Comparison of Tylvalosin with Tylosin for the control of subclinical ileitis in swine

P. POMMIER[1]*, A. KEITA[1], E. PAGOT[1], O. DURAN[2], P.R. CLOET[3]

[1]*CTPA, ZOOPOLE développement, 2 rue Jean Rostand, BP 7, F-22440 Ploufragan, FRANCE.*
[2]*ECO Animal Health, P.O. Box 47542, London N14 6WS, UNITED KINGDOM.*
[3]*SCHERING-PLOUGH Vétérinaire, 92, Rue Baudin, 92307 Levallois-Perret Cedex, FRANCE.*

**Corresponding author: patrick.pommier@zoopole.asso.fr*

SUMMARY

In a comparative, mono-centric, randomised, blind, Good Clinical Practice field trial 2 treatments against subclinical ileitis were evaluated. The trial involved 20 pens (440 pigs) with subclinical ileitis that were randomly assigned to two groups. One group received a feed supplemented with 85 ppm Tylvalosin daily for 10 days (group A) and the other one (group C) the same feed, supplemented with 100 ppm Tylosin daily for 21 days.

From the beginning of treatment to slaughter (i.e. during the whole fattening period), the ADWG was 821 g in group A versus 788 g in group C (NS), and mortality was 7.3 per cent in group A versus. 5.0 per cent in group C (NS). The average age at slaughter was 194.3 days in group A versus 196.2 days in group C (*p=0.045*). The average percentage of lean meat at slaughter was 59.8 per cent in group A versus 59.2% in group C (*p=0.025*).

In this trial, Tylvalosin (Aivlosin®) was effective when given for a short period at the start of the fattening period, at controlling subclinical ileitis. Compared with the positive control Tylosin, several significant improvements were recorded, including a 2 day reduction in age at slaughter, an improved growth homogeneity during fattening and a 0.6 point increase in the percentage of lean meat.

Keywords: *Lawsonia intracellularis*, pig, swine, ileitis, Tylvalosin, Tylosin.

RÉSUMÉ

Comparaison de la Tylvalosine et de la Tylosine pour le contrôle de l'iléite subclinique chez le porc

Dans cet essai clinique terrain comparatif, monocentrique, randomisé, réalisé en double aveugle et selon les Bonnes Pratiques Cliniques, 20 cases de porcs atteints d'iléite subclinique (soit 440 animaux) ont été répartis au hasard en deux lots. Le premier (A) a reçu pendant 10 jours un aliment supplémenté avec 85 ppm de Tylvalosine et le second (C) le même aliment, supplémenté pendant 21 jours avec 100 ppm de Tylosine.

Entre le début du traitement et l'abattage (soit sur toute la période d'engraissement), le GMQ s'est établi à 821 g dans le lot A contre 788 g dans le lot C (NS) et la mortalité à 7,3 pour cent dans le lot A contre 5,0 pour cent dans le lot C (NS).

L'âge moyen à l'abattage a été de 194,3 jours dans le lot A contre 196,2 jours dans le lot C (*p=0.045*). Le taux moyen de muscle des carcasses a été de 59,8 pour cent dans le lot A contre 59,2 pour cent dans le lot C (*p=0.025*).

Dans cet essai, la Tylvalosine (Aivlosin®), administrée pendant une courte période en début d'engraissement, s'est montrée efficace dans le contrôle de l'iléite subclinique. Comparativement à un témoin positif (Tylosine), plusieurs améliorations significatives ont été observées, comme une réduction de 2 jours de l'âge à l'abattage, une croissance plus homogène en engraissement et une amélioration de 0,6 point du taux de muscle des carcasses.

Mots clés : *Lawsonia intracellularis*, porc, iléite, Tylvalosine, Tylosine.

Introduction

Ileitis (Porcine Proliferative Enteropathy) is a common enteric pig disease in France and, more generally, European pigs herds [16, 1, 7]. The causative agent is the anaerobic bacterium *Lawsonia intracellularis* [5]. On many farms, the infection takes a subclinical form [12], which generally has a high incidence within a group of growing pigs, but mild clinical signs [1, 7]. Subclinical Ileitis is defined by the presence of infection with *L. intracellularis* leading to typical proliferative enteropathy lesions, but causing very mild diarrhoea accompanied by reduced weight gain and increased weight variation at the time of slaughter.

Tylvalosin is a recently approved macrolide antibiotic, with proven efficacy for the treatment and control of Porcine Proliferative Enteropathy or ileitis caused by *L. intracellularis* [15, 11, 14, 17]. The aim of this field trial was to compare the effectiveness of Tylvalosin with a known effective antimicrobial, Tylosin, for the control of subclinical ileitis.

Materials and Methods

STUDY SITE

This was a comparative, mono-centric, randomised, double-masked, clinical field trial, conducted in accordance with Good Clinical Practice and welfare regulations. The trial site selected was a 1200 sows commercial farrow-to-finish farm in Finistère (Brittany, France) where young pigs are naturally infected with *Lawsonia intracellularis* causing subclinical ileitis. Each week, 700 piglets are weaned at 21 days of age. Feed is made on farm, usually including the following antibiotics: Colistin during the whole post weaning period, Tilmicosin and Trimethoprim-Sulfonamide association at the end of the post weaning period, then Tylosin during the first three weeks of the fattening period. All these antibiotics (except Colistin) were removed during the trial period.

The diagnosis of *L. intracellularis* was based on previous responses to treatments of diarrhoea and serological data.

Four weeks before the implementation of treatments, 55 animals were blood-sampled at the farm for *L. intracellularis* serology, using an ELISA test. The results of the serological profile are as follows:
- sows (multiparous): 5/5 positive,
- gilts (primiparous): 4/5 positive, 1/5 doubtful,
- piglets at weaning: 3/5 positive, 1/5 doubtful, 1/5 negative,
- 10 weeks old pigs: 2/10 positive, 3/10 doubtful, 5/10 negative,
- 14 weeks old pigs: 5/10 positive, 3/10 doubtful, 2/10 negative,
- 18 weeks old pigs: 7/10 positive, 3/10 doubtful,
- at the end of the fattening period: 4/10 positive, 3/10 doubtful, 3/10 negative.

These results demonstrate *L. intracellularis* circulation in the farm.

Seroconversion usually takes place when pigs are 10-14 weeks of age (see Figure 1). So the treatments were implemented at 10-11 weeks of age (actually 75 days). Since the farmer systematically used antibiotics for treatment against Lawsonia intracellularis, PCR analyses and clinical symptoms could not be used consistently for diagnosis of ileitis.

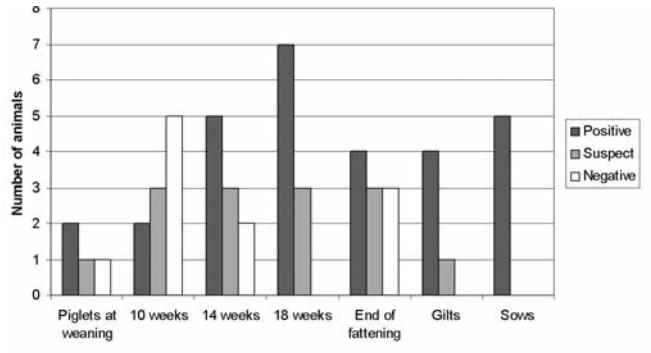

FIGURE 1 : Serological profile of the herd.

TREATMENT REGIMEN

A total of 440 seventy-five day old pigs housed in 20 pens in three rooms, were randomly assigned to two groups (A or C). Pigs in group A (10 pens, 220 pigs) received a feed supplemented with 85 ppm Tylvalosin (Aivlosin® Premix) daily for 10 days. Pigs in group C (10 pens, 220 pigs) received the same feed, supplemented with 100 ppm Tylosin (Concentrat® VO 07 – SOGEVAL Laboratory) daily for 21 days. Both products were administered in accordance with the manufacturer's recommendations. Treatment was timed to treat the pigs during the early infection with *L. intracellularis* which coincided with movement to the fattener house.

RANDOMISATION AND BLINDING

Randomisation tables were provided. Groups were balanced for weight (and variance): inside each room, pens were sorted by weight, and then allocated to treatments following a randomisation table. All animals were females. Pens were randomly assigned as belonging to group A or C inside each room. Pens within each room were divided equally between the 2 groups. Treatments were incorporated in feed by the feed manufacturer. During the 3 weeks treatment period, medicated feed was delivered using coded bags.

Piglets were identified using individually numbered ear tags. They were tattooed by group (A or C). The farm personnel, the veterinarians and the statistician were blinded as to the treatment used in each treatment group. They were aware of which pigs were in which group, since fed bags of each group were coded differently (A/B or C/D). Codes were deblinded at the end of the study: group A/B was the Tylvalosin group and group C/D was the Tylosin group.

Tylosin medicated feed was prepared in two different coded bags, in order to maintain the blind conditions all along the trial, because the two treatment periods are different (10 days versus 21 days).

Three categories of feed and four categories of bags were supplied:
- Tylvalosin incorporated feed,
- Not supplemented feed to give from D10 to D21 to the Aivlosin® group,
- Tylosin incorporated feed (one code for D0-10 period, another code for D10-D21 period).

EVALUATION CRITERIA

At the farm, all trial pigs were individually identified with an eartag, and weighed 3 times; at the beginning of the trial, 21 days later (end of experimental treatments) and at the end of the fattening period (just before the first departures to slaughter).

The quantity of feed dispensed between D0 and D21 to each pen was recorded.

Any mortality during the trial including the date and cause of death (when known) was recorded,

At slaughter, the following data were collected: carcass weight (by treatment group), muscle rate (by treatment group) and date of slaughtering.

The effects of treatments were compared using the average daily liveweight gain (ADWG) from the beginning of treatment until slaughter as the main criterion. The other comparison criteria were: liveweight 21 days after the start of treatment, Feed consumption (during the experimental treatment 3 weeks period), Feed Conversion Ratio (FCR) (during the experimental treatment 3 weeks period), mortality, number of days between the beginning of treatment and slaughter, Carcass weight and percentage of lean meat at slaughter.

STATISTICS

The treatment unit was the pen. The statistical unit was the pig, except for feed intake and FCR calculations (pen).

The following statistical analyses were carried out:
- For ADWG and liveweights: nested ANCOVA, with group as factor, and with initial weight as covariate;
- For Feed intake and FCR, ANOVA on pens, with group as factor;

- For days from beginning of treatment until slaughter, Kruskal-Wallis non-parametric test;

- For carcass weight and percentage of lean, ANCOVA, with group as factor and age at slaughter as covariate;

- For mortality, Mantel Haenszel Chi-square, stratified on rooms, or, if not applicable, Fisher's exact test.

The first species risk for the statistical tests is $\alpha = 0.05$. The statistical calculations were designed as two-sided test, and performed using SYSTAT software (9.0 version for Windows).

Results

INITIAL COMPARISON OF THE GROUPS

As a whole 20 pens, each of them hosting 22 pigs, were included in the study. The number of pens (and, so, of pigs) was equally divided between the two groups: 10 pens and 220 pigs in each group.

The average initial weight was 26.7 kg (SD = 3.1) in the Tylvalosin group and 26.7 kg (SD = 3.2) in the Tylosin group (*NS, p=0.973*).

Based on the criteria "number and repartition of cases" and "initial weight" both compared groups were similar at the beginning of the trial.

EFFICACY EVALUATION

The Average Daily Weight Gain (ADWG) between the beginning of treatment and the end of the fattening period was 821 g in the Tylvalosin group and 788 g in the Tylosin group (see Figure 2). These growths are not statistically different (*p = 0.138*).

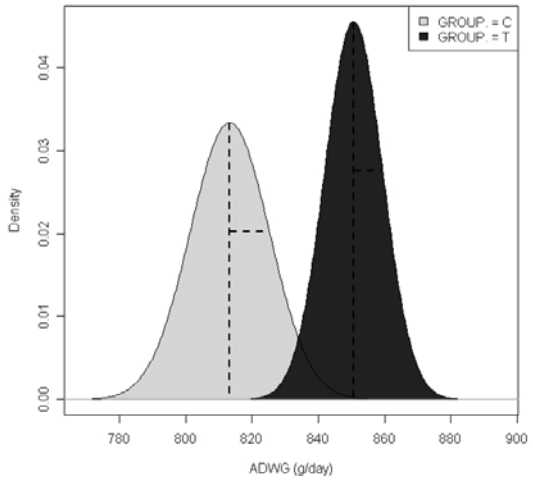

FIGURE 2 : Average Daily Gain from start of treatment until slaughter.

Further analysis concluded that there were significant differences between the group variances, both for ADG and for the final weight. Therefore ADWG and final weight were more homogeneous in the Tylvalosin group ($p<0.001$).

The liveweight at the end of treatment was 41.7 kg in the Tylvalosin group and 41.5 kg in the Tylosin group (*NS, p = 0.715*).

During the 3 weeks treatment period, the feed intake per pig was 38.5 kg in the Tylvalosin group and 37.7 kg in the Tylosin group (*NS, p = 0.429*). During the 3 weeks treatment period, the Feed Conversion Ratio was 2.58 in the Tylvalosin group and 2.57 in the Tylosin group (*NS, p = 0.905*).

The average number of days from the beginning of treatments to slaughter was 119.3 days (i.e. 194.3 days-old at slaughter) in the Tylvalosin group and 121.2 days (i.e. 196.2 days-old at slaughter) in the Tylosin group. This difference is statistically significant (*p=0.045*).

At slaughter, the carcass weight was 95.4 kg in the Tylvalosin group and 94.8 kg in the Tylosin group (*NS, p = 0.291*).

The percentage of lean at slaughter was 59.8 in the Tylvalosin group and 59.2 in the Tylosin group (*p = 0.025*).

The overall mortality rate (from the beginning of treatment to slaughter) was 7.3% (16/220) in the Tylvalosin group and 5.0 % (11/220) in the Tylosin group (*NS, p = 0.461*). The mortality rate from the beginning of treatment to D21 was 6.8% (15/220) in the Tylvalosin group and 2.3% (5/220) in the Tylosin group (*NS, p = 0.114*).

Remark: during the treatment period, mortality in group A was mainly due to an acute E. coli outbreak, centred in 2 pens (resulting in half the mortality).

The mortality rate from D21 to slaughter was 0.5% (1/205) in the Tylvalosin group and 2.8% (6/215) in the Tylosin group (*NS, p = 0.399*).

Discussion

The aim of this trial was to evaluate the use of Tylvalosin (Aivlosin® Premix) for the control of subclinical ileitis, in comparison with a known effective control, Tylosin. Subclinical or endemic ileitis has been estimated to significantly increase the cost of production due to reduced weight gain, increased Feed conversion ratio and increased variation in lots [6,8]. Cost estimates from farms in Australia [2] have projected the cost for the less severe forms of proliferative enteropathy in the range of Aus$15 to $141 per sow per year (€9 to €86/sow/year). In a challenge study reproducing the typical clinical picture with subclinical ileitis, the average daily live-weight gain (ADG) was reduced by 37 to 42% and the feed intake required per kg of weight gain (FCR) was increased by 27 to 37% in the groups with subclinical Ileitis [10]. This could represent costs per pig reared of up to €3 per pig in a typical European pig farm [McCorist, personal communication, 2007]

In this trial, Tylvalosin was effective when given for a short period at the start of the fattening period, aimed at controlling subclinical ileitis. Compared with the positive control Tylosin, several statistically significant improve-

ments were recorded, including a 2 day reduction in the days to slaughter, better growth homogeneity during fattening and a 0.6 point improvement in the percentage of lean meat. Diagnosis of subclinical ileitis is a concern, especially when infection is controlled by the use of antibiotics. It can be documented by historical data of grey diarrhoea and past isolations of *Lawsonia*, efficacy of treatments against *Lawsonia*, and serological data proving the bacteria circulation, but the diagnosis can only be confirmed by detection of pathological lesions and *L. intracellularis* from affected pigs. However, the results of this study support previous findings from field trials where Tylvalosin was used to treat acute ileitis [15, 4]. Tylvalosin (formerly acetyl isovalerylTylosin) is derived from fermentation of factor A Tylosin with *Streptomyces thermotolerans* [3]. This fermentation results in the acetylation of the highly active 16 member lactone ring. These structure changes confer benefits related to rapid absorption from the gut following administration in-feed or in-water, high bioavailability in the target tissues and increased antimicrobial properties due to the addition of the isovaleryl group [9]. Recently, *in vitro* experiments using intestinal epithelial cell lines have demonstrated that Tylvalosin accumulates rapidly and in high concentration inside these cells [13]. These findings support the efficacy of Tylvalosin against the obligate intracellular bacteria *Lawsonia intracellularis* by ensuring that the antimicrobial is present at the site of infection.

In summary, Tylvalosin has been shown in a well controlled blinded study to be effective at reducing the production losses related to subclinical ileitis in a typical commercial farm. Tylvalosin was statistically superior to Tylosin in the reduction of days to slaughter, improved homogeneity of the weights at slaughter and improved lean meat gain.

References

1. - CHOUET S., PRIETO C., MIELI L., VEENHUIZEN M.F., McORIST S. : Some patterns of exposure to *Lawsonia intracellularis* infection on European pig farms. *Vet. Rec*., 2003, **152**, 14-17.
2. - HOLYOAKE P.K., MULLAN B.P., CUTLER R.S. : Simulation of the economic impact of proliferative enteritis on pig production in Australia. *Aust. Vet. J*., 1996, **73**, 89-92.
3. - HUANG G., OKABE M., KAHAR P., TSUNEKAWA H., PARK Y. Optimization of Tylosin feeding rate profile in production of acetylisovalerylTylosin (AIV) from Tylosin by *Streptomyces thermotolerans* YN554. *J. Biosci. Bioeng*., 2001, **91**, 504-508.
4. - IGLESIAS G., TRUJANO M., HOFTIJZER J. : Evaluation of an in-feed medication for the control of porcine proliferative enteritis. *Proc. 16th IPVS Congress*, 2000, **2**, 173.
5. - McORIST S., GEBHART C.J., BOID R., BARNS S.M. : Characterization of *Lawsonia intracellularis* gen.nov., sp. nov., the obligately intracellular bacterium of porcine proliferative enteropathy. *Int. J. Sys. Bacteriol*., 1995, **45**, 820-825.
6. - McORIST S., SMITH S.H., GREEN L.J. : Estimate of direct financial losses due to porcine proliferative enteropathy. *Vet. Rec*., 1997, **140**, 579-581.
7. - McORIST S., BARCELLOS D.E., WILSON R.J.: Global patterns of Proliferative Enteropathy. *Pig Journal*, 2003, **51** ,26-35.
8. - McORIST S. : Defining the full costs of endemic porcine proliferative enteropathy. *Vet. J.,* 2005, **170**, 8-9.
9. - OKAMOTO R., TSUCHIYA M., NOMURA H., IGUCHI H., KIYOSHIMA K., HORI S., INUI T., SAWA T., TAKEUCHI T., UMEZAWA H. : Biological properties of new acyl derivatives of Tylosin. *J. Antibiot*., 1980, **3**, 1309-1315.
10. - PARADIS M.A., MCKAY R.I., WILSON J.B., VESSIE G.H., WINKELMAN N.L., GEBHART C.J.: Subclinical Ileitis produced by sequential dilutions of *Lawsonia intracellularis* in a mucosal homogenate challenge model. *Proc. American AASV Conference*, 2005, 189-192.
11. - SIMS M., WINKELMAN N.L., ELIOPOULOS C., GNOZZIO M., DOMANGUE R.: Efficacy of Aivlosin Premix for the control of Porcine Proliferative Enteropathy (PPE, ileitis) in pigs experimentally infected with *Lawsonia intracellularis*. *Proc. 19th IPVS Congress*, 2006, **2**, 179.
12. - STEGE H., JENSEN T.K., MOLLER K., VESTERGAARD K., BAEKBO P., JORSAL S.E. : Infection dynamics of *Lawsonia intracellularis* in pig herds. *Vet Microbiol*., 2004, **104**,197-206.
13. - STUART A.D., BROWN T.D.K., IMRIE G., TASKER J.B., MOCKETT A.P.A. : Intra-cellular accumulation and trans-epithelial transport of aivlosin, Tylosin and tilmicosin. *The Pig Journal*, 2007, **60**, 26-35.
14. - TASKER J.B., WINKELMAN N.L., KIRWAN P.: Use of Aivlosin in feed for control of ileitis in USA and Europe. *Proc. 18th IPVS Congress*, 2004, **1**, 256.
15. - TASKER J.B.,HAUGEGAARD J., NIELSEN J.P.: The use of Aivlosin in-feed to control porcine proliferative enteropathy in Denmark. *Proc. 19th IPVS Congress*, 2006, **2**, 170.
16. - VAN DER HEIJDEN H.M., BAKKER J., ELBERS A.R., VOS J.H., WEYNS A., DE SMET M., McORIST S. : Prevalence of exposure and infection of *Lawsonia intracellularis* among slaughter-age pigs. *Res. Vet. Sci*., 2004, **77**, 197-202.
17. - WINKELMAN N.L., TASKER J.B.: Efficacy of Aivlosin for therapy of Porcine Proliferative Enteropathy (PPE). *Proc. 17th IPVS Congress*, 2002, **2**, 145.