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Rania Dweek

M. Eisa

M. El-Beskawey

Sabry El- Khodery

See next page for additional authors

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Authors

Rania Dweek, M. Eisa, M. El-Beskawey, Sabry El- Khodery, Abdelaziz A. Yassin, Mohamed Farghli, Hiam Fakhry, and Samar Attwa

ORIGINAL ARTICLE

Development of Foot and Mouth Disease Vaccine Formulation in Egypt by Using Silver Nanoparticles as Immunogenic and Adjuvant

Rania S. Dweek [a,*], Mohamed I. Eisa [b], Mohamed A. El-Beskawy [c], Sabry A. El-Khodery [d], Mohamed A. Farghli [e], Hiam M. Fakhry [f], Abdelaziz A. Yassin [f], Samar M. Atwa [d]

[a] Animal Health Research Institute Mansoura Provincial Lab, Mansoura, Egypt
[b] Department of Animal Medicine, Faculty of Veterinary Medicine, Zagazig University, Zagazig, Egypt
[c] Department of Animal Medicine, Faculty of Veterinary Medicine, Matrouh University, Matrouh, Egypt
[d] Department of Internal Medicine, Infectious Diseases and Fish Diseases., Faculty of Veterinary Medicine, Mansoura University, Egypt
[e] Department of Animal and Poultry Hygiene, Environmental Sanitation Faculty of Veterinary Medicine, Assiut University, Assiut, Egypt
[f] Department of Foot and Mouth Disease at Veterinary Serum and Vaccine Research Institute, Abbasia, Cairo, Egypt

Abstract

OBJECTIVE: To evaluate the effect of silver nanoparticles (AgNPs) combined with Foot and Mouth Disease (FMD) inactivated oil adjuvant vaccine on the immunological response of cattle.
STUDY DESIGN: Randomized clinical trials.
PROCEDURES: AgNPs were prepared and added to the locally produced inactivated trivalent FMD vaccine used in Egypt. Twenty-five cattle were classified into five groups (five/group). The first group was vaccinated with FMD Trivalent inactivated oil adjuvant vaccine plus AgNPs (3 ml subcutaneously (S/C), the second group was vaccinated with FMD trivalent inactivated vaccine (3 ml S/C). The third group was vaccinated with FMD trivalent inactivated vaccine plus AgNPs (2 ml S/C).The fourth group was injected with AgNPs only (1 ml S/C). The fifth (control) group was injected with normal saline (3 ml S/C).
RESULTS: Antibody titer by Serum neutralization test (SNT) for first group reached a protective value at 2 weeks (1.538 log_{10}) and reached a peak at 2 months (2.77 log_{10}). Bovine Interleukein -6 (IL-6) revealed that animals vaccinated with AgNPs appeared more quickly than those vaccinated with FMD inactivated oil adjuvant vaccine.
CONCLUSION: AgNPs potentiated both cellular and humeral immunity against FMD.

Keywords: Foot and mouth disease vaccine, Nanosilver (AgNPs), Serum neutralization test, Bovine interleukin-6

1. Introduction

Foot and mouth disease (FMD), a causative agent identified in 1897, is a highly contagious viral disease of cloven-footed animals [1,2]. The causative agents are foot and mouth disease virus (FMDV), genus aphthovirus, family Picornaviridae, and order Picornaviralae [3].

FMD leads to weight loss, decreased milk production, and loss of draught power in animals, and is considered a disease with a low mortality rate in adults [4], while in young calves, it leads to sudden death due to virus-induced damage in the myocardium [5–7]. In addition, it affects international and national trade, so it considers list A of diseases according to (Officer International des Epizootics).

FMDV has seven serotypes (A, O, C, SAT1, SAT2, SAT3, and Asia 1) and a large number of subtypes, which are serologically and immunologically different. Serotypes O, A, and SAT2 have been detected in Egypt since 2013 [8]. In addition [9], demonstrated the current circulation of FMDV

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* Corresponding author at: Agricultural Research Center (ARC), Animal Health Research Institute-Mansoura provincial Lab (AHRI-Mansoura) P.O. Box 264-Giza, Cairo 12618, Egypt.
E-mail address: raniadweek@yahoo.com (R.S. Dweek).

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serotypes A, O, and SAT2 in cattle and buffaloes in Egypt from August to December 2017.

Nanoparticles play an important role in the diagnosis of some diseases, as well as the delivery of biologically active compounds for disease prevention and treatment, and have made significant progress in nanomedicine [10,11]. Adjuvants enhance the immune response by releasing antigens at the injection site and stimulating innate immunity [12−14]. Silver nanoparticles (AgNPs) have the ability to evoke an immune response against the rabies virus compared with the commercially available adjuvant alum [15].

AgNPs play a very important role in nanoscience and nanotechnology, especially nanomedicine, which is used as antibacterial, antifungal, antiviral, anti-inflammatory, anti-angiogenic, and anticancer agents [16]. This study aimed to evaluate the dual effects of nanosilver on both humeral and cellular immunity. In addition, modification of the FMD vaccine would lead to increased vaccine immunity against this disease and could be used in its control.

2. Materials and methods

2.1. Animals

Twenty-five apparently healthy Baladi breed of 2−3 years of ~300−350 kg body weight were used for the vaccination program, and they were free from antibodies against FMD virus serotypes (A, O, and SAT2) by Serum neutralization test (SNT).

All 25 cattle were divided into five groups (5 animals/group) according to numbering in their ears as follows: first group was vaccinated with the FMD vaccine [trivalent inactivated oil adjuvant vaccine against serotype (O, A, and SAT2) plus AgNPs as adjuvant (3 ml subcutaneously)], second group was vaccinated with the FMD vaccine [trivalent inactivated oil adjuvant vaccine against serotype (O, A, and SAT2) (3 ml subcutaneously)], third group was injected with trivalent inactivated FMDV (A, O, and SAT2) plus AgNPs as an adjuvant (2 ml subcutaneously), fourth group was injected with AgNPs only (1 ml subcutaneously), fifth group (control group) was injected subcutaneously with normal saline (3 ml subcutaneously).

2.2. Samples

Serum samples were collected from each group before and after vaccination. Five milliliters of blood was collected at zero, 7th, 14, 21, 28, 1.5, 2, and 4 months for Serum Neutralization Test (SNT) and for IL-6 collected at zero, 7th, 14, 21, and 28 days.

2.3. Reference FMD virus serotype

FMD virus serotypes (A, O, and SAT2) locally isolated from Egyptian cattle. It was typed and subtyped at the FMD Department Veterinary Serum and Vaccine Research Institute, Abbassia, Cairo (VSVRI), and confirmed by World Reference Laboratories (WRL), Pirbright, UK. Stored at −70 °C until use.

2.4. Cell culture

BHK-21 Clone 13 was supplied by the Animal Virus Research Institute of Perbright. It was maintained in the FMD, VSVRI, Abbassia, and Cairo departments. BHK-21 was used for all steps of the propagation and titration of the FMDV [17].

2.5. FMD vaccine

Local trivalent inactivated FMD oil adjuvant vaccines against FMD virus serotypes (O/PANASIA2, A/IRAN-05, SAT2/LIBIA/2012 and SAT2/EGY (Ghb)/2018) were obtained from the Veterinary Serum and Vaccine Research Institute, Cairo.

2.6. Synthesis of nano-silver solution

The one-step protocol implemented by Vigneshwaran, Nachane [18] and slightly modified by Dosoky et al. [19] was used to synthesize nano-Ag. Transmission electron microscopy (TEM) (JEM-2100 (Tokyo, Japan)) was used to measure the size of nanoparticles.

2.7. Method of SNT

SNT were prepared according to the method described by Ferreira [20]. It was performed at different intervals after the vaccination program and was calculated according to Karber [21].

2.8. Bovine interleukin 6 (IL-6) ELISA kit

SinoGeneClon Biotech Co., Ltd. (catalog No: SG-60134) prepared according to the manufacturer's protocol.

2.9. Statistical analysis

Statistical analysis was performed by one-way analysis of variance using SPSS computer version 22 and repeated measures analysis of variance, post hoc Tukey test, and P less than 0.05 was used for indicate statistically significant.

3. Results

3.1. TEM images of AgNps

TEM was used to characterize the size and distribution of the nanoparticles as well as the shape of the silver nanoparticles. The TEM images of the prepared AgNPs are spherical in shape with particle diameters in the range of 5.80–28.51 nm as illustrated in Fig. 1A,B.

3.2. Postvaccinal clinical observation

All animal groups were investigated during the first week postvaccination. Clinical examination of these cattle appeared normal, healthy, had good appetite, normal body temperature, and the mucus membrane did not show any postvaccinal reaction.

3.3. Assessment of humeral immunity (SNT)

The results of the first group revealed that the mean titer for collected sera samples reached the protective titer in the second week (1.538 log 10), reaching a peak value at 2 month (2.77 log10) also, at 4 month still high (2.33 log10). The results of the second group revealed that the mean titer for collected sera samples reached a protective titer at the third week (1.5 log10), reaching a peak value at 2 month (2.3 log10) at 4 month reach (to 2.11 log10). The results of the third group showed that the antibody titer decreased early in the third week (1.46 log 10) titer of antibodies decrease early. However, the results for the fourth group showed no significant variation throughout the experiment (Table 1) showed that there were significant differences between the injected cattle groups, with P values of less than 0.001 and less than 0.0001.

3.4. Assessment of cellular immunity (bovine Interleukin-6)

The results of bovine IL-6 mean OD values of first group were 403, 1597, 1480, and 710 for the first, second, third, and fourth weeks postvaccination, respectively, at P value less than 0.001 there were significant differences in the titer of OD values illustrated in Table 2 the results of bovine IL-6 mean OD values of second group were 241, 391, 1007, and 654.4 for the first, second, third, and fourth weeks, respectively, at P value less than 0.001 there were significant differences in the titer of OD values at the time postinjection.

However, the results of bovine IL-6 mean OD values of third group were 1351, 924, 789, and 483 for the first, second, third, and fourth weeks, respectively, at P value less than 0.001 there were significant differences in the titer of OD values at the time postinjection. Moreover, the results of bovine IL-6 mean OD values of fourth group were 954, 889, 460, and 280 for the first, second, third, and fourth weeks, respectively (P value <0.001) there were significant differences in the titer of OD values during the postvaccination period.

The results illustrated in Table 3 showed that the mean values of OD by post Hoc Tukey test revealed that at zero day (before vaccination), no significant differences were observed between the studied groups, although there were significant differences between groups at time postvaccination.

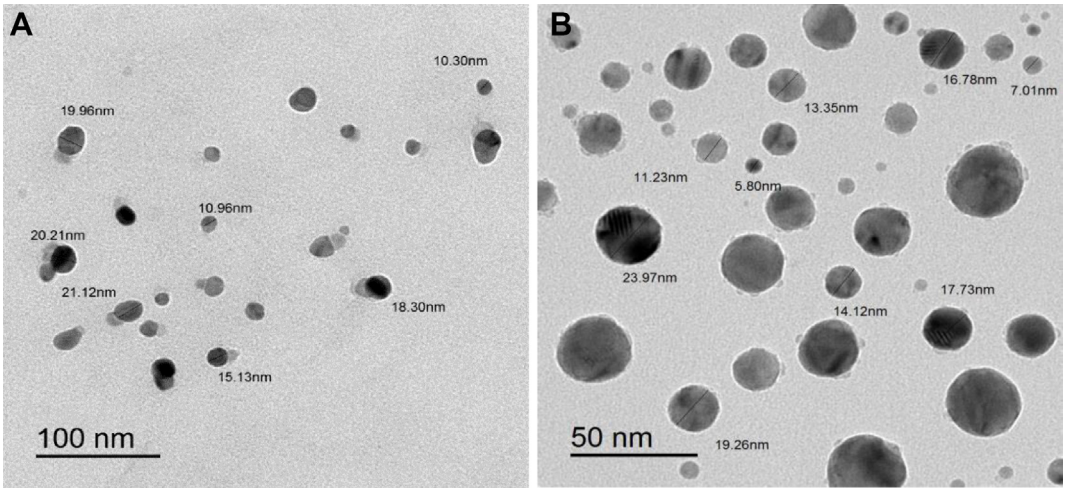

Fig. 1. Transmission electron microscopy images of prepared silver nanoparticles sample.

Table 1. Antibodies means by serum neutralization test in different groups of vaccinated cattle during different times along 16 weeks.

	Subgroups	Time of assessment							Test of significance
		Zero	W1	W2	W3	W4	W8	W16	
Group I n = 5	O	0.45 ± 0.15	1.02 ± 0.12	1.62 ± 0.13	1.89 ± 0.13	2.46 ± 0.17	2.85 ± 0.15	2.46 ± 0.17	<0.001[a]
	A	0.480 ± 0.19	0.96 ± 0.13	1.53 ± 0.13	1.92 ± 0.13	2.37 ± 0.13	2.88 ± 0.13	2.40 ± 0.11	<0.001[a]
	SAT2 2012	0.39 ± 0.13	0.96 ± 0.08	1.50 ± 0.11	1.89 ± 0.13	2.28 ± 0.19	2.64 ± 0.25	2.25 ± 0.26	<0.001[a]
	SAT2 2018	0.39 ± 0.13	0.93 ± 0.07	1.50 ± 0.11	1.86 ± 0.08	2.22 ± 0.13	2.70 ± 0.11	2.22 ± 0.13	<0.001[a]
	0.742	0.604	0.343	0.891	0.125	0.107	0.131		
Group II n = 5	O	0.45 ± 0.25	0.93 ± 0.16	1.23 ± 0.16	1.62 ± 0.13	2.22 ± 0.13	2.52 ± 0.16	2.25 ± 0.11	<0.001[a]
	A	0.39 ± 0.13	0.96 ± 0.08	1.35 ± 0.11	1.65 ± 0.15	2.07 ± 0.19	2.40 ± 0.18	2.13 ± 0.16	<0.001[a]
	SAT2 2012	0.51 ± 0.25	0.93 ± 0.13	1.20 ± 0.11	1.53 ± 0.13	1.80 ± 0.11	2.28 ± 0.19	2.01 ± 0.13	<0.001[a]
	SAT2 2018	0.42 ± 0.19	0.90 ± 0.11	1.23 ± 0.13	1.53 ± 0.13	1.96 ± 0.14	2.34 ± 0.08	2.04 ± 0.17	<0.001[a]
	0.838	0.897	0.292	0.379	0.002[a]	0.157	0.079		
Group III n = 5	O	0.36 ± 0.13	0.87 ± 0.22	1.23 ± 0.16	1.50 ± 0.11	1.43 ± 0.14	1.23 ± 0.16	0.69 ± 0.08	<0.001[a]
	A	0.42 ± 0.13	0.87 ± 0.13	1.29 ± 0.13	1.53 ± 0.13	1.59 ± 0.08	1.35 ± 0.15	0.72 ± 0.13	<0.001[a]
	SAT2 2012	0.39 ± 0.13	0.81 ± 0.08	1.11 ± 0.08	1.44 ± 0.08	1.53 ± 0.07	1.17 ± 0.13	0.66 ± 0.08	<0.001[a]
	SAT2 2018	0.36 ± 0.13	0.78 ± 0.13	1.14 ± 0.08	1.38 ± 0.13	1.44 ± 0.08	1.26 ± 0.08	0.66 ± 0.08	<0.001[a]
	0.87	0.713	0.113	0.190	0.061	0.237	0.715		
Group IV n = 5	O	0.63 ± 0.45	0.63 ± 0.45	0.57 ± 0.42	0.51 ± 0.39	0.42 ± 0.34	0.36 ± 0.33	0.0 ± 0.0	0.039[a]
	A	0.63 ± 0.40	0.63 ± 0.40	0.54 ± 0.35	0.45 ± 0.34	0.42 ± 0.29	0.24 ± 0.25	0.06 ± 0.13	0.03[a]
	SAT2 2012	0.33 ± 0.22	0.33 ± 0.22	0.24 ± 0.13	0.12 ± 0.16	0.12 ± 0.16	0.0 ± 0.0	0.0 ± 0.	0.03[a]
	SAT2 2018	0.36 ± 0.23	0.36 ± 0.22	0.33 ± 0.22	0.30 ± 0.21	0.12 ± 0.16	0.12 ± 0.16	0.0 ± 0.	0.035[a]
		0.356	0.356	0.282	0.189	0.110	0.104	0.418	
Group V (control)		0.46 ± 0.11	0.36 ± 0.13	0.39 ± 0.08	0.30 ± 0.15	0.24 ± 0.08	0.12 ± 0.16	0.0 ± 0.0	**<0.001[a]**

GI: vaccinated by foot and mouth disease trivalent inactivated oil adjuvant vaccine plus silver nanoparticles.
GII: vaccinated by foot and mouth disease trivalent inactivated oil adjuvant vaccine.
GIII: Injected trivalent inactivated foot and mouth disease virus (A, O, and SAT2) plus silver nanoparticles.
GIV: injected by AgNPs alone.
GV: control group injected by normal saline.
[a] Statistically significant (if $P < 0.05$).

Table 2. Comparison of Mean Antibodies Titer by serum neutralization test in different groups of vaccinated cattle during different time along 16 weeks.

	Time of assessment							Test of significance
	Zero	W1	W2	W3	W4	W8	W16	
Group I n = 5	0.428 ± 0.14	0.968 ± 0.10	1.538 ± 0.12	1.89 ± 0.11	2.33 ± 0.17	2.77 ± 0.18	2.33 ± 0.19	F = 948.34 $P < 0.001$[a]
Group II n = 5	0.443 ± 0.20	0.930 ± 0.12	1.253 ± 0.13	1.58 ± 0.13	2.01 ± 0.21	2.39 ± 0.17	2.11 ± 0.16	F = 652.14 $P < 0.001$[a]
Group III n = 5	0.383 ± 0.124	0.833 ± 0.14	1.193 ± 0.13	1.46 ± 0.12	1.49 ± 0.11	1.25 ± 0.14	0.683 ± 0.09	F = 408.38 $P < 0.001$[a]
Group IV n = 5	0.488 ± 0.35	0.488 ± 0.35	0.420 ± 0.31	0.345 ± 0.31	0.27 ± 0.28	0.180 ± 0.25	0.015 ± 0.06	F = 28.13 $P < 0.001$[a]
Group V (control)	0.46 ± 0.11	0.36 ± 0.13	0.39 ± 0.08	0.30 ± 0.15	0.24 ± 0.08	0.12 ± 0.16	0.0 ± 0.0	F = 108.17 $P < 0.001$[a]
	F = 0.603 $P = 0.62$	F = 23.78 $P < 0.001$[a]	F = 113.8 $P < 0.0001$[a]	F = 235.12 $P < 0.001$[a]	F = 368.1 $P < 0.001$[a]	F = 650.22 $P < 0.001$[a]	F = 1137.84 $P < 0.001$[a]	

GI: vaccinated by foot and mouth disease trivalent inactivated oil adjuvant vaccine plus silver nanoparticles.
GII: vaccinated by foot and mouth disease trivalent inactivated oil adjuvant vaccine.
GIII: Injected trivalent inactivated foot and mouth disease virus (A, O, and SAT2) plus silver nanoparticles.
GIV: Injected by silver nanoparticles alone.
GV: control group injected by normal saline.
[a] Statistically significant (if $P < 0.05$).

IL-6 at the level of first week post vaccination, the group III was the highest, followed by group IV. Meanwhile at the level of the second week post vaccination, the group I was the highest followed by group III, while at the level of the third and fourth week, the group I was the highest followed by group II (Table 4).

4. Discussion

FMD leads to trade and devastating economic losses [22]. FMD leads to weight loss, decreased milk production, and loss of draught power in animals, and is considered a disease with a low mortality rate [4]. Nowadays many studies on the use of

Table 3. Mean Values (OD) of bovine Interleukin-6 in sera collected from different group of vaccinated cattle during different time along 4 weeks.

	Time post injection					Test of significance
	Zero	1w	2w	3w	4w	
Group I	120.0 ± 44.72	403.0 ± 142.37	1597 ± 400.19a	1480 ± 218.23[a]	710 ± 139.1	F = 48.26 $P < 0.001$[a]
Group II	130.0 ± 44.72	241.0 ± 43.65	391 ± 76.03	1007 ± 168.80	654.4 ± 142.78	F = 58.47 $P < 0.001$[a]
Group III	114.0 ± 21.91	1351 ± 305.48	924.0 ± 48.14[a]	789 ± 129.92[a]	483 ± 81.67	F = 47.98 $P < 0.001$[a]
Group IV	130.0 ± 44.72	954 ± 97b	889 ± 98.77[b]	460 ± 114.02a	280 ± 103.68a	F = 61.92 $P < 0.001$[a]
Group V (control)	180 ± 27.39	130 ± 27.39[A]	120 ± 27.39[ABC]	100 ± 0.0[BD]	100 ± 0.0[CD]	F = 26.74 $P = 0.007$[a]

GI: vaccinated by foot and mouth disease trivalent inactivated oil adjuvant vaccine plus silver nanoparticles.
GII: vaccinated by foot and mouth disease trivalent inactivated oil adjuvant vaccine.
GIII: Injected trivalent inactivated foot and mouth disease virus (A, O, and SAT2) plus silver nanoparticles.
GIV: Injected by silver nanoparticles alone.
GV: control group injected by normal saline.
[a] Statistically significant (if $P < 0.05$).

Table 4. Comparison Mean Values (OD) of bovine Interleukin-6 in sera collected from different group of vaccinated cattle during different time along 4 weeks.

Time postinjection	Group I	Group II	Group III	Group IV	Group V (control)	Test of significance
Zero	120.0 ± 44.72 abc	130.0 ± 44.72 ade	114.0 ± 21.91bdf	130.0 ± 44.72cef	180 ± 27.39	F = 2.387 $P = 0.087$
1w	403.0 ± 142.37a	241.0 ± 43.65a	1351 ± 305.48	954 ± 97	130 ± 27.39	F = 53.55 $P < 0.001$[a]
2w	1597 ± 400.19	391 ± 76.03	924.0 ± 48.14[a]	889 ± 98.77[a]	120 ± 27.39	F = 44.99 $P < 0.001$[a]
3w	1480 ± 218.23	1007 ± 168.80	789 ± 129.92	460 ± 114.02	100 ± 0.0	F = 65.19 $P < 0.001$[a]
4w	710 ± 139.1a	654.4 ± 142.78a	483 ± 81.67	280 ± 103.68	100 ± 0.0	F = 28.62 $P < 0.001$[a]

GI: vaccinated by foot and mouth disease trivalent inactivated oil adjuvant vaccine plus silver nanoparticles.
GII: vaccinated by foot and mouth disease trivalent inactivated oil adjuvant vaccine.
GIII: Injected trivalent inactivated foot and mouth disease virus (A, O, and SAT2) plus silver nanoparticles.
GIV: Injected by silver nanoparticles alone.
GV: control group injected by normal saline.
[a] Statistically significant (if $P < 0.05$).

NPS as an adjuvant as a follow NPS such as silver, gold, and Caph, have enhanced the immunogenicity of antigen [23–25]. In the last period, nanoparticles showed great promise for vaccine formulations [26].

In this study, the results of TEM images for the sample tested revealed the diameter range from 5.80 to 28.51 nm and spherical in shape illustrate in Fig. 1, this result supported by Temgire and Joshi [27] they said that the particles less than 10 nm are spherical in shape, while the particles more than 30 nm have structures of pectagonal, biprisms or decahedra multiply twinned particles. Many studies have focused on the use of AgNPs as drug carriers, and several in vitro studies have revealed the low toxicity of AgNPs in various cell lines [28,29]. In addition, Asgary et al. [30] used AgNPs as adjuvants in rabies vaccines.

The results of SNT in vaccinated groups revealed that the first group vaccinated with FMD inactivated oil adjuvant vaccine plus AgNPs showed high statistical significance compared with the other groups illustrated in Tables 1 and 2. This result is in agreement with that of Dechamma et al. [31], who showed that Cap nanoparticles produce a higher immune response than oil.

This study, in concurrence with Abd Al-Rhman et al. [32], revealed that AgNPs have a significant adjuvant effect, and the mechanism of this effect is mainly attributed to the recruitment and activation of local leukocytes, especially lymphocytes, which increase cytokine levels in mouse IgG concentration and phagocytes. In addition, cellular and humeral immunities were significantly enhanced in immunized mice, which can be utilized

as an effective adjuvant to improve immune protection.

This result is similar to Rizk et al. [33], who revealed that Cap NPS increased the specific protective immune response in calves vaccinated with oil and NPs adjuvant vaccine titer up to 40 weeks, while calves vaccinated with FMD Vaccine adjuvant with cap remained at 36 weeks and oil adjuvant at 32 weeks.

Vaccines developed in the future should induce high neutralizing antibodies in both pigs and ruminants. In addition, they offer high levels of safety and protective effects after vaccination [34].

Concerning the results of IL-6 in the vaccinated groups, it was revealed that AgNPs elevated IL-6 in the early stage in groups injected with AgNPs Tables 2 and 3.

This study is in agreement with Leal et al. [35], who revealed that IL-6 needs to be present in the early phases of immunization with a T. B-subunit vaccine to allow the differentiation of Th1 cells.

In contrast with Lee et al. [36], IL-6 was not detected in any of the immunized pigs upon challenge against the FMD virus but was detected in one of the control pigs at 1 dpi and in both pigs at 3 dpi. At 28 days post-vaccination, the serum concentrations of C-reactive protein and TNF-α were higher in the immunized pigs than in the non-immunized pigs. The serum concentration of IL-6 in the immunized challenged pigs was undetectable at all time points. In addition, Garcia-Valcarcel et al. [37] stated that cellular immunity vp1 responses were poor, despite two immunizations with recombinant protein.

This results are supported by Su et al. [38], who stated that IL-6 enhances cell-mediated immune responses and promotes the maturation of dendritic cells and their immune function. In addition to Barnett [39] and Cox et al. [40] they revealed that IL-6 was detected in both vaccinated and vaccine-challenged pigs.

This study is in agreement with that of Cox et al. [41], who revealed the potential use of serum IL-6 levels as a marker of FMD vaccine efficacy.

5. Conclusion

In this study, we attempted to modify the FMD vaccine by increasing the immunity of the vaccine for use as a control. Finally, the results of this study showed that AgNPs with FMD vaccine resulted in a high increase in cell-mediated immune response and humeral immune response in cattle.

Funding statement

The study was not supported by any grant from any Foundation.

Ethical compliance

All procedures were in accordance with the ethical standards of Mansoura University ethical committee.

Data availability

Data generated in this study are available within this study.

Author contributions

RD, MI and ME contributed to the design and implementation of the research, HF, SA, MF, AY and SE to the analysis of the results all the authors wrote and approved the manuscript.

Conflicts of interest

The authors declare that they have NO affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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