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Randomized noninferiority study evaluating the efficacy of 2 commercial dry cow mastitis formulations

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ABSTRACT

The study objective was to compare the efficacy of 2 commercial dry cow mastitis formulations containing cloxacillin benzathine or ceftiofur hydrochloride. Quarter-level outcomes included prevalence of intramammary infection (IMI) postcalving, risk for cure of preexisting infections, risk for acquiring a new IMI during the dry period, and risk for clinical mastitis between dry off and 100 d in milk (DIM). Cow-level outcomes included the risk for clinical mastitis and the risk for removal from the herd between dry off and 100 DIM, as well as Dairy Herd Improvement Association (DHIA) test-day milk component and production measures between calving and 100 DIM. A total of 799 cows from 4 Wisconsin dairy herds were enrolled at dry off and randomized to 1 of the 2 commercial dry cow therapy (DCT) treatments: cloxacillin benzathine (DC; n = 401) or ceftiofur hydrochloride (SM; n = 398). Aseptic quarter milk samples were collected for routine bacteriological culture before DCT at dry off and again at 0 to 10 DIM. Data describing clinical mastitis cases and DHIA test-day results were retrieved from on-farm electronic records. The overall crude quarter-level prevalence of IMI at dry off was 34.7% and was not different between treatment groups. Ninety-six percent of infections at dry off were of gram-positive organisms, with coagulase-negative *Staphylococcus* and *Aerococcus* spp. isolated most frequently. Mixed logistic regression analysis showed no difference between treatments as to the risk for presence of IMI at 0 to 10 DIM (DC = 22.4%, SM = 19.9%) or on the risk for acquiring a new IMI between dry off and 0 to 10 DIM (DC = 16.6%, SM = 14.1%). Noninferiority analysis and mixed logistic regression analysis both showed no treatment difference in risk for a cure between dry off and 0 to 10 DIM (DC = 84.8%, SM = 85.7%). Cox proportional hazards regression showed no difference between treatments in quarter-level risk for clinical mastitis (DC = 1.99%, SM = 2.96%), cow-level risk for clinical mastitis (DC = 17.0%, SM = 15.3%), or on risk for removal from the herd (DC = 10.7%, SM = 10.3%) between dry off and 100 DIM. Finally, multivariable linear regression with repeated measures showed no overall no difference between treatments in DHIA test-day somatic cell count linear score (DC = 2.19, SM = 2.22), butterfat test (DC = 3.84%, SM = 3.86%), protein test (DC = 3.02%, SM = 3.02%), or 305-d mature-equivalent milk production (DC = 11,817 kg, SM = 11,932 kg) between calving and 100 DIM. In conclusion, DC was noninferior to SM in effecting a cure, and there was no difference in efficacy between these 2 DCT formulations as related to all other udder health or cow performance measures evaluated between dry off and 100 DIM.
Key words: dry cow mastitis, dry cow therapy, udder health, cure, intramammary infection

INTRODUCTION

Dry cow mastitis, which considers the persistence of preexisting IMI through the dry period as well as development of new IMI (**NIMI**) during the dry period, is a critical determinant for subclinical and clinical mastitis in the next lactation (Smith et al., 1985; Erskine, 2001; Green et al., 2002). North American studies estimate that between 13 and 35% of quarters are infected subclinically at dry off, and that between 8 and 25% of quarters develop a NIMI during the dry period (Godden et al., 2003; Cook et al., 2005; Pantoja et al., 2009; Arruda et al., 2013a). Todhunter et al. (1995) estimated that 55% of environmental infections established early in the dry period persist into the next lactation and can possibly cause clinical mastitis flare ups. Bradley and Green (2000) reported that 52% of all clinical coliform mastitis cases occurring in the first 100 d of lactation may originate during the previous dry period.

Blanket dry cow therapy (**DCT**), or the practice of infusing all quarters with a long-acting antibiotic at dry off, is a long-standing and widely adopted mastitis control strategy recommended by the National Mastitis

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Council (**NMC**). Blanket DCT works by curing existing subclinical infections caused by susceptible bacteria and by preventing NIMI that may be acquired during the early dry period. It is estimated that 72.3% of US dairy operations use blanket DCT, which corresponds to 81.7% of US dairy cows (USDA-NAHMS, 2008). Currently, 7 commercial DCT products have been approved by the Food and Drug Administration for use in US dairy herds (National Milk Producers Federation, 2014). Milk and meat withholding period, minimum dry period length, claimed spectrum of action, and cost for these products vary considerably.

Whereas all DCT formulations available in the United States originally underwent testing to demonstrate efficacy against a negative control as a requirement for licensure by the Food and Drug Administration, relatively few studies exist to compare efficacy among DCT products. One recent randomized clinical trial of 1,091 cows from 6 commercial dairy herds in 4 states (CA, IA, MN, and WI) compared efficacy among 3 dry cow mastitis formulations: penicillin/dihydrostreptomycin, ceftiofur hydrochloride, and cephapirin benzathine (Arruda et al. 2013a,b). The results of that study indicated no difference among the 3 DCT products studied regarding the prevalence of IMI postcalving, cure of preexisting IMI during the dry period, or development of new IMI during the dry period. Furthermore, that study reported no difference among the 3 treatments when considering quarter- and cow-level risk for a clinical mastitis event before 100 DIM, removal from the herd before 100 DIM, and SCC linear score (**LS**) and milk production up to 100 DIM (Arruda et al., 2013a,b). In another study, Hallberg et al. (2006) evaluated the efficacy of different doses of ceftiofur hydrochloride for the treatment of existing IMI at dry off and prevention of NIMI during the dry period using a negative control and a positive control (cephapirin benzathine). However, that study was not designed to compare efficacy between the 2 different antimicrobial formulations used (ceftiofur hydrochloride vs. cephapirin benzathine). Furthermore, Hallberg et al. (2006) only enrolled cows with an elevated SCC (>400,000 cells/ mL) and results may not be generalizable to commercial dairy herds wherein blanket DCT is usually applied to all cows. A recent study conducted in Florida compared treatment with ceftiofur hydrochloride versus cephapirin benzathine at the cow level, but the authors did not report quarter-level outcomes such as risk for NIMI or risk for cure of preexisting IMI (Pinedo et al., 2012).

Although the aforementioned efficacy study conducted by Arruda et al. (2013a,b) provides producers with good information comparing the efficacy of the 3 available DCT formulations containing ceftiofur hydrochloride, cephapirin benzathine, and penicillin/dihydrostreptomycin, additional comparative efficacy studies are needed to evaluate other DCT formulations available to North American dairy producers. One DCT formulation which is lacking comparative efficacy data is Dry-Clox (**DC**; Boehringer Ingelheim Vetmedica Inc., St Joseph, MO). Dry-Clox is composed of 500 mg of cloxacillin benzathine and is labeled for the treatment of mastitis during the dry period caused by *Streptococcus agalactiae* and *Staphylococcus aureus*, including penicillin-resistant strains. It has a 30-d meat withholding time postinfusion and zero hour milk discard postcalving, following a minimum dry period length of 30 d. Another commonly used DCT formulation is Spectramast DC (**SM**; Zoetis, Florham Park, NJ), which is composed of 500 mg of ceftiofur hydrochloride and labeled for subclinical mastitis associated with *Staphylococcus aureus*, *Streptococcus dysgalactiae*, and *Streptococcus uberis.* This product has a meat withdrawal period of 16 d postinfusion and, similar to DC, has a required dry period length of 30 d and no milk withholding time following calving. As both the DC and SM formulations are labeled against gram-positive infections, have a 30-d required dry period, and have a zero hour milk discard following calving, it would be very useful for producers to know of any differences in efficacy when considering DCT products for use on their farm.

The current study objective was to compare the efficacy of DC (cloxacillin benzathine) versus SM (ceftiofur hydrochloride) as assessed by both quarter- and cow-level measures of udder health, as well as cow performance measures during the first 100 DIM. Our hypothesis was that quarters infused with DC at the time of dry off would have a noninferior proportion of quarters cured from preexisting IMI as compared with SM. Furthermore, we hypothesized no difference would be noted between DC and SM in terms of the quarter-level risk for presence of IMI postcalving, the risk for acquiring NIMI during the dry period, and the risk for a clinical mastitis event between dry off and 100 DIM. At the cow-level we hypothesized no effect of treatment would be observed on risk for clinical mastitis or risk for removal from the herd (death or culling) between dry off and 100 DIM, and no difference in DHIA test-day milk component and production measures during the first 100 DIM.

MATERIALS AND METHODS

Herd Selection

This randomized clinical trial was conducted in a convenience sample of 4 commercial Wisconsin Holstein dairy farms between July 2014 and April 2015, under