Ovine progressive pneumonia research at the Texas Agricultural Experiment Station: What we have learned in the last decade

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Abstract: Ovine progressive pneumonia (OPP) is a chronic disease of sheep caused by ovine lentivirus (OvLV), also called OPP virus. Economic losses that result from this disease include the cost of treatment of secondary infections, losses associated with reduced productivity of affected animals, animal deaths, and loss of marketing opportunities as a result of restrictions that countries impose on the importation of sheep from places where the infection exists. Ovine progressive pneumonia is considered one of the most important diseases of sheep in North America. For over a decade, a major effort of the veterinary research program at the Texas Agricultural Experiment Station-San Angelo (TAES-SA) has been the understanding of basic concepts on the epidemiology, transmission, diagnosis, treatment and prevention of this disease.

A major finding was that the prevalence of OPP in range sheep of western Texas was significantly lower than in sheep from other states. This divergence in infection rate may be the result of differences in flock management practices and climate. Because production objectives, sheep breeds and management are changing in Texas, producers in this state need to be aware of the potential risk of introducing this infection into their flocks.

We also determined that some of the commercially available ELISA tests used to identify infected sheep are unreliable. Although the agar gel immunodiffusion (AGID) test has high specificity, the test may be unable to detect sheep infected with slow replicating OPP virus strains. Preliminary results indicate that a new commercially available "competitive" ELISA may be more sensitive than the AGID test and other ELISA formats.

Close contact transmission between infected and non-infected sheep under western Texas environmental conditions does not seem to occur, but semen of OPP-infected rams that have concurrent inflammatory lesions in the reproductive tract may be a source of virus for non-infected ewes. Recombinant ovine interferon-tau (roIFN-τ), a new antiviral drug, has proven to be highly effective in reducing virus replication *in vitro* and *in vivo* and in preventing OPP virus-induced disease in lambs that are treated soon after infection. Due to its high cost, treatment of OPP with roIFN-τ is not economically feasible at this point. The utilization of gene delivery vectors or slow-release drug delivery systems may help overcome this barrier.

Past attempts by other investigators to produce a vaccine for OPP have failed. Recently, we genetically engineered an OPP virus in which one viral gene (dUTPase) was replaced by the green fluorescent protein (GFP) gene (a gene from jelly fish). This recombinant OPP-GFP virus is attenuated for pathogenicity *in vitro* and *in vivo*. Because it contains the GFP gene, it can be easily differentiated from wild type OPP virus. For these reasons, the OPP-GFP virus could be used as a vaccine to protect sheep against OPP.

Key Words: Ovine Progressive Pneumonia (OPP), Ovine Interferon-Tau (roIFN-τ), Recombinant Lentivirus, Vaccine

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Introduction

Ovine progressive pneumonia (OPP), also called maedi-visna, is a chronic disease of sheep produced by ovine lentivirus (OvLV), a member of a family of viruses called Retroviruses (Joag et al., 1996). This family also includes caprine arthritis encephalitis virus (CAEV) of goats and the human immunodeficiency virus (HIV), the cause of AIDS in humans (de la Concha-Bermejillo et al., 1995b). Ovine lentivirus or OPP virus produces a persistent infection in infected sheep. Therefore, infected animals remain infected for life and are the source of virus for other sheep (de la Concha-Bermejillo, 1997). For this reason, infection with OPP virus is a major concern to sheep producers worldwide, not only for the economic losses it causes as a result of decreased animal productivity and death of affected animals, but also for the national and international barriers that are imposed to countries and flocks where the infection exists (de la Concha-Bermejillo et al., 1998a; Pekelder et al., 1994; Petursson et al., 1990; Smith, 1992). In a survey conducted among small ruminant veterinary practitioners and producers throughout the United States, OPP was considered among the most important diseases of sheep (de la Concha-Bermejillo et al., 1998a).

Sheep infected with OPP virus often develop a complex disease characterized by chronic inflammation (swelling) of the lungs (pneumonia), lymph glands (lymphadenitis), joints (arthritis), mammary gland (mastitis) and less often brain (encephalitis) (Cutlip et al., 1979; Cutlip et al., 1988). As a result of this, OPP virus-infected sheep may show signs of progressive respiratory failure without fever that affects animals 2-3 yr or older (Brahic and Haase, 1981). Initially, affected animals lag behind when driven to pasture, and after exercise the respiration becomes rapid and shallow. As the disease progresses, the respiration becomes gradually more difficult, and affected sheep develop open-mouth breathing with extension of the neck and flaring of the nostrils to gasp for air. These sheep also show gradual loss of weight and body condition despite good appetite. Once clinical disease becomes apparent, sheep die within one yr usually due to respiratory failure or secondary bacterial infections (Bulgin, 1990).

More than one clinical manifestation may coexist in the same flock or animal (Petursson et al., 1990). Over 60% of ewes in OPP-affected flocks may present evidence of mammary gland swelling. This form of the disease is characterized by diffuse, symmetrical hardening of the udder ("hardbag") and reduction in milk production, although the scant amount of milk may have a normal color and consistency (Houwers et al., 1988). The gland's and milk's appearance in mastitis caused by OPP virus is different from mastitis caused by bacteria ("blue bag"). In the latter the gland is asymmetrical, may develop lumps and the milk may contain flakes and clots. Lambs born to ewes with mastitis caused by OPP virus are constantly hungry and have poor growth, particularly in ewes with twins or triplets (Lechner et al., 1997).

Sheep with arthritis due to OPP become lame and lose body condition despite having good appetite. These clinical signs occur typically two to three yr after infection. The condition begins insidiously with weight loss and swelling of the carpal and tarsal joints. Other joints are less frequently affected (Harkiss et al., 1995; Kennedy-Stoskopf et al., 1989; Narayan et al., 1992). In the US, the form of the disease affecting the brain occurs only occasionally, but it is a common manifestation in some infected flocks in Europe (Constable et al., 1996; Georgsson, 1994). Sheep affected by this form of the disease may show gait abnormalities, initially affecting the hindquarters. Then, there is progressive weakening of the hind legs that results in posterior paralysis. The disease eventually leads to complete immobility of affected sheep. These animals lose body condition, and twitching of the lips and facial muscles or blindness may be observed

(Georgsson, 1994; Oliver et al., 1981). This form of the disease needs to be differentiated from scrapie (de la Concha-Bermejillo, 1997).

THE MAJORITY OF SHEEP FLOCKS IN WESTERN TEXAS ARE FREE OF OPP VIRUS. TEXAS SHEEP PRODUCERS COULD BENEFIT FROM THIS COMPETITIVE ADVANTAGE WHEN SELLING SHEEP.

For the last 11 yr, TAES-SA has maintained a very active OPP research program. We were the first to isolate OPP virus from a ram in Texas and demonstrate the presence of the infection in the state (de la Concha-Bermejillo et al., 1992). Subsequently, we were interested in finding out the extent of OPP virus infection in sheep flocks of western Texas. Previous reports indicated that approximately 26% of all sheep in the US were persistently infected with OPP virus (Cutlip et al., 1992). However, in this study there was great variability in the prevalence of OPP in different states and flocks. While OPP seroprevalence in the Rocky Mountain region was 49%, only 9% of sheep in the Northern Atlantic region were positive. Another study found that the average OPP seroprevalence in a large Idaho sheep range flock was 58% (Gates et al., 1978). To determine the prevalence of OPP in sheep from western Texas, we collected over two thousand serum samples from sheep in that part of the State. To our surprise, only 0.05% of the tested sera were positive for OPP. Furthermore, the majority of OPP positive sheep in these flocks were animals that had been bought from states with high OPP prevalence. We concluded that the low prevalence of OPP in sheep from western Texas may be the result of differences in flock management (lambing on pasture versus pen lambing) and climate (hot and dry) that is unfavorable for the survival of OPP virus in the environment (de la Concha-Bermejillo et al., 1998b). Of great importance in this study was the finding that acquiring replacement sheep from states with high OPP seroprevalence represented a risk of introducing the infection in non-affected flocks. Production objectives, breeds of sheep, and management practices are changing in some flocks in western Texas. Sheep producers in Texas need to maintain awareness of the risks of introducing this disease in their flocks. Replacement sheep should always be tested for OPP.

THE AGAR GEL IMMUNODIFFUSION (AGID) TEST MAY BE A GOOD METHOD TO SCREEN OPP VIRUS-INFECTED FLOCKS, BUT MAY FAIL TO DETECT SOME INDIVIDUAL INFECTED SHEEP.

Having determined that OPP prevalence in western Texas sheep was much lower than the National average, we were interested in finding out the best test to detect infected sheep. Serological methods, including several ELISA formats and the agar gel immunodiffusion (AGID) test, have been the methods of choice to test for OPP antibodies in sheep (Brodie et al., 1998; de la Concha-Bermejillo, 1997). To determine the specificity (ability of a test to detect non-infected animals as negative) and sensitivity (ability of a test to detect infected animals as positive) of the AGID test and two recombinant ELISAs, the three tests were compared using serum samples collected weekly from sheep experimentally inoculated with OPP virus or placebo. Our results showed that the specificitiy and sensitivity of the two ELISA tests were variable. While an ELISA test originally developed by Dr. J. Kwang from the US Meat Animal Research Center in Clay Center Nebraska had a specificity of more than 94% and a sensitivity of 86%, the results of an ELISA test performed by a private veterinary diagnostic laboratory were unreliable. The specificity and sensitivity of the AGID test were 100% and 91.5%, respectively. These results suggest that the AGID test may be a good screening test to identify OPP infected flocks (Juste et al., 1995). However, because the time of seroconversion may be as long as 12 wk or more, repeated testing

of sheep is recommended. In addition, a recent experiment by this research group using sheep experimentally infected with a slow replicating, genetically modified OPP virus showed that the AGID test was unable to detect infected sheep (author's unpublished observation). At the same time, antibodies against OPP were detected in the sera of four lambs by a new "competitive" ELISA that uses a monoclonal antibody against the surface envelope protein of CAEV, but that crossreacts with OPP virus (Ozyoruk et al., 2001). Although this competitive ELISA seems to have high sensitivity to detect OPP serum antibodies, further testing using clinical samples will be necessary to confirm this observation.

CLOSE CONTACT BETWEEN OPP VIRUS-INFECTED AND NON-INFECTED SHEEP UNDER WESTERN TEXAS WEATHER AND MANAGEMENT PRACTICES MAY NOT BE A RISK OF OPP TRANSMISSION.

Close contact between infected and non-infected sheep, ingestion of colostrum or milk from infected ewes, and the transplacental route are thought to be the methods of OPP virus transmission (Brodie et al., 1994; DeMartini et al., 1999; Petursson et al., 1990). However, the most important route of OPP virus transmission is still controversial. Once OPP infection is introduced, eliminating the infection from the flock is difficult and expensive. Another important issue regarding the OPP research program at TAES-SA was to assess the risk of spreading the infection into Texas OPP-free flocks by introducing infected sheep. For this purpose, we experimentally infected 32 lambs with OPP virus in the spring and kept them in shaded, open pens for eight months. Eight non-infected lambs were introduced into the same pens and kept together for the entire length of the experiment as contact non-infected controls. The OPP status in these forty lambs was determined biweekly for eight months by ELISA, virus isolation and the polymerase chain reaction (PCR), the latter a highly sensitive technique to detect OPP virus DNA in cells and tissues. While all virus-inoculated lambs became infected with OPP virus, none of the non-infected contact controls was detected as positive by any of these tests. These results suggest that introducing OPP virus into OPP-free flocks by mingling infected and non-infected sheep in open pens under western Texas weather conditions does not represents a risk of transmission (Aber et al., 1998). However, because there are differences in sheep breed susceptibility, variations in yr to yr weather conditions, and virus strain virulence (Cutlip et al., 1986; de la Concha-Bermejillo et al., 1995a; Lairmore et al., 1988), we still recommend that replacement sheep be acquired from OPP-free flocks or that all new sheep test negative before being introduced into the premises.

OPP-INFECTED RAMS ARE POTENTIAL SOURCES OF VIRUS FOR NON-INFECTED EWES.

Veneral transmission is the most common route of transmission for HIV, a human lentivirus similar to OPP virus (Levy, 1993). However, information about the potential transmission of OPP virus through contaminated semen was non existent. We were the first research group in the world to report that OPP-infected rams that have inflammatory lesions in the reproductive tract shed the virus in the semen (de la Concha-Bermejillo et al., 1996). In this study, OPP-infected rams co-infected with *Brucella ovis*, the cause of ram epididymitis, excreted large amounts of OPP virus in semen. On the other hand, OPP virus-infected rams without epididymitis did not shed the virus in semen. These results indicate that OPP virus-infected sheep with inflammatory lesion in the reproductive tract may be potential sources of OPP virus for non-infected sheep.

OPP VIRUS REPLICATES RAPIDLY SOON AFTER INFECTION. REPLACEMENT SHEEP MUST BE QUARANTINED AND TESTED FOR OPP SEVERAL TIMES BEFORE MIXING THEM WITH OTHER SHEEP.

As mentioned previously, OPP virus is a lentivirus. The name lentivirus was given to this group of viruses because they were thought to replicate slowly (lenti means slow). Previously, it was believed that after initial infection, OPP virus would hide in tissues of infected sheep (remain latent), and that several yr later for unknown reasons, the virus would start multiplying; only then, inducing clinical disease (Bulgin, 1990). We were the first research team to demonstrate that this theory was incorrect. To prove this, we inoculated 16 lambs with OPP virus. Every other wk after infection, the amount of OPP virus in blood was measured. What we found was that OPP virus replicated to high titers soon after infection. In most sheep, the maximum virus titer in blood was reached between 4 and 6 wk. Then, a strong immune response by the infected animal partially controlled virus replication causing a decline in virus titer by 8 wk after infection. From then on, there is a constant battle between the sheep's immune system and OPP virus. In this battle, the virus first replicates rapidly; then, the immune system partially controls the virus. A small amount of remaining virus in the infected sheep mutates; thus, escaping the initial immune response and producing a new spike in blood virus titer. This is followed by a secondary immune response against the new mutated virus. Eventually, the constant fight between new virus mutants and the immune system leads to tissue damage and the development of clinical disease. A major finding of this project was that because during the first few wk after infection infected sheep have high titers of virus in blood but lack antibodies against the virus, shedding and transmission of the virus are more likely to occur during this period (Juste et al., 1998). For this reason, sheep producers obtaining replacement sheep from flocks where the infection exists should quarantine new sheep for several wk and test them several times before mixing them with other sheep.

SOME SHEEP MAY BE GENETICALLY PREDISPOSED TO THE DEVELOPMENT OF OPP VIRUS-INDUCED PNEUMONIA.

Using artificially created identical twin lambs, we had shown previously that sheep genetic factors play a major role in determining the susceptibility to OPP virus-induced disease (de la Concha-Bermejillo et al., 1995a). To determine if some breeds of sheep were more susceptible to OPP virus-induced pneumonia, thirty-two lambs from four breeds (Barbado, Rambouillet, Suffolk and Florida Native) representing seven flocks were inoculated with OPP virus and response (infectious virus, proviral DNA load and antibody profiles) was evaluated in order to estimate variation among breeds. The degree of OPP virus-induced pneumonia was evaluated by microscopic examination of lung sections, 8 months after virus inoculation. Our hypothesis was that OPP virus-induced disease was controlled by host genetic factors. Although differences among breeds were observed, there were also substantial differences that were attributed to flock of origin, suggesting that resistance/susceptibility to OPP virus-induced pneumonia may be related to individual genetic factors of the host. Despite this, breed differences were apparent, and these differences facilitated their classification as susceptible, intermediate, or resistant to developing OPP virus-induced pneumonia. Overall Barbados appear to be a more susceptible breed while Suffolks may be more resistant (Aber et al., 1998).

RECOMBINANT OVINE INTERFERON-TAU (ROIFN-T) INHIBITS OPP VIRUS REPLICATION AND PREVENTS THE DEVELOPMENT OF OPP VIRUS-INDUCED PNEUMONIA.

There are no effective treatments available for OPP. Since the discovery of HIV as the cause of AIDS in humans, a series of antiviral drugs have been developed. Ovine interferon-tau (oIFN-τ) is a new type of interferon with potent antiviral, immunomodulatory and antiproliferative activities. A series of experiments were conducted to determine the effectiveness of roIFN-τ on OPP virus replication *in vitro* and *in vivo*. *In vitro*, it was found that the amount of OPP proviral DNA measured by PCR, the number of OPP virus-induced syncytia, and the amount of infectious virus were reduced by 90 to 99% in cell cultures treated with roIFN-τ compared to the placebo-treated controls ($p<0.01$). Recombinant oIFN-τ also reduced other parameters indicative of OPP virus replication, such as reverse transcriptase activity, and protected cells from OPP virus-induced cell destruction. Results of experiments to determine the optimal dose of roIFN-τ followed a logistic model, in which roIFN-τ anti-OPP virus activity augmented with increasing amounts of IFN up to 100 AVU/ml, after which its activity remained fairly constant (Juste et al., 1996).

The *in vivo* antiviral effects of roIFN-τ were studied in 26 newborn lambs inoculated intratracheally with OPP virus strain 85/34 or placebo (Juste et al., 2000). Six of the OPP virus- and three of the placebo-inoculated lambs were treated with roIFN-τ once a d for 30 d starting at post-inoculation (PI) d 0 and twice a wk thereafter (early treatment). Six of the OPP virus- and three of the placebo-inoculated lambs were treated with roIFN-τ once a d for 30 d starting at PI d 150 and twice a wk thereafter (late treatment). Six OPP virus-infected and 2 non-infected lambs were treated either early or late with non-transformed *Pichia pastoris* supernatants (placebo) and used as controls.

Cell-associated viremia was determined every other wk by an end point dilution method. All experimental animals were killed at 27 wk post-inoculation and histologic sections of lung were examined and scored for the degree of lymphoid interstitial pneumonia (LIP) and bronchus-associated lymphoid tissue (BALT). A 90% reduction in OPP virus titers was observed at 4 wk post-treatment in the experimental group that received early IFN treatment ($p<0.01$). Significant differences in virus titers were also observed at wk 2 and 6 ($p<0.05$). Scores of LIP/BALT degree were significantly higher in infected lambs treated with placebo or late interferon regime than in the non-infected lambs or in the infected lambs that received early IFN treatment. LIP scores were not significantly different between non-infected and OPP virus infected lambs treated early with IFN. Results of these experiments indicate that roIFN-τ significantly decreases OPP virus replication *in vitro* and *in vivo* and prevents the development of OPP virus-induced LIP when infected animals are treated during the initial phases of the infection (Juste et al., 2000).

RECOMBINANT OIFN-T ENHANCES THE IMMUNE RESPONSE OF THE HOST AGAINST OPP VIRUS.

We examined the effects of recombinant ovine IFN-τ (roIFN-τ) on blood mononuclear cells in OPP virus-infected and mock-infected lambs using a panel of monoclonal antibodies directed against various cell surface markers. Cells expressing the CD4, the CD8, and the γδ markers (cells expressing these markers are critical in the immune response against viruses) were elevated in all the groups at different time intervals over the course of this study in comparison to wk 0. Higher proportions of $CD4^+$, $CD8^+$, $\gamma\delta^+$ and L-selectin$^+$ (the latter is a cell surface adhesion molecule important in cell migration) and lower proportions of MHC class II^+ cells were found in roIFN-τ-treated, OPP virus-infected lambs when compared to the placebo-treated, OPP virus-infected

lambs ($P \leq 0.05$) (Singh et al., 1997). rOvIFN-τ also increased the proportions of primary antiviral $\gamma\delta^+$ and $CD8^+$ immune cells in the lung of OPP virus-infected lambs (Singh et al., 2001). These results suggest that in addition to direct antiviral activity, roIFN-τ modulates the proportions of circulating cytotoxic and helper lymphocytes in response to OPP virus infection. This immuno-potentiator effect of roIFN-τ may contribute to the therapeutic effect of this protein by promoting the killing and elimination of OPP virus-infected cells. Furthermore, when we evaluated the toxic side effects of roIFN-τ, we found that red and white blood cells in sheep treated roIFN-τ remained within normal values through out the six month daily-treatment trial (de la Concha-Bermejillo et al., 2000). This indicates that roIFN-τ at the dose used in our experiments is non-toxic for sheep.

A GENETICALLY ENGINEERED OPP VIRUS THAT EXPRESSES THE GREEN FLUORESCENT PROTEIN (GFP) GENE IS A PRIME CANDIDATE TO BE USED AS A VACCINE TO PROTECT SHEEP AGAINST OPP.

Currently, there are no commercially available vaccines to protect sheep against OPP. For the last four yr, we have been working to develop OPP viruses that are attenuated for pathogenicity (do not cause disease), but induce a strong protective immunity. For this purpose, we genetically engineered an OPP virus that contains the green fluorescent protein (GFP) gene (OPP/GFP virus); (Zhang et al., 2000). This recombinant virus is attenuated for pathogenicity *in vitro* and *in vivo*. Lambs vaccinated with OPP/GFP virus had lower titers of virus in blood after being challenged with pathogenic OPP virus than one non-vaccinated lamb. These preliminary results suggest that the OPP/GFP recombinant virus could be used effectively as a vaccine to protect sheep against OPP.

Conclusions

Although the prevalence of OPP in range sheep of western Texas is significantly lower than that in other sheep-producing states, Texas sheep producers need to be aware of the risks of introducing the infection into their flocks. Existing serological tests to identify infected animals vary in their sensitivity and specificity and in some cases may be unreliable. Shedding of OPP virus in the semen of rams with epididymitis may be a risk factor for spreading the virus to non-infected sheep. Recombinant IFN-τ is an effective but expensive OPP treatment. The use of recombinant OPP viruses with reduced replication ability and pathogenicity may be the best way to prevent OPP clinical disease.

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