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Original article

Effects of coadministration of foot and mouth disease vaccine and inactivated parapoxvirus ovis on humoral immunity in cattle

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Abstract

Foot and mouth disease (FMD) is an acute viral disease in animals. Inactive parapoxvirus ovis (IPPVO) strengthens humoral immunity. This study aimed to determine the effect of IPPVO application together with FMD vaccine on cattle immunity. It included 30 Holstein cattle randomly divided into two groups: one was administered only the FMD vaccine, and the other was administered the FMD vaccine and IPPVO simultaneously. Control blood was collected from all animals at 0 hours. Serum TNF-α, IL-1β, and IL-6 levels were measured in blood samples collected at 4, 8, 12, 16, and 24 hours post-vaccination, while serum IgG and IgM levels were measured in blood samples collected at 4, 8, 12, 16, and 20 days post-vaccination using ELISA kits. While no changes in serum TNF-α, IL-1β, and IL-6 levels were detected in the FMD group, IL-1β levels significantly increased (peaking at four hours) in the FMD + IPPVO group. In the FMD group, while IgG levels increased significantly (peaking at 16 days), IgM levels did not change. In the FMD + IPPVO group, IgG level on day 8 days was higher than the 16 days value. Also, the IgM level increased significantly on day 16. In conclusion, the application of FMD with IPPVO increases the primary immune response (IgM), but it does not effect the long-term immune response (IgM).

Keywords: FMD vaccine, inactive parapoxvirus ovis, cytokine, immunoglobulin

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Introduction

The parapoxvirus ovis (orf virus, PPVO) DNA virus is reported to cause lesions around the mouth, vulva, between the nails, nose, and udder in animals (Ülgenalp et al. 2018). Studies have shown that administering PPVO induces secretion of interleukin (IL)-12, tumor necrosis factor alpha (TNF-α), and interferon-gamma (IFN-γ) by leukocytes against the herpes simplex and hepatitis B viruses (Weber et al. 2003). PPVO has been shown to induce cell-mediated immune reactions. PPVO also encodes host cytokine and cytokine receptor homologs. After PPVO infection, colony-stimulating factor (CSF) induces immune-modulating molecules such as IFN alpha, IL-2, and TNF-α (Büttner et al. 1995, Haig 1998, Rziha et al. 1999). PPVO also encodes viral IL-10, vascular endothelial growth factor (VEGF; ORFV132), orf virus IFN resistance protein (OVIFNR; ORFV020), chemokine binding protein (CBP; ORFV112), inhibitor of granulocyte-macrophage CSF and IL-2 (GIF; ORFV117), inhibitor of nuclear factor-kappa B (NF-κB; ORFV125), and deoxy uridine pyrophosphoric acid pyrophosphatase (dUTPase; ORFV007) (Wang et al. 2019).

Administering inactive PPVO (IPPVO) to calves was found to cause fluctuations in serum malondialdehyde levels and reduce glutathione levels (Kart et al. 2010). Moreover, it can be administered as a prophylactic in cats against calicivirus infections (Traeder et al. 2005). Notably, IPPVO reduced the clinical symptoms of *Streptococcus equi* and equine herpes virus type 1 (EHV-1) diseases in horses and is safe for use in horses (Ons et al. 2014).

The foot and mouth disease (FMD) virus is a prototype member of the *Aphthovirus* genus in the *Picornaviridae* family, which comprises RNA viruses (Diaz-San Segundo et al. 2017). The FMD virus causes acute disease in animals characterized by fever, lameness, and vesicular lesions on the feet, tongue, nose, and teats. While there are generally no deaths in its acute phase, it reduces animal production values, such as growth rate and milk yield, and mobility (Arzt et al. 2011). FMD affects more than 70 animal species, including domestic cloven-hoofed animals such as cattle, pigs, sheep and goats, and deer. Its incubation period is between 2 and 14 days, depending on the amount and route of infection (Grubman and Baxt 2004).

With the implementation of vaccination policies in the 1950s, FMD was eradicated in North America, Western Europe, and some parts of Asia (Diaz-San Segundo et al. 2017). Turkey is reportedly a reservoir country for the FMD virus, which could spread to Europe. Therefore, the European Commission provided 65 million Euros of funding to Turkey for an FMD vaccination program between 2008 and 2011. It has been estimated that approximately 10% of the 11 million cattle aged under two years in Turkey have FMD, causing economic losses of $150-300 per animal (Knight-Jones and Rushton 2013). Studies on vaccines against FMD started in 1987. The protection of vaccinated or infected animals against FMD correlates positively with the formation of neutralizing antibodies in the serum (Doel 2003).

Cytokines can be secreted by any cell in the body, not only by macrophages, monocytes, and activated T cells. They have a polypeptide structure and regulate cell growth, inflammation, cell healing, antiviral activity, and immune and inflammatory responses after injury (Akdoğan and Yöntem 2018). Acute phase proteins such as haptoglobin (HP), serum amyloid A, and ceruloplasmin (CP) are released after activation by proinflammatory cytokines (IL-1β, IL-6, and TNF-α). In response to infection, IFN-γ is secreted by mononuclear inflammatory cells, and TNF-α, IL-6 and IL-1β are secreted by lung cells (Gruys et al. 2005, Koj 1998, Van Reeth et al. 1998). Reactive oxygen species is produced in NF-κB activation due to inflammation (Zhuan et al. 2017). It has been reported that the transcription of some cytokines such as TNF-α, IL-1, IL-6 increases due to the activation of NF-κB (Smith et al. 1998). IL-12 is produced by transformed B cells. IL-12 can also stimulate NK cell cytotoxicity and IFN-γ production and has been reported to have mitogenic effects on T cells (Wojno et al. 2019). TNF-α stimulates the release of IL-1, IL-6, and CXCL8 during septic shock (Akdoğan and Yöntem 2018). Especially during sepsis, TNF-α, IL-1, IL-6, IL-12, IL-18 and IFN are secreted, and their serum levels vary with the disease course, known as a cytokine storm (Camcıoğlu and Aytaç 2007).

Immunoglobulins (Ig) are divided into five isotypes (G, M, E, A, and D), of which IgD is found only in humans, monkeys, dogs and rats (Yılmaz and Akgül 2014). IgG is produced by plasma cells in the spleen, lymph nodes and bone marrow. Ig levels are highest in the blood and play an important role in antibody-mediated defense. IgM is produced by plasma cells in secondary lymphoid organs and has the second highest serum concentration after IgG in most mammals. IgM is the major Ig produced during primary immune responses. It is also produced in smaller amounts in secondary responses. Although produced in small amounts, IgM is reported to be more effective than IgG in complement activation, opsonization, neutralization of viruses, and agglutination (Tizard 2017).

FMD is a herd-based disease that causes serious economic losses in cattle. In the fight against the dis-

ease, prevention through vaccination is more important than treatment. Since IPPVO changes immune-related parameters positively (Haig 1998, Rziha et al. 1999, Weber et al. 2003), we hypothesized that coadministration of the FMD vaccine with IPPVO to cattle may elicit greater immunity than the FMD vaccine alone. This study aimed to determine how coadministering IPPVO with the FMD vaccine affects humoral immunity.

Materials and Methods

Experimental design and animal applications

The animals used in this study were provided by a commercial enterprise located in the Ereğli district of Konya province, Turkey. The study protocol was approved by the Ethics Committee of the Experimental Animal Production and Research Center, Faculty of Veterinary Medicine, Selçuk University (approval number: 2023/061).

This study used 30 Holstein cattle (2-5 years old) in different lactation periods, which were randomly divided into two groups (n=15/group): one group was administered only the single dose FMD vaccine (2 mL/animal, subcutaneous, Turvac oil tetra; Alum Institute Directorate, Ankara, Turkey), and the other was coadministered the single dose FMD vaccine (2 mL/animal, subcutaneous, Turvac oil tetra; Alum Institute Directorate, Ankara, Turkey) with single dose IPPVO (2 mL/animal, intramuscular, Zylexis® flocane; Zoetis, Istanbul, Turkey). FMD vaccine was injected into the right neck region of the animals and IPPVO was injected into the left neck region. 7 ml blood samples were taken from the coccygeal veins of the animals using a vacutainer into tubes that did not contain any chemical substances. A separate control group was not created in the study to minimize changes due to individual differences. Instead, blood was taken from all animals at the 0 hour before the treatment and evaluated as a self-control group. Blood samples were then collected 0, 4, 8, 12, 16, and 24 hours after vaccination to determine serum TNF-α, IL-1β, and IL-6 levels and at 4, 8, 12, 16, and 20 days after vaccination to determine serum IgG and IgM levels. The samples were centrifuged at 4000 *g* for 10 minutes to isolate the serum, which was stored at -80°C until needed.

Serum analysis

TNF-α (BT Lab, Jiaxing, Zhejiang, China), IL-1β (BT Lab, Jiaxing, Zhejiang, China), IL-6 (BT Lab, Jiaxing, Zhejiang, China), IgG (BT Lab, Jiaxing, Zhejiang, China) and IgM (BT Lab, Jiaxing, Zhejiang, China) levels were measured in the serum samples using commercial enzyme-linked immunosorbent assay (ELISA) kits and an ELISA plate reader (MWGt Lambda Scan 200; Bio-Tec Instruments, Winooski, VT, USA) according to the kit's instructions.

Statistical analysis

The data were analyzed using SPSS (version 22; IBM, Armonk, NY, USA). The data are presented as mean ± standard error (SE) and were compared between groups and time points using analysis of variance (ANOVA) with post-hoc Duncan's tests. A $p<0.05$ was considered statistically significant.

Results

The cytokine levels are presented in Fig 1, and the Ig levels are presented in Fig 2. While serum levels of the cytokines (TNF-α, IL-1β, and IL-6) did not change significantly in the FMD vaccine-only group ($p>0.05$), IL-1β levels peaked at four hours ($p<0.05$) in the FMD vaccine + IPPVO group. In the FMD group, while IgG levels increased significantly, peaking at 16 days ($p<0.05$), IgM levels did not change significantly ($p>0.05$). The IgG level in the FMD+IPPVO group was lower, not fluctuating in comparison to the FMD group ($p<0.05$), and IgM levels increased significantly ($p<0.05$), peaking at 16 days.

Discussion

While animal deaths are not generally observed with FMD infections, they cause productivity losses (Arzt et al. 2011). Vaccination is crucial in preventing FMD (Diaz-San Segundo et al. 2017).

This study determined that administering the FMD vaccine did not significantly change serum TNF-α, IL-1β, and IL-6 levels ($p>0.05$). While coadministering the FMD vaccine with IPPVO did not significantly change TNF-α and IL-6 levels ($p>0.05$), it did significantly increase IL-1β levels, which peaked at four hours ($p<0.05$, Fig 1).

Activation of macrophages can regulate the onset and end of multiple inflammations. The combination of IFN-γ secreted by Th1, CD8+ and B cells and the IFN-γ receptor triggers a series of signaling pathways that lead to the activation and differentiation of M1 macrophages, resulting in the production of numerous cytokines such as TNF-α, IL-1β, and IL-6. On the other hand, M2 macrophages are activated by various cell factors (IL-4, IL-10, IL-13, etc.) and contribute to the repair of damaged tissues (Guo et al. 2022). Studies

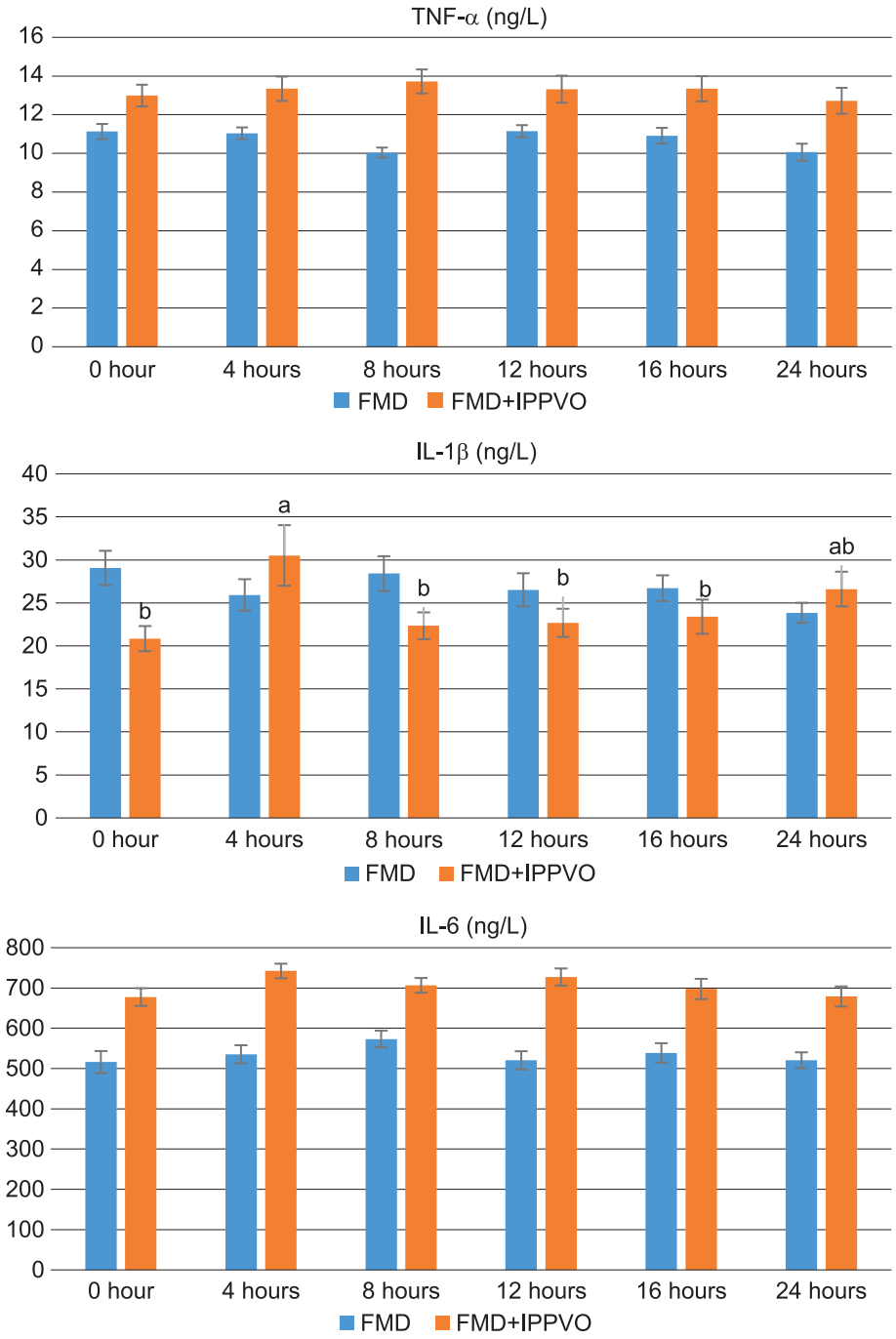

Fig 1. Effect of the foot and mouth disease (FMD) vaccine with and without inactive parapoxvirus ovis (IPPVO) on cytokine levels in cattle (mean±SE).

[a, b] Different letters in columns with the same colors differ significantly (ANOVA with post-hoc Duncan test $p<0.05$).

have shown that in mice, IPPVO administration elicited a strong cytokine response by inducing proinflammatory (IL-1β and TNF-α) and Th1-related (IFN-γ and IL-12) cytokines, followed by Th2-related (IL-4 and IL-10) cytokines (Anziliero et al. 2014). In rats, IPPVO administration increased TNF-α and IL-6 levels (Avci et al. 2016) addition, IPPVO administration in rats with liver fibrosis induced the hepatic expression of IFN-γ and IL-10 and had an antifibrotic effect (Nowatzky et al. 2013). In humans, IPPVO was associated with Th1-related (IFN-γ, TNF-α, IL-6, CXCL8, IL-12, and IL-18) and Th2-related (IL-4, IL-10, and IL-1) cytokines. IPPVO strongly affected the secretion of the IL-1 receptor antagonist (IL-1RA) (Friebe et al. 2004). IL-1 is identified as an important hematopoietic factor that induces the expression of progenitor cells and colony-stimulating factors in leukocytes and stroma cells. IL-1β is reported to promote APC stimulatory activity, which is necessary for the migration of leukocytes to the infection site in acute inflammation, and up-regula-

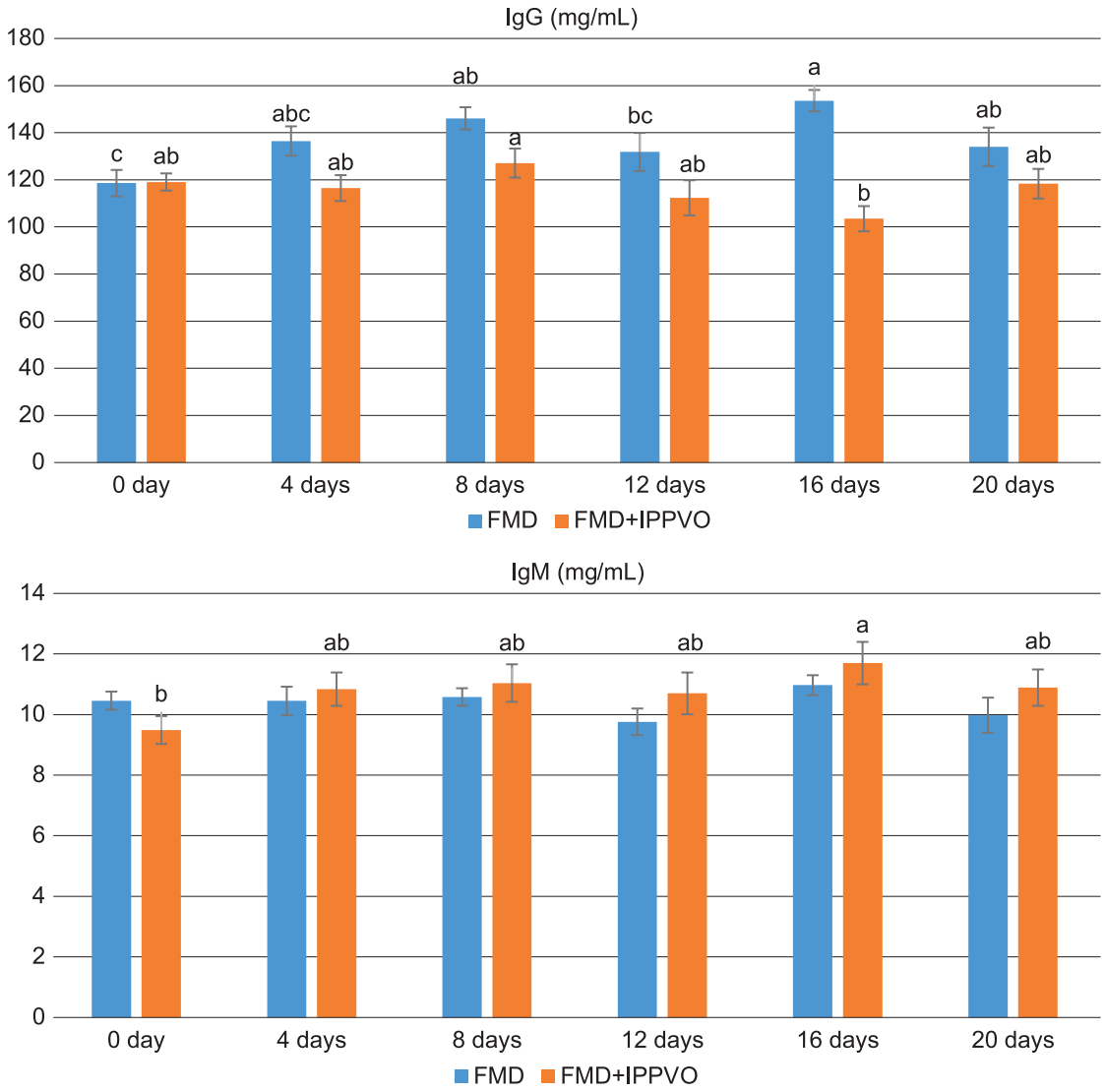

Fig 2. Effect of the foot and mouth disease (FMD) vaccine with and without inactive parapoxvirus ovis (IPPVO) on Ig levels in cattle (mean ± SE).

[a, b, c] Different letters in columns with the same colors differ significantly (ANOVA with post-hoc Duncan test $p<0.05$).

tion of adhesion receptors on immune and endothelial cells (Bent et al. 2018). A study administering the infectious rhinotracheitis vaccine and IPPVO alone and combined in cattle reported that the levels of cytokines IFN-γ, IL-2, IL-6, and IL-12 were significantly higher in the combined group than in the uncombined groups (Erbasan and Mamak 2023). An in vitro study reported that IPPVO induced IL-12, TNF-α, and IFN-γ in leukocytes against herpes simplex and hepatitis B virus (Weber et al. 2003). When our findings are jointly evaluated with those in the literature, coadministering IPPVO with the FMD vaccine to cattle can provide immune modulation by stimulating IL-1β.

Our study, it was found that the administration of FMD vaccine alone significantly increased IgG levels and reached a peak on the 16th day ($p<0.05$), When FMD vaccine was administered together with IPPVO, the highest level of IgG levels was determined on the 8th day and the lowest level was determined on the 16th day ($p<0.05$; Fig 2). While administering the FMD vaccine alone did not significantly change IgM levels ($p>0.05$), coadministering the FMD vaccine with IPPVO significantly increased IgM levels, which peaked at 16 days ($p<0.05$, Fig 2).

IgM is reported to be the Ig produced in the early stages of B cell-mediated immunity before sufficient IgG is formed (Megha and Mohanan 2021). IgM is particularly effective in activating the complement system. Infection in the bloodstream can lead to serious consequences if not brought under control quickly, and rapid production of IgM and effective activation of the complement system are reported to be important in controlling such infections (Janeway et al. 2001). IgG has important effector functions such as antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), antibody-dependent cellular

phagocytosis (ADCP) and activation of neutrophils (Wu et al. 2024). Similarly, coadministering the enterotoxemia vaccine with the immunomodulator levamisole in sheep increased IgM levels, while coadministering zinc with the enterotoxemia vaccine increased IgG levels (Rashıd and Yüksek 2019). In addition, coadministering the FMD vaccine with levamisole in sheep significantly increased IgG and IgM levels, with immunomodulator coadministration increasing the effectiveness of vaccination (Abdullah 2016). When the literature information and study data are evaluated, it is observed that the IgG level is low and the IgM level is highest on the 16th day in the group that received FMD vaccine together with IPPVO. The reason for this can be expressed as IPPVO increasing the IgM level, which is the first immune response, and prolonging the IgG production.

An in vitro study reported that IPPVO increased the phagocytosis of *Listeria monocytogenes* by monocytes and neutrophils, increased major histocompatibility-II expression in monocytes, and activated oligoclonal proliferation in T helper cells. It was also reported to stimulate both phagocytotic and T-cell-dependent immune mechanisms in leukocytes (Schütze et al. 2009). Another study reported that coadministering the bovine respiratory disease vaccine with IPPVO to calves increased humoral immunity (El-Fadeel et al. 2019). In addition, coadministering IPPVO with the EHV-1 vaccine to horses reportedly increased the effectiveness and duration of immunity against EHV-1 (Ibrahim et al. 2017). Another study in horses reported that coadministering IPPVO with the equine influenza virus vaccine generated higher antibody levels than the control group (Carnet et al. 2022). Therefore, coadministering IPPVO with vaccines can be used in vaccination protocols in horses and other species. When our results are jointly evaluated with those in the literature, it can be concluded that coadministering IPPVO with the FMD vaccine strengthens humoral immunity through IgM.

Conclusions

This study examined the effect of administering IPPVO on the humoral defense system to increase the effectiveness of vaccination against FMD disease, which causes economic losses in cattle. It determined that IPPVO mainly stimulates Il-1β and stimulates IgM more strongly. IPPVO can be coadministered safely with vaccines in at-risk facilities to increase IgM levels, which are highly effective in the primary response, through IL-1β. However, this study examined total serum Ig levels. Examining antibodies specific to FMD is necessary to better understand the effectiveness of developing humoral immunity.

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References

Abdullah KMA **(2016)** The effect of immunstimulant drugs used together with fmd vaccine on immunoglobulins in sheep. (Phd thesis). Yüzüncü Yıl Univ., Graduate School of Health Sciences, Dep. of Internal Medicine: 49.

Akdoğan M, Yöntem M **(2018)** Cytokines. Online Turkish Journal of Health Sciences 3: 36-45.

Anziliero D, Weiblen R, Kreutz L, Spilki F, Flores E **(2014)** Inactivated Parapoxvirus ovis induces a transient increase in the expression of proinflammatory, Th1-related, and autoregulatory cytokines in mice. Braz J Med Biol Res 47: 110-118.

Arzt J, Juleff N, Zhang Z, Rodriguez L **(2011)** The pathogenesis of foot-and-mouth disease I: viral pathways in cattle. Transbound Emerg Dis 58: 291-304.

Avci O, Bulut O, Dik I **(2016)** Effects of inactive parapoxvirus ovis on cytokine levels in rats. J Vet Med Sci 78: 129-131.

Bent R, Moll L, Grabbe S, Bros M **(2018)** Interleukin-1 beta – a friend or foe in malignancies? Int J Mol Sci 19: 2155.

Büttner M, Czerny C-P, Lehner K-H, Wertz K **(1995)** Interferon induction in peripheral blood mononuclear leukocytes of man and farm animals by poxvirus vector candidates and some poxvirus constructs. Vet Immunol Immunopathol 46: 237-250.

Camcıoğlu Y, Aytaç E **(2007)** Immunopathogenesis of sepsis. Turkish J. Intensive Care 5: 81-85.

Carnet F, Paillot R, Fortier C, Hue E S, Briot L, de Geoffroy F, Vidalain P-O, Pronost S **(2022)** Immunostimulating Effect of Inactivated Parapoxvirus Ovis on the Serological Response to Equine Influenza Booster Vaccination. Vaccines 10: 2139.

Diaz-San Segundo F, Medina G N, Stenfeldt C, Arzt J, de Los Santos T **(2017)** Foot-and-mouth disease vaccines. Vet. Microbiol 206: 102-112.

Doel T **(2003)** FMD vaccines. Virus Res 91: 81-99.

El-Fadeel M, Mohamed MM, Khafagy HA, Kotb EE, El-Hawary RI **(2019)** Immunomodulating effect of zylexis on the immune response of cattle vaccinated with (Pneumo-4) vaccine. Int J Vet Sci 8(4): 380-384.

Erbasan S, Mamak N **(2023)** Investigation of the immunomodulatory effect of inactive parapoxvirus (iPPVO) on infectious bovine rhinotracheitis (IBR) vaccine in cattle. Medit Vet J 8: 183-189.

Friebe A, Siegling A, Friederichs S, Volk H-D, Weber O **(2004)** Immunomodulatory effects of inactivated parapoxvirus ovis (ORF virus) on human peripheral immune cells: induction of cytokine secretion in monocytes and Th1-like cells. J Virol 78: 9400-9411.

Grubman M J, Baxt B **(2004)** Foot-and-mouth disease. Clin Microbiol Rev 17: 465-493.

Gruys E, Toussaint M, Niewold T, Koopmans S **(2005)** Acute

phase reaction and acute phase proteins. J Zhejiang Univ Sci 6: 1045-1056.

Guo P, Li R, Piao T H, Wang C L, Wu X L, Cai H Y **(2022)** Pathological mechanism and targeted drugs of COPD. Int J Chron Obstruct Pulmon Dis: 1565-1575.

Haig D M **(1998)** Poxvirus interference with the host cytokine response. Vet Immunol 63: 149-156.

Ibrahim M, Warda F F, Nermeen G S, Abdel-Baky M, Kalad M A **(2017)** Effect of Inactivated Sheep Pox Vaccine and Parapox Ovis Virus as Immunomodulators on Response of Equines to Inactivated Herpes Vaccine. J Egypt Vet Med Assoc 77: 61-72.

Janeway C, Travers P, Walport M, Shlomchik M J **(2001)** The immune system in health and disease Immunobiology 5. Garland Pub. New York, USA 20.05.2025 https://www.ncbi.nlm.nih.gov/books/NBK27162/

Kart A, Uzlu E, Karapehlivan M, Öğün M, Merhan O **(2010)** Effect of Immunomodulator Zylexis on Blood Glutathione, Malondialdehyde, Nitric Oxide, Total and Lipid Bound Sialic Acids Levels in Calves. Vet Sci Pract 5: 43-48.

Knight-Jones T J, Rushton J **(2013)** The economic impacts of foot and mouth disease–What are they, how big are they and where do they occur? Prev Vet Med 112: 161-173.

Koj A **(1998)** Termination of acute-phase response: role of some cytokines and anti-inflammatory drugs. Gen Pharmacol 31: 9-18.

Megha K, Mohanan P **(2021)** Role of immunoglobulin and antibodies in disease management. Int J Biol Macromol 169: 28-38.

Nowatzky J, Knorr A, Hirth-Dietrich C, Siegling A, Volk HD, Limmer A, Knolle P, Weber O **(2013)** Inactivated Orf virus (Parapoxvirus ovis) elicits antifibrotic activity in models of liver fibrosis. Hepatol Res 43: 535-546.

Ons E, Van Brussel L, Lane S, King V, Cullinane A, Kenna R, Lyons P, Hammond T-A, Salt J, Raue R **(2014)** Efficacy of a Parapoxvirus ovis-based immunomodulator against equine herpesvirus type 1 and Streptococcus equi equi infections in horses. Vet Microbiol 173: 232-240.

Rashıd B M, Yüksek N **(2019)** The effects of immunostimulants (zinc, levamisole, vitamin AD3E) use together with enterotoxemia vaccine on immunoglobulins in sheep. Turkish J Vet Res 3: 57-65.

Rziha H-J, Henkel M, Cottone R, Meyer M, Dehio C, Büttner M **(1999)** Parapoxviruses: potential alternative vectors for directing the immune response in permissive and non-permissive hosts. Journal of biotechnology 73: 235-242.

Schütze N, Raue R, Büttner M, Alber G **(2009)** Inactivated parapoxvirus ovis activates canine blood phagocytes and T lymphocytes. Vet Microbiol 137: 260-267.

Smith R E, Strieter R M, Phan S H, Lukacs N, Kunkel S L **(1998)** TNF and IL-6 mediate MIP-1α expression in bleomycin--induced lung injury. J Leukoc Biol 64: 528-536.

Tizard I R **(2017)** Veterinary Immunology. 10: 480-482. Elsevier Health Sciences 032352348X 20.05.2025 https: //books.google.com.tr/books?hl=tr&lr=&id=JuM2DwAAQBAJ&oi=fnd&pg=PP1&dq=Veterinary+Immunology-E-Book:+Veterinary+Immunology-E-Book+2017&ots=ZIfAECTtEq&sig=tXc2BcA7zQTEu4c6-q8P-bgm4pk&redir_esc=y#v=onepage&q=Veterinary%20Immunology-E-Book%3A%20Veterinary%20Immunology-E-Book%202017&f=false

Traeder W, Brune A, Rehagen M **(2005)** Protective effect of the paramunity inducer Parapoxvirus ovis (Zylexis) in kittens experimentally infected with Calicivirus (strain FCV-KS 20). Prakt Tierarzt 86: 230-238.

Ülgenalp O, Koç B T, Oğuzoğlu T Ç **(2018)** A Review on Parapoxviruses Observed in Ruminants: History, Epidemiology, Molecular Characterization, Pathogenesis, Clinical Findings, Immunotherapy and Use as a Vector in Recombinant Vaccines. Anim Health Prod Hyg 7: 551-557.

Van Reeth K, Nauwynck H, Pensaert M **(1998)** Bronchoalveolar interferon-α, tumor necrosis factor-α, interleukin-1, and inflammation during acute influenza in pigs: a possible model for humans? J Infect Dis 177: 1076-1079.

Wang R, Wang Y, Liu F, Luo S **(2019)** Orf virus: A promising new therapeutic agent. Rev Med Virol 29: e2013.

Weber O, Siegling A, Friebe A, Limmer A, Schlapp T, Knolle P, Mercer A, Schaller H, Volk H-D **(2003)** Inactivated parapoxvirus ovis (Orf virus) has antiviral activity against hepatitis B virus and herpes simplex virus. J Gen Virol 84: 1843-1852.

Wojno E D T, Hunter C A, Stumhofer J S **(2019)** The immunobiology of the interleukin-12 family: room for discovery. Immunity 50: 851-870.

Wu Y, Zhang Z, Chen L, Sun S **(2024)** Immunoglobulin G glycosylation and its alterations in aging-related diseases: IgG glycosylation with aging-related diseases. Acta Biochim Biophys Sin 56: 1221.

Yılmaz N, Akgül Y **(2014)** Immunglobulins and Septicemia. Uludag Univ. J. Vet. Fac 33: 33-42.

Zhuan B, Yu Y, Yang Z, Zhao X, Li P **(2017)** Mechanisms of oxidative stress effects of the NADPH oxidase-ROS-NF-κB transduction pathway and VPO1 on patients with chronic obstructive pulmonary disease combined with pulmonary hypertension. Eur Rev Med Pharmacol Sci 21: 3459-3464.