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Efficacy of extended cefquinome treatment of clinical *Staphylococcus aureus* mastitis

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ABSTRACT

Clinical *Staphylococcus aureus* mastitis is difficult to cure. Extended antimicrobial treatment is often advocated as a practical approach to improve cure rates; however, scientific evidence of this hypothesis is lacking. A multi-centered, nonblinded, randomized, positive-controlled clinical trial was conducted in 5 European countries—France, Hungary, Italy, the Netherlands, and the United Kingdom—to study the efficacy of an extended intramammary cefquinome treatment (5 d) compared with a standard intramammary cefquinome treatment (1.5 d) of *Staph. aureus* clinical mastitis. Least squares means estimates of bacteriological cure during lactation were 34% [standard error (SE) = 9.9%] for the standard treatment group and 27% (SE = 8.4%) for the extended treatment group. In the final model, extended therapy was not significantly better. The only factor predicting bacteriological cure was pretreatment cow somatic cell count (SCC). Cows with >250,000 cells/mL in milk before treatment were less likely to cure. Least squares means of clinical cure during lactation was 60% (SE = 19%) for the standard treatment group and 82% (SE = 12%) for the extended treatment group. In the final model, clinical cure after extended treatment was significantly better. Pretreatment cow udder firmness predicted clinical cure. Firm udders were less likely to cure clinically. Irrespective of treatment regimen, new infection rates with pathogens other than *Staph. aureus* were higher (42%) after bacteriological cure than after nonbacteriological cure (22%) and cured cows had a significantly lower SCC. In conclusion, independent of the treatment protocol, cows with an SCC <250,000 cells/mL before treatment showed a higher probability of bacteriological cure. It appears that successful treatment of clinical *Staph. aureus* mastitis with cefquinome is associated with an increased number of new infections with coagulase-negative staphylococci. Extended treatment improved clinical, but not bacteriological, cure rates compared with the standard treatment. These results indicate that extending treatment of clinical *Staph. aureus* mastitis with cefquinome should not be recommended.
Key words: dairy cow, lactation, mammary gland, antimicrobial

INTRODUCTION

Contagious mastitis has been successfully controlled in recent decades on many farms in many countries due to the large scale adoption of the 5-point plan: optimization of milking and milking machine, blanket dry cow treatment, postmilking teat disinfection, treatment of clinical mastitis, and culling of chronically infected cows (Neave et al., 1969). As a result, the incidence of contagious pathogens, such as *Streptococcus agalactiae* and *Staphylococcus aureus*, has declined, resulting in a dramatic decrease of the average bulk milk SCC (**BMSCC**) in the majority of European countries. Despite this, *Staph. aureus* remains an important mastitis-causing pathogen on many farms, even when BMSCC is low (Barkema et al., 1998; Olde Riekerink et al., 2010).

An important reason the prevalence of *Staph. aureus* remains high in herds is the degree of difficulty to cure existing infections, leading to both repeat clinical episodes and spreading of bacteria to herd mates. Bacteriological cure (**BC**) of *Staph. aureus* mastitis during lactation is generally low, both for subclinical (Sol et al., 1997) and clinical cases (Sol et al., 2000; Bradley and Green, 2009), and is mainly dependent on the duration of infection, the bacterial strain, and the duration of treatment (Barkema et al., 2006). Also, some *Staph. aureus* strains have a stronger clinical manifestation than others (Zadoks et al., 2000; Haveri et al., 2005; Fournier et al., 2008), a lower persistence, and a higher probability of cure (Haveri et al., 2005).

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Subclinical *Staph. aureus*-infected cows can be selected for treatment based on their estimated probability of cure. In *Staph. aureus* clinical mastitis (**CM**), however, treatment is necessary to fight the clinical symptoms and to bring the cow back into production as soon as possible. Increased duration of treatment is often used in practice because it is an easy way to possibly improve the probability of cure. Research showing the beneficial effect of extended antimicrobial treatment of subclinical *Staph. aureus* mastitis during lactation are numerous and conclusive (Gillespie et al., 2002; Oliver et al., 2004; Deluyker et al., 2005). However, studies of extended antimicrobial treatment of clinical *Staph. aureus* mastitis are limited and less conclusive, showing a better effect (Jarp et al., 1989), only a numerical difference (Pyörälä and Pyörälä, 1998), or a significantly higher cure only for β-lactamase negative *Staph. aureus* cases (Sol et al., 2000). Thus, more research on the effects of extended treatment is needed for clinical *Staph. aureus* mastitis.

Cefquinome is a broad-spectrum cephalosporin which is commonly used for the intramammary (**IMM**) treatment of CM throughout Europe, where it has been approved for the treatment of CM caused by the major mastitis-causing pathogens, including *Staph. aureus*. The objective of this study is to compare different aspects of the efficacy of a standard versus an extended duration of IMM cefquinome treatment against clinical *Staph. aureus* mastitis.

MATERIALS AND METHODS

Study Design

This was a multi-centered, nonblinded, randomized, positive controlled clinical trial that was conducted in 5 countries: France, Hungary, Italy, the Netherlands, and the United Kingdom. The protocol was in accordance with the note for Guidance on statistical principles for veterinary clinical trials (EMEA, 2002), the legal requirements in the countries where it was implemented, and the European Guideline for the conduct of efficacy studies for intramammary products for use in cattle (EMEA, 2003).

Lactating cows with clinical *Staph. aureus* mastitis from different herds were randomly assigned to 2 treatment groups, receiving either a standard 1.5-d or an extended 5-d IMM cefquinome treatment. Milk samples were taken around 14 and 21 d after the last treatment to determine the primary efficacy criteria, BC, and clinical cure (**CC**).

Animals and Herds

No specific animal management or housing was required for the selection of herds. Herd-specific data, such as herd size (number of dairy cows), herd management (housing, bedding, feeding), or udder health management (average milking interval, teat disinfecting practices, that is, pre- and postdipping and blanket, selective or no dry cow treatment), were recorded, as well as the 3 most recent BMSCC.

Criteria for Selection of Clinical Mastitis Cases

Lactating cows with CM in a single quarter were included in this study. Clinical mastitis was defined as a quarter with clinical signs (swelling, heat, pain) or any changes in the appearance of milk, with or without associated general clinical signs. For the included cows, historic cow data, such as breed, date of birth, number of lactation, date of last calving, estimated or measured milk yield at time of treatment, cow SCC, and history of previous mastitis cases, were recorded. Excluded were cows with CM occurring less than 30 d from the planned day of drying-off, cows with severe systemic signs needing other systemic treatment, cows with other intercurrent diseases at the time of CM, cows given systemic or IMM anti-inflammatory or antimicrobial treatments within a 30-d period before inclusion, cows with visible teat damage, and cows with daily milk yield less than 5 kg before the onset of clinical signs.

Postadmission Withdrawal

A cow was withdrawn after enrolment if the pretreatment milk sample was contaminated (>2 bacteria species) or if no *Staph. aureus* was isolated. If 2 bacteria were cultured pretreatment, *Staph. aureus* had to be the primary pathogen, having equal or more bacteria than the other pathogen based on semiquantitative analysis (low/moderate/high), to keep the cow in the study. Also withdrawn were cows experiencing an adverse event, injury, or illness, including mastitis in another quarter or treatment with another antimicrobial or anti-inflammatory. If any other significant deviation from the protocol occurred, the corresponding case was also withdrawn from the study.

Number of Animals

The tested hypothesis was that the extended treatment resulted in a higher cure rate (50%) than the standard treatment (25%). Based on a one-sided, Chi-squared test with type I error $\alpha = 0.05$ and type II error $\beta = 0.20$, the estimated sample size is 48 cows per treatment group. Assuming 70% bacteriological positive and noncontaminated milk cultures, a *Staph. aureus* prevalence among these of 10%, and 10% exclu-

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