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Pegbovigrastim treatment resulted in an economic benefit in a large randomized clinical trial in grazing dairy cows

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ABSTRACT

This randomized controlled trial on 4 commercial grazing dairy farms investigated whether pegbovigrastim (PEG) treatment affected partial net return as calculated from milk revenues and costs for feed, medical treatments [clinical mastitis, uterine disease, and other diseases (i.e., any medical treatment that was not intended for clinical mastitis or uterine disease)], inseminations, and culling during a full lactation in grazing dairy cows. We also explored the effect of potential interactions of PEG treatment with parity, prepartum body condition score, and prepartum nonesterified fatty acids concentration on partial net return, milk revenues, and the costs mentioned above. Holstein cows were randomly assigned to 1 of the 2 following trial arms: a first PEG dose 9.4 ± 0.3 (mean ± standard error) days before the calving date and a second dose within 24 hours after calving (PEG: primiparous = 342; multiparous = 697) compared with untreated controls (control: primiparous = 391; multiparous = 723). The effect of PEG treatment on the outcomes of interest expressed per year was tested using general linear mixed models. Results are presented as least squares means ± standard error. Overall, PEG treatment increased the partial net return, resulting in an economic benefit per cow per year of $210 ± 100. The cost of treatment of clinical mastitis was lower for PEG treated cows compared with control cows ($9 ± 3). The largest nonsignificant difference was seen for the cost of culling; additionally, PEG treatment numerically reduced the cost of culling by $145 ± 77.

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INTRODUCTION

Animal diseases associated with the transition period in dairy cows, such as clinical mastitis (**CM**), uterine disease (**UD**), and metabolic diseases, have a negative effect on health, welfare, and the economic performance of dairy farming (Overton and Fetrow, 2008; Hogeveen et al., 2019; Steeneveld et al., 2020). Production loss, discarded milk during the withdrawal period after medical treatment, and the actual cost of treatments are important direct economic effects of early lactation diseases (Hogeveen et al., 2011; Pérez-Báez et al., 2021). Moreover, indirect effects of these diseases can be seen in impaired reproductive performance (Fourichon et al., 2000; LeBlanc et al., 2002; Dolecheck et al., 2019) and culling (Kossaibati and Esslemont, 1997; Bar et al., 2008; Carvalho et al., 2019). Multiple studies have shown that culling makes an important contribution to the costs of clinical disease (Galligan, 2006; Overton and Fetrow, 2008; Heikkilä et al., 2012).

Pegbovigrastim, a long-acting analog of bovine granulocyte colony-stimulating factor (**PEG**, marketed as Imrestor by Elanco Animal Health), has been used as a tool to improve dairy cows' immune response during the transition period. Pegbovigrastim treatment consistently increases circulating white blood cell counts (McDougall et al., 2017; Van Schyndel et al., 2018; Barca et al., 2021a). Moreover, PEG treatment improves immune function at plasma cytokine profile and white blood cell gene expression level (Lopreiato et al., 2019, 2020). Several field trials have evaluated the effect of PEG treatment, mainly on early lactation clinical disease. Several these studies also report milk production, fertility, and culling (Canning et al., 2017;

Ruiz et al., 2017; Freick et al., 2018; Zinicola et al., 2018; Van Schyndel et al., 2021). A lower early lactation CM incidence due to PEG treatment was reported by Canning et al. (2017) and Ruiz et al. (2017), but 2 studies (Zinicola et al., 2018; Van Schyndel et al., 2021) reported no effects on early lactation CM incidence. Overall, PEG treatment results ranged from a preventive effect for early lactation clinical disease (Canning et al., 2017; Freick et al., 2018) to increased morbidity (Zinicola et al., 2018), particularly for metritis (Ruiz et al., 2017). Recently, based upon results from a large clinical trial, we reported that PEG reduced the occurrence of a first case of CM during the first 30 DIM, particularly in cows with excessive prepartum BCS, and in cows with elevated prepartum nonesterified fatty acids (**NEFA**) concentrations (Barca et al., 2021b). Moreover, PEG treatment reduced the occurrence of endometritis in cows that had a previous case of metritis in the same lactation. In addition, in cows with elevated NEFA, PEG treatment increased the first insemination rate and counteracted the negative association of early lactation CM and UD [i.e., a cow with a record of retained fetal membranes (placenta), metritis, or both] with the pregnancy rate. Ultimately, in cows with elevated NEFA, PEG treatment decreased the hazard of culling (Barca et al., 2022).

An important question to answer is whether the economic benefits of improved health, fertility, and longevity due to PEG treatment outweigh the cost of PEG and its application under field conditions (2 doses). Bio-economic simulation models are often used for this type of economic evaluations. In such bio-economic models, the available knowledge on the effect of an intervention is implemented in a simulation model of the relevant dairy cow disease or diseases, and the model is consequently used to mimic the use of the intervention and evaluate the economic effect of the intervention compared with a situation without it. This approach was used in recent literature to evaluate the economic impact of different durations of CM treatment (Pinzón-Sánchez and Ruegg, 2011; Steeneveld et al., 2011), the economic benefit of using nonsteroidal anti-inflammatory drugs in the treatment of CM (van Soest et al., 2018), and the economic impact of implementing selective dry cow therapy (Hommels et al., 2021). However, this bio-economic simulation approach does not account for heterogeneity between cows. If sufficient longitudinal data are present, another possible approach is to study the economic performance of control and treated cows in a randomized clinical trial. In such longitudinal studies, the partial net return for each cow in the study may be determined (Burgers et al., 2022). In this report, the hypothesis to be tested is whether PEG treatment increases partial net return as calculated from milk revenues and costs for feed, medical treatments, inseminations, and culling during a full lactation in grazing dairy cows, thereby taking the interaction with BCS and NEFA status of cows into account.

The objective of this study is, therefore, to investigate whether PEG treatment affects partial net return, milk revenues and costs for feed, medical treatments, insemination, and culling during a full lactation. We also explored the effect of potential interactions of PEG treatment with parity, BCS, and NEFA on these outcomes.

MATERIALS AND METHODS

The experimental protocol (CEUAFVET-PI-162) was evaluated and approved by the Honorary Committee for Animal Experimentation in Uruguay, University of the Republic, Uruguay.

Study Design

This randomized controlled trial was carried out on 4 commercial grazing dairy farms and has recently been described in companion publications (Barca et al., 2021b, 2022). In short, 2,153 (farm 1 = 759; farm 2 = 314; farm 3 = 664; farm 4 = 416) Holstein primiparous (animals that were enrolled in the study shortly before their first calving) and multiparous cows (animals that were enrolled shortly before their second or later calving) that calved from February 13 to September 30 of 2018 were included in the study. Twice a week, at −10 to −7 d relative to the expected calving date, cows were randomly assigned to either treatment group or untreated control group based on their unique national ear tag number, which is assigned to cattle at birth. Animals with an even national ear tag number were injected with 15 mg of PEG according to the product label (PEG) and animals with an odd national ear tag number remained as untreated controls (control). Animals assigned to the PEG treatment received a second dose within 24 h after calving; however, only cows that received both doses were included in the study. The national ear tags used for treatment allocation are not related to the large visible ear tags that are used for on-farm identification and management decisions. Research assistants, who did not belong to the farm staff, applied treatments (Barca et al., 2021b, 2022). This meant that all people involved in daily farm management were blinded as to which cows had been treated. The resulting study population consisted of 733 primiparous cows (control = 391; PEG 342) and 1,420 multiparous cows (control: 723; PEG = 697). The interval in days between enrollment and calving (in case of PEG this is the interval between PEG doses), did not differ between treatment groups (control = 9.1 ± 0.2; PEG = 9.4 ± 0.3; $P = 0.42$).

At the time of treatment assignment (−10 to −7 d relative to the expected calving date) BCS was assessed according to Ferguson et al. (1994) and blood was drawn for determination of NEFA (Barca et al., 2021b, 2022). Throughout the study, milk yield and fat and protein concentration per cow were determined from monthly test-day samples [fat and protein determinations were performed by Cooperativa Laboratorio Veterinario de Colonia (COLAVECO)]. Clinical diseases were diagnosed and recorded as described before (Barca et al., 2021b, 2022), and all treatments were recorded. All farms used AI with estrus detection performed by trained farm personnel. Pregnancy diagnoses were performed by transrectal palpation or ultrasonography by the farm veterinarian. All inseminations and pregnancy diagnoses were recorded by farm personnel or by the farm veterinarian, or both. Dry-off date and date of culling or on-farm death were also recorded. The study ended 305 d after the last recorded calving in the study, which was 529 d after the first recorded calving in the study.

Economic Calculations, Partial Budgeting

The collected data were used to determine partial net return for each of the 2,153 cows in the trial. Consequently, the cow is the economic unit of interest. Partial net return is defined as combination of milk revenues where all relevant costs are subtracted for each cow i during the experimental days (**ED**) for cow i. Partial budgeting is widely used to evaluate the economic impact of interventions (for example Rowe et al., 2021) and partial net return as used here was previously defined by Burgers et al. (2022). Equal to a partial budget, the cow-level partial net return only takes into account economic factors that are, in theory, affected by the intervention of interest. Consequently, we based the partial net returns calculation on factors that could be potentially affected by PEG treatment. Briefly, milk revenues $\left(R_i^{Milk}\right)$ were included as the income potentially affected by PEG treatment (Ruiz et al., 2017; Powell et al., 2018; Van Schyndel et al., 2021). Although feed costs in relation to PEG has not been studied, feed intake in relation to PEG treatment has been studied preliminarily, in a CM challenge model, and Powell et al. (2018), reported that post infection, PEG treated cows consumed more feed than untreated control cows. Therefore, costs for feed $\left(C_i^{Feed}\right)$ were included in the partial net return. Pegbovigrastim treatment is associated with the occurrence of diseases and reproductive performance (Canning et al., 2017; Ruiz et al., 2017; Zinicola et al., 2018; Barca et al., 2022). Therefore, expenditures for treatment of CM $\left(C_i^{CM}\right)$, UD $\left(C_i^{UD}\right)$,and treatments for other diseases $\left(C_i^{Other}\right.$; i.e., any medical treatment that was not intended for CM or UD) and cost of inseminations $\left(C_i^{Ins}\right)$ were included. Finally, because diseases are known to be associated with hazard of culling (Carvalho et al., 2019), and that in cows with elevated NEFA, we showed that PEG treatment decreased the hazard of culling (Barca et al., 2022). Also, cost of culling $\left(C_i^{Cull}\right)$ was included. As far as we know, there are no indications that other cow-level costs are affected by PEG treatment. Consequently, the partial net return for each individual cow i was calculated as follows:

$$Partial\ \ net\ \ return_i = R_i^{Milk} - \left(C_i^{Feed} + C_i^{CM} + C_i^{UD} + C_i^{Other} + C_i^{Ins} + C_i^{Cull}\right).$$

Because ED differed between cows, $partial\ net\ return_i$ was standardized and expressed per cow per year (Burgers et al., 2022) as follows:

$$Partial\,net\,return_i^{\text{Year}} = \frac{Partial\,net\,return_i}{ED_i} \times 365.$$

Milk Revenues and Costs Calculations

From the monthly test-day milk samples, milk returns were calculated per individual cow as follows: first, for each cow i and test-day j, the returns for milk $\left(R_{ij}^{Milk}\right)$ were calculated as follows based on the milk yield $\left(MY_{ij}\right)$, percentage protein $\left(Perc_{ij}^{Prot}\right)$ and fat $\left(Perc_{ij}^{Fat}\right)$, and average prices for protein and fat for 2018 (P^{Prot} and P^{Fat}, respectively):

$$R_{ij}^{Milk} = MY_{ij} \times Perc_{ij}^{Prot} \times P^{Prot} + MY_{ij} \times Perc_{ij}^{Fat} \times P^{Fat}.$$

Based on the returns per cow per test-day, the total milk returns per cow $\left(R_i^{Milk}\right)$ were calculated for each cow i by multiplying the average milk returns in the period leading to the test-day by the number of days in that period as follows:

$$R_i^{Milk} = \frac{R_{i1}^{Milk}}{2} \times DIM_{i1} + \sum_{j=1}^{n} \frac{R_{ij}^{Milk} + R_{ij-1}^{Milk}}{2} \times \left(DIM_{ij} - DIM_{ij-1}\right) + R_{in}^{Milk} \times \left(ED_i - DIM_{in}\right),$$

where DIM_{ij} is the DIM for test-day 1 to n_j (n_j is total number of test-days of cow i). We assumed a linear change of the daily milk returns between test-days. For the time until the first test-day of a cow, the milk return was taken as the average of the first test-day postpartum (DIM_{i1}) and 0, thereby assuming that milk yield started at 0 kg. For the period after the last test-day (DIM_{in}), it was assumed that the milk returns were equal to the milk returns at the last test-day with a period duration from the last test-day to exit from the study for each cow i.

Costs for feed supply were estimated per individual cow as follows:

$$C_i^{Feed} = \left(ED_i \times NE^{Maintenance} + FPCM_i \times NE^{Milk} + NE_i^{Gestation} / \left(\frac{NE}{PMR(\text{kg DM})} \right) \right) \times P^{PMR},$$

where $NE^{Maintenance}$ is net energy for maintenance, considering a 20% increase for grazing activity in mixed systems (NRC, 2001); FPCM is fat- and protein-corrected milk, calculated as (Manzanilla Pech et al., 2014) 0.337 × total milk (kg) + 11.6 × total fat (kg) + 5.999 × total protein (kg); NE^{Milk} is net energy for milk production, calculated from milk composition as (NRC, 2001) NE^{Milk} (Mcal/kg) = 0.0929 × fat yield (%) + 0.0547 × protein yield (%) + 0.0395 × lactose (%; assuming lactose content of 4.9%); $NE^{Gestation}$ is the energy required for pregnancy (Mcal/d) calculated from 190 to 279 d of gestation as follows (NRC, 2001): (0.00318 × d − 0.0352) × (CBW/45)/0.218, where d is day of gestation and CBW is calf birth weight in kilograms (assuming here a CBW of 35 kg); NE/partial mixed ration (**PMR**), kilograms of DM is net energy (Mcal) per kilogram of DM of PMR, and P^{PMR} is the price ($/kg) of PMR (kg/DM).

The C_i^{CM} was calculated per individual cow, similar to Steeneveld et al. (2011), as follows:

$$C_i^{CM} = CM_i \times \left(C_i^{Milkwithheld} + C_i^{Medicine} + C_i^{Labor} - C_i^{Milkfedtocalves} \right),$$

where CM_i are number of CM cases for cow i. We also calculated

$$C_i^{Milkwithheld} = \sum_{cc=0}^{n} D_c^{Withheld} \times \left(MY_{ic} \times Perc_{ic}^{Prot} \times P^{Prot} + MY_{ic} \times Perc_{ic}^{Fat} \times P^{Fat} \right),$$

where $D_c^{Milkwithheld}$ is the number of days of treatment and milk withhold, MY_{ic} is milk yield at the time of CM case c for cow i, and $Perc_{ic}^{Prot}$ and $Perc_{ic}^{Fat}$ are percentage protein and fat at the time of a CM case c for cow i, respectively.

$C_i^{Medicine}$ is the price for medicine, C_i^{Labor} is the labor price for treatment application, and $C_i^{Milkfedtocalves}$ is MY_{ic} by the value of the milk replacer, all for cow i.

Similarly, C_i^{UD} and C_i^{Other} were calculated for each cow i.

Costs for insemination $\left(C_i^{Ins}\right)$ were calculated per individual cow as follows:

$$C_i^{Ins} = N_i^{Ins} \times P^{Ins},$$

where N_i^{Ins} is the number of inseminations for each cow i and P^{Ins} is the price per insemination including costs of labor.

The C_i^{Cull} was calculated similar to Mostert et al. (2018) and Burgers et al. (2022) as

$$C_i^{Cull} = \left(\left(P^{Heifer} - P^{Slaughter} \right) / L^{Max} \right) \times \left(L^{Max} - L_i \right),$$

where P^{Heifer} is the price of a replacement heifer and $P^{Slaughter}$ is the revenue of a culled cow at the slaughterhouse, assuming a weight of 550 kg (INALE, 2021). In case of a dead cow, the $P^{Slaughter}$ is equal to 0. The variable L^{Max} is the lactation number of the oldest cow in the experiment and L_i is the actual lactation of a culled cow i. More than 5 lactations were considered as 6 lactations; thus, L^{Max} is equal to 6 and L_i is an integer number from 1 to 6.

Costs of PEG and its application (2 doses) were not included in the economic calculations.

Prices

Input values regarding price levels (Table 1) were based on prices for 2018, available at the governmental national institute for dairy production (INALE, 2021). Prices for medicines and milk replacer to feed calves were based on information supplied by one of the biggest medicine suppliers for dairy in Uruguay (PROLESA, 2021). Beef price at the slaughterhouse was based on available information at the Asociación de Consignatarios de Ganado (ACG, 2021). Prices were given in local currency and transformed to US dollars using the average currency exchange rate of 2018 (INALE, 2021).

Table 1. Prices ($) used to calculate the economic result of control and cows treated with pegbovigrastim in a randomized controlled trial on 4 commercial grazing dairy farms

Variable[1]	Item	Reference
Milk solids		
Protein[2] ($P^{Protein}$/kg)	6.64	INALE, 2021
Min	5.31	INALE, 2021
Max	7.97	INALE, 2021
Fat[3] (P^{Fat}/kg)	2.65	INALE, 2021
Min	2.12	INALE, 2021
Max	3.18	INALE, 2021
Replacement heifer (P^{Heifer})	1,000	INALE, 2021
Max	1,200	INALE, 2021
Beef price		
$P^{Slaughter}$/kg	0.85	ACG, 2021
Min	0.65	ACG, 2021
Milk replacer (L)	0.22	PROLESA, 2021
Feed		
PMR[4] (P^{PMR}/kg)	135	INALE, 2021
Treatments clinical mastitis		
Products	Supplemental Table S1	PROLESA, 2021
Farm personnel labor/treatment[5]	2.15	INALE, 2021
Veterinary labor/treatment[5]	2.25	INALE, 2021
Treatments retained placenta/metritis		
Products	Supplemental Table S1	PROLESA, 2021
Farm personnel labor/treatment[5]	2.15	INALE, 2021
Veterinary labor/treatment[5]	2.25	INALE, 2021
Treatments other diseases		
Products	Supplemental Table S1	PROLESA, 2021
Farm personnel labor/treatment[6]	2.9	INALE, 2021; Liang et al., 2017
Veterinary labor/treatment[6]	3	INALE, 2021
Insemination		
$/insemination	25	Author's expertise

[1]Minimum (min) and maximum (max) are the values assumed in sensitivity analyses to assess the effect of changes in revenues and costs on the partial net return per year; $P^{Protein}$ = price of protein; P^{Fat} = price of fat; $P^{Slaughter}$ = revenue of a culled cow at the slaughterhouse; P^{PMR} = price of PMR (partial mixed ration). Supplemental Table S1 (https://doi.org/10.17632/7n77zzn2p2.3; Barca, 2022).

[2]Average national price paid to farmer, 2018.

[3]Average national price paid to farmer, 2018.

[4]Partially mixed ration (30% concentrate, 20% conserved forage, 50% fresh forage).

[5]Fifteen minutes for farm personnel (adapted from Liang et al., 2017), 3 min for veterinarian.

[6]Twenty minutes for farm personnel (adapted from Liang et al., 2017), 4 min for veterinarian.

Statistical Analysis

Data were analyzed using SAS software (SAS University Edition, SAS Institute Inc.).

The effect of PEG treatment on partial net return, R^{Milk}, and on the costs expressed per cow per year was tested using general linear mixed models (PROC MIXED). The following were considered as class variables: parity (primiparous/multiparous), BCS (under: <3; acceptable: 3 to 3.5; over: >3.5; Roche et al., 2009), NEFA (low ≤0.3; high >0.3 m*M*, Overton et al., 2017), treatment (control/PEG), and calving month (6 classes: February/March, April, May, June, July, and August/September). Farm, also as a class variable, was included as a random effect. Two-way interactions between parity, BCS, NEFA, and treatment were checked for significance.

The general model was then

$$Partial\,net\,return_i^{Year} = intercept + lactation_i + BCS_i + NEFA_i + treatment_i + calving\ month_i + \ interactions + farm(random) + error.$$

After the initial full model lay-out, a backward variable selection process was performed. Parity and treatment were forced into all models. All other variables or their 2-way interaction with treatment remained in the model when $P \leq 0.10$ (significance level to stay, SLSTAY). Exceptionally, variables or an interaction term remained in the model when removal of the variable resulted in an important change in the treatment effect. Such variables would be considered potential confounders. Statistical significance was decided at a level of $P \leq 0.05$. The result of variables that remained in the final models are presented as least squares means (**LSM**) ± standard error. All P-values of pair-wise comparisons

Table 2. Experimental days, production performance, partial net return, milk revenues, and costs in control and cows treated with pegbovigrastim (PEG) in a randomized controlled trial on 4 commercial grazing dairy farms

	Control		PEG	
Item	n	Mean ± SEM	n	Mean ± SEM
Experimental days	1,102	348 ± 4	1,026	350 ± 4
Death	51	138 ± 18	43	107 ± 14
Cull	166	212 ± 10	143	230 ± 10
Dry pregnant	587	381 ± 2	544	380 ± 2
Dry not pregnant[1]	107	292 ± 10	116	303 ± 10
End-date pregnant	98	500 ± 11	72	501 ± 12
End-date not pregnant[1]	93	398 ± 6	108	400 ± 6
Milk yield (kg)	1,102	7,508 ± 99	1,026	7,552 ± 98
Protein yield (kg)	1,102	249 ± 4	1,026	250 ± 3
Fat yield (kg)	1,102	272 ± 4	1,026	275 ± 4
Economic factor[2] ($/cow per year)				
Partial net return	1,102	1,023 ± 57	1,026	1,100 ± 52
R^{Milk}	1,102	2,401 ± 27	1,026	2,429 ± 26
C^{Feed}	1,102	877 ± 6	1,026	883 ± 6
C^{Cull}	1,102	387 ± 44	1,026	340 ± 38
C^{CM}	1,102	40 ± 3	1,026	31 ± 2
C^{UD}	1,102	8 ± 2	1,026	16 ± 4
C^{Other}	1,102	18 ± 5	1,026	10 ± 3
C^{Ins}	1,102	48 ± 1	1,026	49 ± 1

[1]Cows that were not pregnant at the end-date were assumed to be culled at that date.
[2]R^{Milk} = returns for milk; C^{Feed} = costs for feed; C^{Cull} = cost of culling; C^{CM} = cost of clinical mastitis; C^{UD} = cost of uterine disease (cost of treatment for retained placenta, metritis or both); C^{Other} = cost of any medical treatment recorded that was not intended for clinical mastitis, retained placenta, or metritis; C^{Ins} = cost for insemination.

of LSM were corrected with the Tukey-Kramer adjustment.

Sensitivity Analysis

To assess the effect of changes in revenues and costs on the partial net return per cow per year, a sensitivity analysis was performed. First, considering the variations observed in prices of protein and fat from 2012 to 2020 (INALE, 2021), milk revenues were based on either the average price for protein and fat for 2018, or on a 20% lower or higher price (Table 1). Second, it was assumed that milk withheld due to medical treatments would or would not be fed to calves. Third, we assumed either the normal or the lowest beef price at slaughterhouse. The lowest beef price is the price paid for cows in an inferior health condition (ACG, 2021; Table 1). Fourth, we varied the price of a replacement heifer from the normal price to a 20% higher price (INALE, 2021; Table 1).

RESULTS

Descriptive Statistics

Table 2 presents an overview of ED, end-of-study status, productive performance, and economic factors for control and PEG cows. During the study, 4.4% of the cows died (control = 4.6%; PEG = 4.2%), 14.5% were culled (control = 15.1%; PEG = 13.9%), 53.1% were dried-off being pregnant (control = 53.3%; PEG = 53.0%), 10.5% were dried-off being not pregnant (assumed culled at that date; control = 9.7%; PEG = 11.3%), 8.0% ended the study period being pregnant (control = 8.9%; PEG = 7.0%), and 9.4% ended the study period being not pregnant (assumed culled at the end-of-study date; control = 8.4%; PEG = 10.5%).

Economic descriptive results, presented in Table 2, showed that R^{Milk} per year were \$2,401 ± 27 and \$2,429 ± 26, in control and PEG treated cows respectively. The biggest cost was C^{Feed} per year, which represented 36.9% of the R^{Milk} per year in the control group and 36.4% in PEG cows. The C^{Cull} per year represented 16.1% of the R^{Milk} per year in control cows and 14.0% in PEG cows. A descriptive evaluation of C^{Cull} per year showed some extremely high values (right skewed) that made statistical analysis difficult. Consequently, cows with a C^{Cull} per year > mean + 2 × standard deviation were treated as outliers and not included in the final data set (Burgers et al., 2022) as presented in Table 2. Thus, control = 12 (death = 11, cull = 1), PEG = 13 (death = 12; cull = 1) cows, which were defined as outliers, were not considered for the final statistical analyses, resulting in several remaining cows of control

Table 3. Partial net return, milk revenues, and costs per year ($) in control (n = 1,102) and pegbovigrastim (PEG) treated (n = 1,026) cows in a randomized controlled trial on 4 commercial grazing dairy farms

Variable[1]	Class	LSM ± SE			P-value[2]
		Control	PEG	Treatment effect	
Partial net return	Overall	938 ± 279	1,147 ± 280	210 ± 100	0.036
	Prepartum BCS[3]				
	Under	672 ± 323	1,110 ± 326	438 ± 242	0.46
	Acceptable	1,138 ± 278	1,106 ± 278	−33 ± 92	0.99
	Over	1,002 ± 289	1,226 ± 293	224 ± 150	0.67
C^{Cull}	Overall	467 ± 63	322 ± 66	−145 ± 77	0.061
	Prepartum BCS				
	Under	617 ± 139	299 ± 145	−318 ± 188	0.54
	Acceptable	346 ± 62	380 ± 61	34 ± 72	0.99
	Over	438 ± 289	287 ± 94	−151 ± 117	0.79
C^{CM}	Overall	40 ± 9	31 ± 9	−9 ± 3	0.008
C^{Other}	Prepartum NEFA[4]				
	Low	2 ± 7	10 ± 7	8 ± 10	0.85
	High	24 ± 5	6 ± 6	−19 ± 8	0.07
C^{UD}	Overall	10 ± 6	19 ± 5	9 ± 5	0.07
R^{Milk}	Overall	2,454 ± 285	2,485 ± 285	32 ± 29	0.28
C^{Feed}	Overall	885 ± 60	893 ± 60	8 ± 6	0.22
C^{Ins}	Overall	49 ± 4	50 ± 4	1 ± 2	0.58

[1]C^{Cull} = cost of culling; C^{CM} = cost of clinical mastitis; C^{Other} = cost of any medical treatment recorded that was not intended for clinical mastitis, retained placenta, or metritis; C^{UD} = cost of uterine disease; R^{Milk} = returns for milk; C^{Feed} = costs for feed; C^{Ins} = cost for insemination.

[2]P-values of pair-wise comparisons of LSM corrected with the Tukey-Kramer adjustment.

[3]Prepartum BCS: under (<3): control = 106; PEG = 97; acceptable (3 to 3.5): control = 694; PEG = 696; over (>3.5): control = 302; PEG = 233.

[4]Prepartum nonesterified fatty acid concentration (NEFA): low (≤0.3 mM): control = 431; PEG = 401; high (>0.3 mM): control = 671; PEG = 625.

= 1,102 and PEG = 1,026 (Table 2). Descriptive data of cows treated as outliers is provided in Supplemental Table S2 (https://doi.org/10.17632/7n77zzn2p2.3; Barca, 2022). For these cows, the ED were 6 ± 2 and 5 ± 1, and the C^{Cull} per year was $72,333 ± 23,731 and $42,446 ± 5,157, in control and PEG cows, respectively. After removing these 25 cows, C^{Cull} per year still showed a relatively large variation (Table 2), but in the original data set, with a much higher mean value, this variation was considerably larger (control = 1,162 ± 334; PEG = 867 ± 162). The C^{CM}, C^{UD}, C^{Other}, and C^{Ins} per year represented 2% or less of the R^{Milk} per year each.

Effect of Pegbovigrastim on Partial Net Return Per Cow Per Year

Final model results showed that PEG treatment affected partial net return per year (P = 0.036). Prepartum BCS was not associated with the partial net return per year (P = 0.24), but the BCS by treatment interaction remained in the model (P = 0.10). Table 3 presents treatment LSM for partial net return per year, overall, and by BCS class. Overall, PEG treatment increased the partial net return per year by $210 ± 100. Figure 1 illustrates PEG treatment effect on the partial net return per year, overall and by BCS class. In addition, parity was associated (primiparous $824 ± 281; multiparous $1,261 ± 275; P < 0.001) and calving month remained in the model (P = 0.07).

Effect of Pegbovigrastim on Milk Revenues and Costs Per Cow Per Year

Final model results of C^{Cull} per year show that PEG treatment effect did not reach statistical significance (P = 0.061). Prepartum BCS was not associated with the C^{Cull} per year (P = 0.65), whereas the removal of the BCS by treatment interaction (P = 0.12) resulted in an important change in the treatment effect and it was therefore maintained in the model. Table 3 presents treatment LSM for C^{Cull} per year, overall, and by BCS class. Overall, PEG treatment numerically reduced the C^{Cull} per year by $145 ± 77. Differentiated by parity, the C^{Cull} per year was $453 ± 68 and 336 ± 53 ($P$ = 0.07) in primiparous and multiparous cows, respectively.

Pegbovigrastim treatment reduced the C^{CM} per year by $9 ± 3 ($P$ = 0.008; Table 3). Parity was associated with C^{CM} (primiparous $26 ± 9; multiparous $45 ± 9; P < 0.001). In addition, BCS was associated with C^{CM} (P = 0.01); we found that over BCS cows presented a higher C^{CM} per year compared with acceptable BCS cows (P = 0.01; under BCS $29 ± 10; acceptable BCS

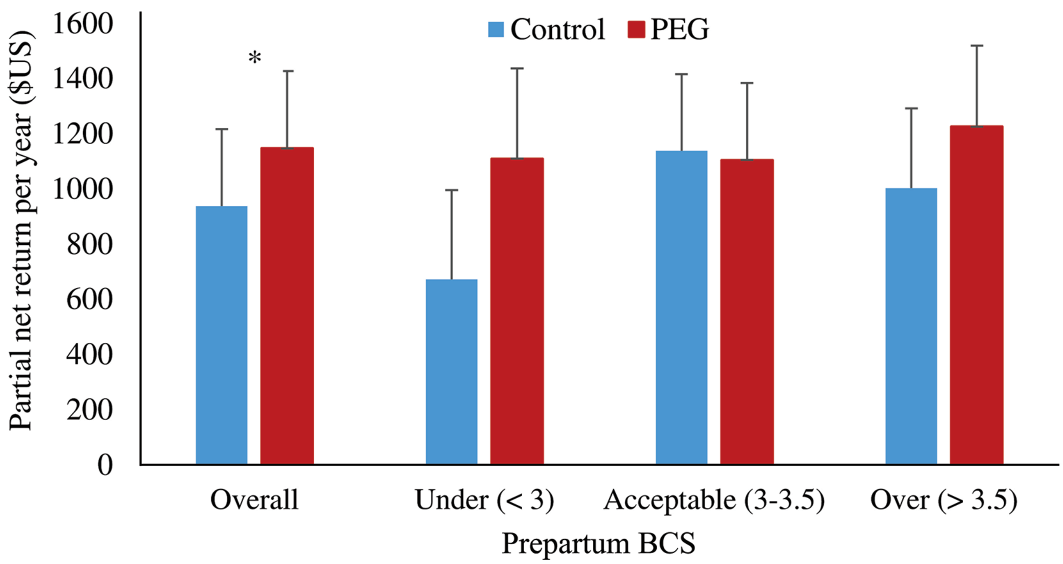

Figure 1. Least squares means (error bars represent SE) for the overall partial net return per year in the control group (n = 1,102) and cows treated with pegbovigrastim (PEG; n = 1,026), and by prepartum BCS class (under: control = 106, PEG = 97; acceptable: control = 694, PEG = 696; over: control = 302, PEG = 233) in a randomized controlled trial on 4 commercial grazing dairy farms. *Overall, PEG treatment increased the partial net return per year by $210 ± 100 (control = 938 ± 279, PEG = 1,147 ± 280; $P = 0.036$).

$32 ± 9; over BCS $45 ± 9). Finally, calving month ($P = 0.003$) was associated with the C^{CM} per year.

Pegbovigrastim treatment did not affect the C^{Other} per year ($P = 0.37$) and NEFA was not associated with the C^{Other} per year ($P = 0.16$); however, NEFA interacted with treatment ($P = 0.03$). Table 3 presents treatment LSM by NEFA class. In addition, parity was associated (primiparous $4 ± 5; multiparous $17 ± 4; $P = 0.05$) with the C^{Other} per year.

Pegbovigrastim treatment did not affect the C^{UD} per year ($P = 0.07$; Table 3). Parity was not associated (primiparous $16 ± 6; multiparous $13 ± 5; $P = 68$), and calving month was associated with the C^{UD} per year ($P < 0.001$).

Pegbovigrastim treatment did not affect the R^{Milk} per year ($P = 0.28$; Table 3). Parity was associated with R^{Milk} per year (primiparous $2,257 ± 285; multiparous $2,682 ± 284; $P < 0.001$), and so was BCS ($P = 0.01$); additionally, under BCS cows presented a lower R^{Milk} per year compared with over BCS ($P = 0.004$) cows (under BCS $2,368 ± 288; acceptable BCS $2,485 ± 284; over BCS $2,555 ± 285). Prepartum NEFA remained in the model (low $2,500 ± 285; high $2,439 ± 285; $P = 0.10$).

Pegbovigrastim treatment did not affect C^{Feed} per year ($P = 0.22$; Table 3). We found an association with parity (primiparous $851 ± 60; multiparous $926 ± 60; $P < 0.001$) and BCS ($P = 0.003$); particularly, under BCS cows presented a lower C^{Feed} per year compared with acceptable BCS ($P = 0.02$) cows and compared with over BCS ($P = 0.002$) cows (under $863 ± 61; acceptable $894 ± 60; over $910 ± 60).

Pegbovigrastim treatment did not affect C^{Ins} per year ($P = 0.58$; Table 3). Parity was not associated (primiparous $48 ± 4; multiparous $50 ± 4; $P = 0.38$), and calving month ($P < 0.001$) was associated with C^{Ins} per year.

Sensitivity Analysis

Supplemental Table S3 (https://doi.org/10.17632/7n77zzn2p2.3; Barca, 2022) provides an overview of the final regression models for partial net return per year assuming different input levels as used for the sensitivity analyses.

Least squares means and the treatment effect on partial net return per year by different variable levels as used in the sensitivity analyses are presented in Table 4. Compared with the price levels assumed in this study, a 20% lower price for milk protein and fat resulted in a 7% lower economic benefit of PEG treatment, whereas a 20% higher price showed a 6% higher economic benefit. Assuming that milk withheld due to medical treatments would not be fed to calves resulted in a 2% higher economic benefit of PEG treatment. Assuming the lowest beef price at slaughter resulted in a 10% higher economic benefit of PEG treatment. Assuming a 20% higher price of a replacement heifer showed a 22% higher economic benefit of PEG treatment.

Table 4. Relative change of partial net return per year ($) by different variable levels as used for sensitivity analyses[1]

Variable[2]	LSM ± SEM			P-value[3]
	Control	PEG	Treatment effect	
Milk fat and protein (min)	464 ± 223	660 ± 224	196 ± 95	0.040
Milk fat and protein (max)	1,427 ± 316	1,650 ± 317	223 ± 105	0.034
Milk withheld discarded[4]	915 ± 257	1,130 ± 258	214 ± 100	0.032
Beef price (min)	891 ± 263	1,122 ± 264	230 ± 106	0.030
Replacement heifer	788 ± 292	1,045 ± 293	257 ± 120	0.032

[1]Analyses were for control (n = 1,102) and pegbovigrastim (PEG) treated (n = 1,026) cows in a randomized controlled trial on 4 commercial grazing dairy farms.

[2]Min = minimum; max = maximum.

[3]P-values of pair-wise comparisons of LSM corrected with the Tukey-Kramer adjustment.

[4]Assuming that milk withheld due to medical treatments would not be fed to calves.

DISCUSSION

In this study, we report for the first time the economic result of using PEG in dairy cows. Based on the economic performance of cows during a full lactation, we determined the partial net return per cow per year. The main finding was that PEG treatment resulted in an overall economic benefit, as it increased the partial net return per cow per year. Interestingly, although numerical differences could be noticed in the descriptive statistics of the underlying economic factors of the partial net return, only the C^{CM} per year was individually statistically significant, whereas all other factors represented in the partial net return (i.e., R^{Milk}, C_i^{Feed}, C_i^{UD}, C_i^{Other} C_i^{Ins}, and C^{Cull} per year) were not significant. However, the total effect of all these economic factors, represented in the partial net return per year, resulted in a statistically significant economic benefit for PEG treated compared with control cows.

The method we used is relatively novel. Previous studies on the economics of cow-level health interventions used bio-economic simulation models [e.g., working on Meloxicam (van Soest et al., 2018) or working on Cabergoline (Steeneveld et al., 2019)]. In such bio-economic simulation modeling studies, specific decisions need to be made on what treatment effects need to be considered. Effects of treatment on occurrence of udder health were derived from clinical trials. In contrast, effects on reproduction or culling were modeled mechanistically using studies other than clinical trials. Such bio-economic simulation studies do not allow to account for heterogeneity between cows. In this study, we used longitudinal data from each enrolled cow during the full lactation. It allowed us to evaluate the combined effect of all cow production factors that may influence the economic performance of that cow. By using the data of all individual cows, we could evaluate the overall economic effect of PEG treatment, accounting for heterogeneity between cows. We consider our current approach as a more reliable method of evaluating the true economic effects of cow-level interventions.

Almost 70% of the increased partial net return per cow per year due to PEG treatment was explained by the reduced C^{Cull} per cow per year. Culling has previously been identified as one of the main contributors to the cost of clinical disease (Galligan, 2006; Overton and Fetrow, 2008; Heikkilä et al., 2012). Rollin et al. (2015) attributed more than 40% of the cost of CM during the first 30 DIM to costs of culling and replacement. van Soest et al. (2018) reported that reducing the proportion of culling had the highest economic impact on the net economic benefit of using nonsteroidal anti-inflammatory drugs in the treatment of CM. In a novel approach, Denis-Robichaud et al. (2021) reported that PEG treatment as an adjunct therapy increased survival after 30 d in cows with severe CM. It may, therefore, be hypothesized that PEG treatment reduces early culling as a consequence of disease, which would be particularly expensive due to the short time that those cows remain in lactation. In our trial, a first case of CM during the first 30 DIM was associated with an almost 2-fold increase in the hazard of culling (Barca et al., 2022). Pegbovigrastim treatment reduced the occurrence of a first case of CM during the first 30 DIM (Barca et al., 2021b) and, in multiparous cows, counteract the negative association of a first case of CM during the first 30 DIM with the hazard of culling (Barca et al., 2022). We also reported that PEG treatment reduced the hazard of a first case of CM and the rate of total cases of CM (Barca et al., 2021b). Hertl et al. (2018) reported that more CM cases in early lactation resulted in an increased rate of CM cases during the lifetime of a cow and that these CM cases also increased the hazard of culling. Thus, the reduced C^{Cull} per year in PEG treated cows may be explained by the preventive effect on CM in combination with a lower rate of repeat CM cases in cows that had a first case of CM during the first 30 DIM.

For partial net return per year, the BCS by treatment interaction remained in the final model, suggesting that the economic benefit of using PEG depends on BCS. Again, this would be mainly explained by the C^{Cull} per year. For the C^{Cull} per year, the removal of the BCS by treatment interaction resulted in an important change in the PEG treatment effect. Therefore, BCS acted as a modifier for the effect of PEG treatment on the C^{Cull} per year. Numerically, PEG treatment increased partial net return per year in under and over BCS cows, but not in cows with an acceptable BCS. Simultaneously, PEG treatment numerically reduced C^{Cull} per year in under and over BCS cows, and not in cows with an acceptable BCS. These results are in line with our earlier results, which suggest PEG treatment reduced the occurrence of a first case of CM during the first 30 DIM in under (only numerically) and over BCS cows, and not in cows with an acceptable BCS (Barca et al., 2021b). It is relevant that, in our study, most of the cows that classified as under BCS were multiparous cows (data not shown). In multiparous cows, a first case of CM during the first 30 DIM was associated with a more than 2.5-fold increase in the hazard of culling. As mentioned, in multiparous cows, PEG treatment counteracted the negative association between a first case of CM during the first 30 DIM and the hazard of culling (Barca et al., 2022). This contributes to explain the numerical differences particularly in under BCS cows.

Pegbovigrastim treatment reduced the C^{CM} per year. This further supports the findings related to the reduced C^{Cull} per year in PEG treated cows. As mentioned, PEG treatment reduced the occurrence of a first case of CM during the first 30 DIM (Barca et al., 2021b), consistent with previous reports (Canning et al., 2017; Ruiz et al., 2017). Moreover, we reported that PEG treatment reduced the hazard of a first case and the rate of total cases of CM during the full lactation (Barca et al., 2021b). All these effects explain the reduction of the C^{CM} per year. Additionally, Powell et al. (2018) reported that PEG treatment reduced the severity of a CM case. In an experimental mastitis challenge, it was reported that PEG treated cows exhibited a less severe milk yield drop (Powell et al., 2018). A less pronounced milk drop would result in an economic benefit. Moreover, reduced severity of a CM case would affect $C^{Medicine}$ and C^{Labor} per year for a CM treatment. To study whether PEG treatment affects severity of CM or whether the CM cases in control and PEG treated cows differ (e.g., causal pathogen, duration, bacteriological cure, and so on) warrants further research.

For the C^{Other} per year, NEFA interacted with treatment, in High NEFA cows, PEG treatment numerically reduced the C^{Other} per year. In this trial, all treatments were recorded. However, we did not evaluate the effect of PEG on the occurrence of diseases other than CM and UD. Further research analyzing the effect of PEG on the occurrence of other diseases would add information about the effect of PEG treatment on the C^{Other} per year. Elevated prepartum NEFA concentrations were associated with an increased risk of disease (Ospina et al., 2013). Previously, we reported that PEG treatment reverted the negative association between prepartum NEFA concentration and postpartum circulating neutrophil counts (Barca et al., 2021a), potentially improving the immune responsiveness in PEG treated cows.

We decided to perform our analyses parametrically, as, despite the usual skewness in the distribution of costs, in pragmatic randomized trials like this one, it is the arithmetic mean that is the most informative measure, and comparisons between treatment groups are reliable if skewness is not too extreme (Thompson and Barber, 2000). We excluded 12 control and 13 PEG cows, due to their extremely high C^{Cull} per year that made statistical analyses using parametric linear models difficult, if not impossible. The extremely high C^{Cull} per year was a consequence of the very few ED ($\leq$15 DIM) of these cows. This same approach with regard to outliers in C^{Cull} per year calculations was recently reported by Burgers et al. (2022). Because of the calculation method and the need to express the economic performance of cows during an equal time period (a year in this study), extremely high costs or returns per year may occur when cows have very few ED. For these 25 cows, the C^{Cull} per year was considerably lower in PEG treated cows compared with control cows. Hence, including these cows in the analyses would only further favor the economic outcome toward the PEG treatment. We acknowledge that our method to calculate the C^{Cull} per year has shortcomings, as it resulted in some extremely high values which were excluded from the final analyses. However, we believe that this method allows us to achieve a realistic estimation in most cows, accounting for the future value of a cow, as it calculates the C^{Cull} of each cow according to its actual lactation while accounting for the ED that each cow remained in the experiment. We consider this to be the best approach with the available data, as any revenue or cost of each cow should be spread out over the ED of each cow.

Sensitivity analyses showed that different variable levels did not have large effects on the economic consequences of PEG treatment. This indicates that the results are robust and not particularly sensitive with regard to differences in inputs (mainly price levels). The most influential variable with regard to the economic benefit of using PEG was the price of a replacement heifer. In this study, we used a conservative price because prices of replacement heifer are higher in most scenarios (INALE, 2021).

As mentioned, costs of PEG and its application (2 doses) were not included in the economic calculations. From an economic point of view, the calculated differences between control and PEG treated cows may be considered as the maximum amount of money that can be spent on PEG treatment. The costs of PEG treatment consist of the expenditure on the product, as well as the time it takes to administer treatments as part of farm transition cow management. It would consist of the time to identify and restrain the cow, and administer PEG. This may be highly dependent on the cost of labor and the ease with which cows can be identified and restrained. Thus, it could vary in different regions or herds with different management and facilities.

Overall PEG treatment resulted in a net economic benefit per cow per year. However, PEG treatment appears to be particularly beneficial in cows that are metabolically challenged (Barca et al., 2021a,b, 2022). Our results suggest that targeting PEG treatment to cows at a higher risk of disease due to a metabolic challenge and lower immune competence (Roche et al., 2009, 2015; Ingvartsen and Moyes, 2015) would be the more efficient option from an economic point of view. Thus, it would be of great value to develop predictive models to identify high-risk animals to further target the use of PEG. Loss of BCS would be a reliable indicator of metabolic challenge (Sheehy et al., 2017; Barletta et al., 2017). Under and over BCS cows may be identified by routine BCS scoring protocols or by using commercially available automated sensors (e.g., Mullins et al., 2019), whereas big data, metabolomics, and the use of automatic sensors to predict metabolic health (Overton et al., 2017) are promising technologies to identify cows that would benefit most from PEG treatment.

CONCLUSIONS

Based on data from a large randomized clinical trial, we conclude that PEG treatment resulted in an overall economic benefit, as it increased the partial net return per cow per year by \$210 ± 100. Although the difference detected in the partial net return was statistically significant, the individual components of partial net return were not significantly different between control and PEG treated cows. Only the cost of treatment of CM was significantly lower for PEG treated cows compared with control cows (\$9 ± 3). The largest numerical difference was seen for the cost of culling: PEG treatment reduced the cost of culling by \$145 ± 77.

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