tr>
<td>Cure</td>
<td>90.0%</td>
<td>89.8%</td>
<td>88.6%</td>
<td>0.72</td>
</tr>
<tr>
<td>New IMI at 0–6 DIM</td>
<td>14.2%</td>
<td>14.9%</td>
<td>12.3%</td>
<td>0.27</td>
</tr>
<tr>
<td>New IMI at 7–16 DIM</td>
<td>16%</td>
<td>17.9%</td>
<td>17.2%</td>
<td>0.6</td>
</tr>
<tr>
<td>Risk of clinical mastitis in qtr to 100 DIM</td>
<td>4.1%</td>
<td>5.3%</td>
<td>3.8%</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*Significance declared at P < 0.05

Cow level variables analyzed are shown in Table 2:

<table>
<thead>
<tr>
<th></th>
<th>ToMORROW® (cephapirin benzathine)</th>
<th>Quartermaster® (penicillin-dihydrostreptomycin in oil)</th>
<th>Spectramast® DC (ceftiofur hydrochloride)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of mastitis to 100 DIM</td>
<td>15%</td>
<td>14.8%</td>
<td>12.7%</td>
<td>0.8</td>
</tr>
<tr>
<td>Milk production (kg/day)</td>
<td>42.8</td>
<td>42.9</td>
<td>42.1</td>
<td>0.14</td>
</tr>
<tr>
<td>Linear score</td>
<td>1.7</td>
<td>1.9</td>
<td>2.0</td>
<td>0.12</td>
</tr>
<tr>
<td>Risk of leaving herd to 100 DIM</td>
<td>10.3%</td>
<td>7.5%</td>
<td>9.2%</td>
<td>0.55</td>
</tr>
<tr>
<td>Risk of pregnancy by 100 DIM</td>
<td>26.9%</td>
<td>31.5%</td>
<td>26.1%</td>
<td>0.26</td>
</tr>
</tbody>
</table>

*Significance declared at P < 0.05.
Discussion

This study, which was designed as a non-inferiority study, demonstrated no significant difference among the three dry-cow intramammary preparations.

The majority of pathogens isolated in this study were CNS spp., and the results reflect the preponderance of this organism in all sampling stages. Although the numbers are small, the biggest disparity in cure rates by pathogen was for \textit{Staphylococcus aureus}. The number of quarters at risk of a cure and the cure rate (CR) are as follows for each treatment: QM ($n = 5$); CR = 80%; SP ($n = 7$); CR = 42.7%; TM ($n = 9$); CR = 88.9%. ToMORROW\textsuperscript{®} (cephapirin benzathine), a first-generation cephalosporin, has a more robust Gram-positive spectrum than a third-generation cephalosporin. ToMORROW’s cure rate for \textit{S. aureus} at 88.9% approached statistical significance (one-sided $p$-value <0.08) when compared to Spectramast\textsuperscript{®} DC’s (ceftiofur HCL) cure rate at 42.7%.

The factors (cure rate, prevention of new infections, risk of clinical mastitis, milk production, linear score, and risks for culling and pregnancy) examined in this study are the most economically important to consider in selecting a dry-cow intramammary preparation. However, given that all these preparations yielded similar results, other factors would need to be considered in herds that have a similar pathogen profile.

These factors include judicious use of antimicrobials, milk withhold after calving, meat withhold times and the cost of dry-cow therapy.

From the point of view of judicious use of antibiotics, the authors suggest that the veterinary community should consider the use of first-generation cephalosporins over the use of third-generation cephalosporins.

The cost of the different dry-cow preparations with regard to milk withhold depends on available uses for milk from treated animals. This nonsalable milk can be very valuable if fed to calves, so the cost may in fact be zero or minimal, depending on the market milk price and the cost of milk replacer powder.

The milk withhold (hours nonsalable) difference between two products should be calculated as the time difference to when milk is marketed. Most dairies still collect colostrum from zero-milk-hold dry-cow therapies, and it may be 12 to 24 hours before these cows actually have milk marketed.

A dairy manager may elect to sell a cow after treatment with a dry cow preparation due to abortion or other problems. These cows need to clear the meat residue withhold times before sale. However, because these cows represent a very small percentage of all the cows dry-treated, the cost is minimal.

Conclusion

There were no significant differences among the three dry-cow preparations. As such, dairy producers could potentially put aside concerns about differences in product efficacy, and instead base their selection decision between these three products on other characteristics, such as milk and meat withholding time, targeted dry-period length, and cost. From the standpoint of promoting prudent use of antimicrobials, the veterinary community might consider recommending the use of the older, simpler antimicrobials as a first choice among DCT products.

References

ToMORROW®
(cephapirin benzathine)
Intramammary Infusion
For dry cows only

Description: ToMORROW for intramammary infusion into the dry cow is a product which provides a wide range of bactericidal activity against Gram-positive and Gram-negative organisms. It is derived biosynthetically from 7-aminocephalosporanic acid. Each 10 mL disposable syringe contains 300 mg of cephapirin activity in a stable peanut oil gel. This product was manufactured by a non-sterilizing process.

Storage: Store at or below 25°C (77°F). Do not freeze. Avoid excessive heat.

Action: In the non-lactating mammary gland, ToMORROW provides bactericidal levels of the active antibiotic, cephapirin, for a prolonged period of time. This prolonged activity is due to the low solubility of the cephapirin benzathine and to the slow release gel base.

Cephapirin is bactericidal to susceptible organisms; it is known to be highly active against *Streptococcus agalactiae* and *Staphylococcus aureus* including strains resistant to penicillin.

To determine the susceptibility of bacteria to cephapirin in the laboratory, the class disc, Cephalothin Susceptibility Test Discs, 30 mcg, should be used.

Indications: For the treatment of mastitis in dairy cows during the dry period. ToMORROW has been shown by extensive clinical studies to be efficacious in the treatment of mastitis in dry cows, when caused by *Streptococcus agalactiae* and *Staphylococcus aureus* including penicillin-resistant strains. Treatment of the dry cow with ToMORROW is indicated in any cow known to harbor any of these organisms in the udder at drying off.

Dosage and Directions For Use: ToMORROW is for use in dry cows only. Infuse each quarter at the time of drying off with a single 10 mL syringe. Use no later than 30 days prior to calving.

Completely milk out all four quarters. The udder and teats should be thoroughly washed with warm water containing a suitable dairy antiseptic and dried, preferably using individual paper towels. Carefully scrub the teat end and orifice with 70% alcohol, using a separate swab for each teat. Allow to dry.

ToMORROW is packaged with the Opti-Sert® protective cap.

For Partial Insertion: Twist off upper portion of the OPTI-SERT protective cap to expose 3–4 mm of the syringe tip.

For Full Insertion: Remove protective cap to expose the full length of the syringe tip.

Insert syringe tip into the teat canal and expel the entire contents of syringe into the quarter. Withdraw the syringe and gently massage the quarter to distribute the medication.

Do not infuse contents of the mastitis syringe into the teat canal if the OPTI-SERT protective cap is broken or damaged.

Residue Warnings: 1. For use in dry cows only. 2. Not to be used within 30 days of calving. 3. Milk from treated cows must not be used for food during the first 72 hours after calving. 4. Any animal infused with this product must not be slaughtered for food until 42 days after the latest infusion.

Precautions: ToMORROW should be administered with caution to subjects which have demonstrated some form of allergy, particularly to penicillin. Such reactions are rare; however, should they occur, consult your veterinarian.

How Supplied: ToMORROW for intramammary infusion into the dry cow. Cephapirin benzathine equivalent to 300 mg cephapirin activity per syringe. Each pail contains 144 x 10 mL syringes and 144 convenient single use alcohol pads. NDC 0010-4718-03. ToMORROW is also supplied in cartons containing 12 x 10 mL syringes with 12 convenient single use alcohol pads. NDC 0010-4718-02.

Not for Human Use.

Restricted Drug (California) – Use only as directed

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Opti-Sert is a registered trademark of Zoetis W LLC - used under license.

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Manufactured for:
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