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RESEARCH ARTICLE

The effect of interferon alpha administration on cytokine levels in sheep

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Koyunlara interferon alfa uygulamasının sitokinler üzerine etkisi

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Öz

Amaç: Bu çalışmanın temel amacı, sağlıklı koyunlara parenteral rekombinant insan interferon (rHuIFN)-α2a uygulamasının serum tümör nekroz faktör (TNF)-α, interlöykin (IL)-6 ve IL-10 seviyeleri üzerindeki etkisini belirlemektir. Ayrıca sağlıklı koyunlarda temel fizyolojik parametreler (vücut ısısı, nabız, solunum hızı), hemogram ve kan gazı parametrelerine etkisini tespit etmektir.

Gereç ve Yöntem: Bu çalışmada 10 Merinos koyuna 9.000.000 IU rHuIFN-α2a deri altı yolla uygulandı. Kan örnekleri uygulamadan önce (0 saat) ve sonra 4, 8, 12, 24, 48, 72, 96 ve 120 saatlerde alındı. Aynı örnekleme zamanlarında vücut ısısı, nabız ve solunum hızı da belirlendi. Serum örneklerinden koyun spesifik TNF-α, IL-6 ve IL-10 seviyeleri ELISA okuyucu ile ölçüldü. Hemogram ve kan gazı parametreleri sırasıyla tam kan hücresi sayım cihazı ve kan gazı analiz cihazında ölçüldü.

Bulgular: rHuIFN-α2a uygulaması sonrasında TNF-α ve IL-10 konsantrasyonları 96. saatte pik düzeye ($p<0.05$) ulaşırken, IL-6 konsantrasyonunda istatistiksel olarak anlamlı değişim belirlenmedi ($p>0.05$). Ayrıca vücut ısısı ve pO2 düzeylerinde geçici artışlar ($p<0.05$) belirlenirken, potasyum ve iyonize kalsiyum seviyelerinde düşmeler ($p<0.05$) belirlendi. Nabız, akyuvar sayımı, pH, base(ecf) ve sodyum değerlerinde ise istatistiki dalgalanmalar ($p<0.05$) tespit edildi.

Öneri: Koyunlara rHuIFN-α2a uygulamasının immünolojik etkiler gösterebileceği, genel olarak güvenli kabul edilebileceği ve tedavide kullanım için düşünülebileceği ifade edilebilir.

Anahtar kelimeler: Koyun, interferon, sitokinler, hemogram, kan gazları

Abstract

Aim: The primary aim of this study was to determine the effect of parenteral recombinant human interferon (rHuIFN)-α2a administration on serum tumor necrosis factor (TNF)-α, interleukin (IL)-6 and IL-10 levels in healthy sheep. In addition, the main physiological parameters (rectal temperature, pulse rate, respiratory rate), hemogram and blood gas parameters were determined, as well.

Materials and Methods: In this study, 9.000.000 IU rHuIFN-α2a was administered subcutaneously in 10 Merinos sheep. Blood samples were taken before (0 hours) and after at 4, 8, 12, 24, 48, 72, 96 and 120 hours. Rectal temperature, pulse and respiratory rate were also determined at the same sampling times. Sheep-specific TNF-α, IL-6 and IL-10 levels were determined from serum samples by the ELISA reader. Hemogram and blood gas parameters were measured by complete blood cell counter and blood gas analyzer, respectively.

Results: After rHuIFN-α2a treatment, TNF-α and IL-10 concentrations reached peak levels ($p<0.05$) at the 96 hours, whereas the IL-6 level did not change in a statistically significant ($p>0.05$). On the other hand, a temporary increase in rectal temperature and pO2 levels ($p<0.05$) were determined, while decreased potassium and ionized calcium levels ($p<0.05$) were measured. Statistically significantly ($p<0.05$) fluctuations were determined in pulse rate, white blood cell counts, pH, base(ecf) and sodium values.

Conclusion: It may be stated that administration of rHuIFN-α2a showed immunological effects in sheep, as it is generally accepted as safe and can be considered for use in treatment.

Keywords: Sheep, interferon, cytokines, hemogram, blood gases

Introduction

Interferons (IFNs) have antiviral, anti-proliferative and immunomodulatory effects. According to the structure of IFNs, they are evaluated as 3 groups (type I, II and III). Alpha (α) and omega IFNs belongs to the type I (Canbar and Yazar 2020a, Canbar and Yazar 2020b). Although the level of IFN-α in the bloodstream is too low or at undetectable levels in normal healthy conditions, microorganisms (viruses, mycoplasmas, chlamydiae or protozoans) may stimulate INF-α production in the host (Dec and Puchalski 2008). Although there is no consensus on the cells from which IFNs is produced, their productions are attributed to fibroblasts, T cells, macrophages, dendritic cells, B cells, monocytes and natural killer cells (Fitzgerald-Bocarsly 1993, Brassard et al 2002). Production of IFN-α in the viral infections is an early non-specific defense mechanism, and it prevents viral replication. Many viruses can induce endogenous IFN-α production in cattle (Dec and Puchalski 2008).

Recombinant feline interferon omega is the only recombinant product commercially available in veterinary medicine. Manufacturer identified the cats and dogs as target animal species and are recommended for the treatment of some viral infections (Yazar 2018, Canbar and Yazar 2020a). However, veterinarians can also use products containing recombinant human interferon alpha (rHuIFN-α) used in human medicine, especially in pet clinics (Cave et al 2004, Carvalho et al 2014). Commercially available rHuIFN-α2a is recommended for treating some viral infections and cancer types (Roche 2020). Cummins et al (2005) has stated that the effectiveness of the IFN alpha species is not species specific but may have limited effects on different species.

The clinical effectiveness of applying rHuIFN-α2a to sheep and has not been reached in the current literature. However, much research has been done about its effectiveness with other animal species. Cummins et al (1993a) reported that application of oral rHuIFN-α2a to calves reduced mortality rate and increased weight gain, and oral HuIFN-α administration has positive effects on calves with experimentally infected with infectious bovine rhinotracheitis (Cummins et al 1993b) or bovine respiratory disease complex (Cummins et al 1999). There are also studies on HuIFN-α in pet clinics in veterinary medicine. Beneficial effects have been reported after treatments of HuIFN-α2a, rHuIFN-α2b or HuIFN-α in calicivirus infected (da Silva et al 2018), neoplasia (Cave et al 2004) or experimental retroviral infected cats (Cummins et al 1988), respectively. In addition to the these, HuINFs can be used in treating some types of cancer and viral infections in dogs (Canbar and Yazar 2020b). Carvalho et al (2014) has reported that rHuIFN-α2a application prevents canine distemper virus replication in vitro, and Kim et al (2009) has stated that rHuIFN-α2a can be used in epitheliotropic lymphoma treatment. In addition, it has been observed that IFNs can be used in horses (Moore et al 2004) and chickens (Jarosinski et al 2001).

There is no detailed information about the effect of IFNs on tumor necrosis factor (TNF)-α, interleukin (IL)-6 and IL-10 levels in healthy subjects. However, Brassard et al (2002) has stated that IFN-α can regulate cytokine activities, and Dec and Puchalski (2008) has reported that IFN-α may induces the transcription of many cytokines under in vitro conditions. In addition to these, Vial and Descotes (2007) asserted that some side effect of IFN can be derived from the acute release of proinflammatory cytokines.

Considering that IFN-α causes cytokine transcription, fever, anemia, granulocytopenia and thrombocytopenia (Hanaoka et al 1999, Dec and Puchalski 2008), it has been hypothesized that the application of rHuIFN-α2a may affect some cytokine levels and basic physiological, hemogram and blood gas parameters in sheep.

The primary aim of this study was to determine the effect of parenteral rHuIFN-α2a administration on sheep-specific serum TNF-α, IL-6 and IL-10 levels in healthy sheep. In addition, the main physiological (rectal temperature, pulse rate, respiratory rate), hemogram and blood gases parameters were determined.

Material and Methods

In this research, 10 Merino sheep (2.5 to 3 years, 51 to 59 kg) were used and study protocol was approved by ethic committee. Each sheep was administered with rHuIFN-α2a (9.000.000 IU, SC, SID, Roferon-A 9 Mio II, Istanbul, Turkey) as a single dose. Blood samples were taken before at 0 hour (control) and at 4, 8, 12, 24, 48, 72, 96 and 120 hours after the treatments. Sheep-specific TNF-α (sheep tumor necrosis factor alpha ELISA kit, Bioassay Technology Laboratory, Shanghai, China), IL-6 (sheep interleukin 6 ELISA kit, Bioassay Technology Laboratory, Shanghai, China) and IL-10 (sheep interleukin 10 ELISA kit, Bioassay Technology Laboratory, Shanghai, China) levels were determined with ELISA reader (MWGt Lambda Scan 200, Bio-Tec Instruments, Winooski, VT, USA). Hemogram [white blood cell count (WBC), red blood cell count (RBC), platelet count, hemoglobin, hematocrit] and blood gas parameters [blood pH, partial carbon dioxide pressure (pCO2), partial oxygen pressure (pO2), oxygen saturation (sO2 %), base excess of extracellular fluid (base(ecf)), bicarbonate (HCO3-), potassium (K), sodium, (Na), ionized calcium (iCa)] were measured with complete blood cell counter (MS4E Hematology Cell Counter, Melet Schloesing Laboratories, France) and blood gas analyzer (ABL90 Flex Analyzer, Denmark), respectively. Rectal temperature, pulse and respiratory rate were determined at the same sampling times, as well.

The results of the study were given as mean ± standard error (SE). The data were evaluated by the ANOVA and Tukey test (SPSS 22.0). P<0.05 level was considered statistically significant.

Results

Levels of serum TNF-α, IL-6 and IL-10 are presented in Figures 1, 2 and 3, respectively. After rHuIFN-α2a treatments, TNF-α and IL-10 concentrations reached to peak levels (p<0.05) at the 96 hours. At the IL-6 level, there were no statistical changes (p>0.05).

Rectal temperature is presented in Figure 4, while respiratory rate, pulse rate, hemogram and blood gas parameters are presented in Table 1. Increased rectal temperature (4 and 8 hours) and pO2 (4 and 12 hours) levels were determined (p<0.05), whereas decreased K (8, 12, 24, 48, 72 and 96 hours) and iCa (8, 24, 48, 72, 96 and 120 hour) levels (p<0.05) were measured after rHuIFN-α2a treatments.

Statistical fluctuations (p<0.05) were determined in pulse rate, WBC, pH, base(ecf) and Na values. No clinical negativity was observed in the animals used in the study.

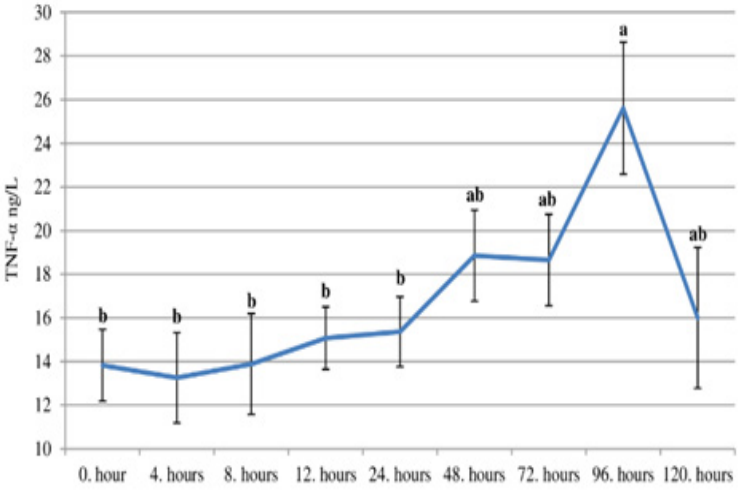

Figure 1. The effect of recombinant human interferon-α2a (9.000.000 IU, SC) on tumor necrosis factor (TNF)-α levelsin sheep (mean ± SE, p<0.05)

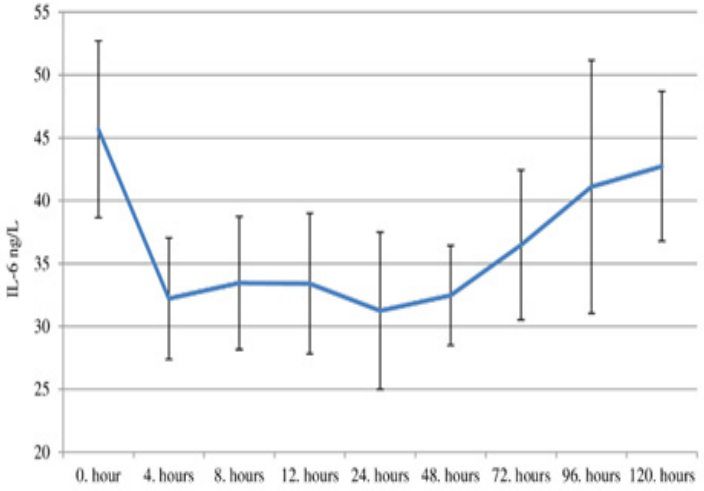

Figure 2. The effect of recombinant human interferon-α2a (9.000.000 IU, SC) on interleukin-6 (IL-6) levels in sheep (mean ± SE, p>0.05)

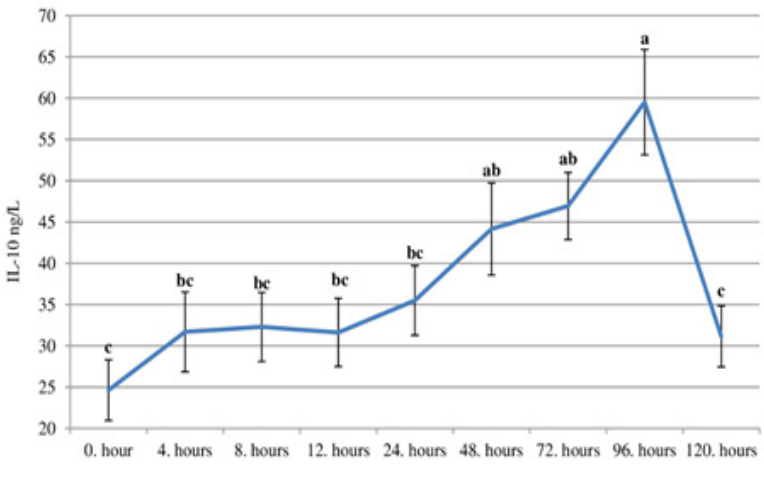

Figure 3. The effect of recombinant human interferon-α2a (9.000.000 IU, SC) on interleukin-10 (IL-10) levels in sheep (mean ± SE, p<0.05)

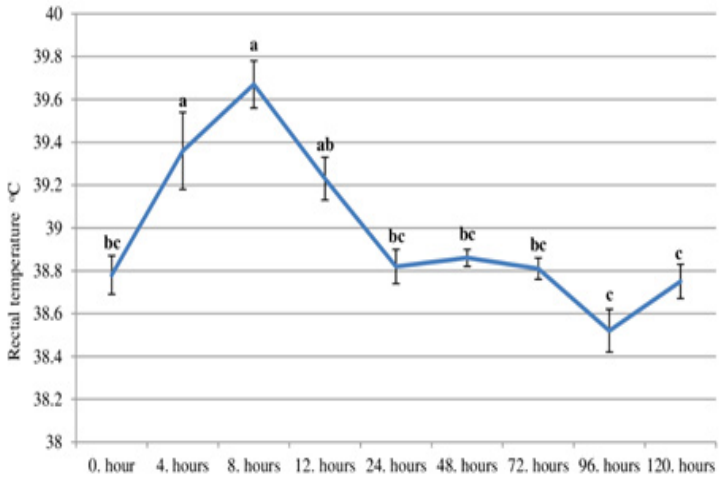

Figure 4. The effect of recombinant human interferon-α2a (9.000.000 IU, SC) on the rectal temperature levels in sheep (mean ± SE,p<0.05)

Table 1. The effect of recombinant human interferon-α2a (9.000.000 IU, SC) administration on pulse rate, respiratory rate, hemogram and blood gas parameters (mean ± SE)

Parameters	0. hour	4. hours	8. hours	12. hours	24. hours	48. hours	72. hours	96. hours	120. hours
Pulse/min	73,80±3,71^{ab}	84,80±4,78^{ab}	90,50±4,62^{a}	88,40±4,27^{ab}	84,40±4,87^{ab}	81,40±3,19^{ab}	83,40±3,61^{ab}	71,20±2,60^{b}	74,80±4,40^{ab}
Respiratory/min	44,40±7,47	52,50±11,60	57,90±5,83	46,40±8,70	43,50±6,42	40,00±7,33	36,10±7,38	33,20±7,96	33,80±7,44
WBC 10^9/L	5,54±0,41^{ab}	4,46±0,39^{ab}	4,06±0,39^{b}	4,39±0,74^{ab}	4,83±0,39^{ab}	5,44±0,81^{ab}	5,38±0,94^{ab}	7,11±1,19^{ab}	7,68±0,84^{a}
RBC 10^{12}/L	12,60±0,36	11,85±0,47	12,22±0,39	12,39±0,66	12,52±0,37	11,52±0,43	11,28±0,38	12,37±0,40	12,09±0,40
Platelet 10^9/L	286,00±47,61	473,50±163,42	400,70±95,59	489,20±203,12	334,90±69,54	193,80±32,22	190,30±33,75	269,60±41,51	278,20±37,94
Hgb g/dL	10,84±0,34	10,02±0,50	9,77±0,39	9,73±0,46	10,42±0,34	9,79±0,41	9,82±0,36	10,38±0,35	10,28±0,29
Htc %	33,23±1,03	30,89±1,50	30,20±1,16	30,06±1,36	31,97±1,05	29,98±1,26	30,12±1,10	31,84±1,08	31,50±0,90
pH	7,44±0,01^{ab}	7,45±0,01^{ab}	7,46±0,01^{a}	7,46±0,01^{a}	7,42±0,01^{b}	7,42±0,01^{b}	7,43±0,01^{ab}	7,43±0,01^{ab}	7,44±0,01^{ab}
pCO_2 mmHg	37,06±0,92	35,13±0,91	36,04±0,82	36,66±0,80	36,10±0,59	37,56±0,68	37,82±0,81	38,08±0,67	37,10±0,57
pO_2 mmHg	36,60±1,11^{b}	44,52±3,01^{a}	42,95±1,68^{ab}	45,02±1,74^{a}	38,96±1,07^{ab}	36,83±1,32^{b}	35,66±1,64^{b}	36,82±1,26^{b}	36,70±1,43^{b}
sO_2 %	56,38±2,67	65,00±2,97	62,17±2,92	63,52±2,58	60,73±1,98	56,13±2,98	53,82±2,94	56,37±2,24	56,08±2,82
Base(ecf) mmol/L	1,95±0,33^{ab}	0,64±0,68^{ab}	2,12±0,50^{ab}	2,58±0,56^{a}	-0,46±0,58^{b}	0,71±0,82^{ab}	1,32±0,46^{ab}	1,67±0,61^{ab}	1,44±0,55^{ab}
HCO_3- mmol/L	25,72±0,38	24,26±0,63	25,72±0,46	26,14±0,54	23,88±0,48	24,92±0,63	25,50±0,44	25,35±0,42	25,44±0,48
K mmol/L	4,44±0,05^{a}	4,22±0,11^{ab}	4,03±0,03^{b}	4,01±0,06^{b}	3,95±0,04^{b}	3,98±0,06^{b}	3,93±0,08^{b}	3,96±0,08^{b}	4,12±0,11^{ab}
Na mmol/L	150,60±0,61^{ab}	148,70±1,03^{b}	151,20±0,87^{ab}	150,70±0,73^{ab}	153,60±0,42^{a}	152,80±0,41^{a}	153,00±0,55^{a}	153,60±0,47^{a}	153,40±0,71^{a}
iCa mmol/L	1,05±0,01^{a}	0,97±0,02^{ab}	0,93±0,02^{b}	0,95±0,02^{ab}	0,88±0,02^{b}	0,88±0,01^{b}	0,89±0,02^{b}	0,88±0,03^{b}	0,89±0,02^{b}

$^{a, b}$: Different letters on the same line are statistically significant (P<0.05, tukey test). WBC: White blood cell count, RBC: Red blood cell count, Hgb: Hemoglobin, Htc: Hematocrit, pCO_2: Partial carbon dioxide pressure, pO_2: Partial oxygen pressure, sO_2: Oxygen saturation, Base(ecf): Base excess (extracellular fluid), HCO_3- : Bicarbonate, K: Potassium, Na: Sodium, iCa: Ionized calcium

Discussion

In this study, no negative clinical symptoms were observed in sheep during the experiment. It was reported that weak diarrhea was observed after oral IFN-α application to calves, while depression and anorexia were not observed (Ohtsuka et al 2006). As direct observation, it can be stated that a single dose of 9.000.000 IU (SC) rHuIFN-α2a administration to sheep may not cause clinical side effects.

In the literature, information could not be obtained with the effects of IFNs on TNF-α, IL-6 and IL-10 in sheep. In this study, it was determined that the concentrations of TNF-α (Figure 1) and IL-10 (Figure 3) increased to peak levels at 96 hours ($p<0.05$) after the application of rHuIFN-α2a to sheep, while there were no statistical changes ($p>0.05$) at the IL-6 levels (Figure 2). Nuclear factor-kappaB (NF-κB) has been identified as a first determined transcription factor in the B-cell nucleus, and it plays a role in regulating genes related to cell survival, cell growth, inflammation and immunity (Pfeffer 2011). The effects of Type I IFNs on NF-κB may be unstable (Moschos et al 2007), and NF-κB activation stimulates the synthesis of IFNs, TNF-α and IL-1β (Boo and Yang 2010). It has been reported that IFN-α can stimulate IL-10 transcription (Dec and Puchalski 2008) and regulate the activities of TNF-α and IL-6 (Brassard et al 2002). In addition to the use of rHuIFN-α in the pet clinic (Canbar and Yazar 2020b), it has been stated that human IFN-α can be used in calves and have positive effects against infections (Cummins et al 1993a, Cummins et al 1993b, Cummins et al 1999, Cummins et al 2005). Considering the effect of rHuIFN-α2a on cytokines in the current study, it has been stated that rHuIFN-α2a may affect the immune systems of sheep as well as cats, dogs and calves, and it can be taken into consideration in treatment.

In the current study, while rHuIFN-α2a caused temporary elevation in rectal temperature ($p<0.05$, Figure 4), it had no effect on the respiratory rate ($p>0.05$, Table 1). As a general side effect, fever can be observed after administration of rHuIFN-α2a (Roche 2020). The application of natural HuIFN-α (Hanaoka et al 1999) or recombinant ovine IFN-tau (Ott et al 1997) to sheep and rHuIFN-α2a (van Miert et al 1990) to goats caused fever in the first hours. Side-effect mechanisms of INFs has not been clearly defined. However, Vial and Descotes (2007) have stated that side effects of IFNs may develop as a result of the direct toxic effects and/or the indirect immunity-related effects. Fever caused by IFNs is associated with the release of substances such as eicosanoids and proinflammatory cytokines known as endogenous febrile agents. Hence, it may be stated that temporary fever, which is expressed as the general side effect of rHuIFN-α2a, can also be observed in sheep.

In this study, statistically significantly ($p<0.05$) fluctuations were determined in pulse rate, WBC, pH, base(ecf) and sodium values (Table 1). Transient elevations ($p<0.05$) were determined at the pO2 levels, whereas transient decreases at the potassium levels and permanent decreases in ionized calcium levels were determined until the end of the experiment ($p<0.05$, Table 1). There is no certainty in the literature about the effects of rHuIFN-α2a on hemogram and blood gas parameters in healthy sheep. Leukopenia, thrombocytopenia (Finter et al 1991, Roche 2020) and erythrocytopenia (Roche 2020) can be observed after IFN-α or rHuIFN-α2a administration. It has been reported that IFN-α can increase monocyte function in calves (Ohtsuka et al 2006), while natural HuIFN-α has no effect on WBC count and pO2 level in sheep (Hanaoka et al 1999). Moderate granulocytopenia and thrombocytopenia are frequently observed after IFN application (Leaman et al 2006). The suppressive effect of IFNs on bone marrow (Moschos et al 2007) may explain developing leukopenia, thrombocytopenia and erythrocytopenia. It can be stated that rHuIFN-α2a can cause temporary and non-serious changes when the effect of hemogram and blood gas parameters is evaluated in sheep.

Conclusion

As a result, it can be stated that a single dose of rHuIFN-α2a (9.000.000 IU, SC) causes immunological effects in sheep as well as calves, dogs and cats. In addition, it may cause temporary fever and minimal changes in hemogram and blood gas parameters. However, more research is needed, especially on sick subjects to determine the safety and effectiveness of rHuIFN-α2a in sheep.

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Conflict of Interest

The authors did not report any conflict of interest or financial support.

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