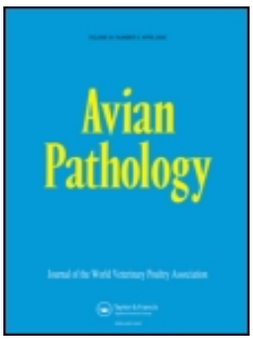

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The effects of vitamin A, pentoxyfylline and methylprednisolone on experimentally induced amyloid arthropathy in brown layer chicks

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The effects of vitamin A, pentoxyfylline and methylprednisolone on experimentally induced amyloid arthropathy were investigated. In this study, 175 1-day-old brown layer chicks were used. Throughout the study Group II (vitamin A) received high doses of vitamin A (75 000 IU/kg), whereas Group I (negative control), Group III (positive control), Group IV (pentoxyfylline) and Group V (methylprednisolone) received normal levels of vitamin A in the diet. At the fifth week, the experimental Groups II, III, IV and V were injected with Freund's adjuvant intra-articularly to induce amyloid arthropathy. Group IV received pentoxyfylline and Group V received methylprednisolone (10 mg/kg, intramuscularly) once. Joint and blood samples were examined 13 weeks after the injections. The values in Groups I, II, III, IV and V, respectively, were as follows: amyloid arthropathy formation (%), 0, 100, 87, 76, 66; serum amyloid A (ng/ml), 166 ± 17, 607 ± 40, 423 ± 39, 342 ± 27, 293 ± 22; serum retinol (μg/dl): 59.75 ± 3.8, 42.72 ± 3, 59.24 ± 3.6, 102 ± 9.1, 101.3 ± 12.3; heterophil/lymphocyte ratio: 0.504, 0.75, 0.75, 0.087, 0.44. In conclusion, it was observed that vitamin A enhanced the development of amyloid arthropathy and there were positive associations between amyloidosis, increased levels of serum amyloid A and increased numbers of tissue infiltrating macrophages. Methylprednisolone had a more successful inhibitory effect on amyloid arthropathy than pentoxyfylline.

Introduction

It has been widely recognized that amyloid arthropathy, characterized by the accumulation of amyloid in joints, is a common pathological disorder in certain kinds of birds (Landman, 1999) and the biochemical mechanism of the pathogenesis of amyloidosis in avians remains obscure (Landman *et al*., 1998b). It has been demonstrated that predisposing conditions such as chronic infections, inflammation or tumours cause an increase in the serum levels of serum amyloid A (SAA), a precursor protein of amyloid protein A of hepatic origin (Urieli-Shoval *et al*., 2000). This unstable precursor protein of amyloid proteins accumulates in the target tissues or organs and reorganizes into fibrillar form to cause amyloidosis by an unknown mechanism (Glenner, 1980; Landman *et al*., 1998b). Zschiesche & Linke (1986) and Landman *et al*. (1996) demonstrated that SAA is the precursor protein of type AA amyloidosis also in avians. It is thought that serine proteinases located on the surface of granular macrophages play a very important role in the reorganization of SAA into amyloid fibrils in tissues (Glenner, 1980; Landman *et al*., 1998b).

Amyloidosis can be defined as the deposition of soluble proteins or their fragments in the extracellular space of many different tissues and identified as a non-branching, 7 to 10 nm fibrillar form (Glenner, 1980).

Avian amyloidosis has been shown to affect certain kinds of birds causing quite a number of different diseases (Landman, 1999). Joint amyloidosis is one of the clinical problems associated with growth depression and lameness in brown layers (Landman *et al*., 1994). Landman *et al*. (1998a) reported that *Enterococcus faecalis* was isolated from a case of joint amyloidosis that occurred in a field outbreak in chickens and experimentally induced *E. faecalis* amyloidosis that was reactive-type amyloid (AA amyloid).

It has been shown that the type AA amyloid-related precursor protein (SAA) of amyloid fibrils is increased by cytokines such as interleukin (IL)-1 (Ramadori *et al*., 1985), IL-6 (Marinkovic *et al*., 1989), tumour necrosis factor alpha (TNF-α), macrophage colony stimulating factor (M-CSF) (Betts *et al*., 1993). Retinoids have been shown to influence many aspects of immunity including the function of leucocytes and the expression of cytokines (TNF-α, IL-1, IL-2, IL-3 and IL-6) (Dillahay *et al*., 1988; Turpin *et al*., 1990; Göttgens & Green, 1995; Ross, 1999). Furthermore, Katz *et al*. (1987) showed that retinoids stimulate both an increase in the number of

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macrophages *in vivo* and enhance their activity *in vitro*. Therefore anti-inflammatory agents such as colchicine and dimethylsulfoxide are used for amyloid treatment in humans (Kisilevsky *et al*., 1995; Soto *et al*., 1996) and mice (Inoue *et al*., 1996). However, there have been no reports concerned with the treatment of avian amyloidosis.

Pentoxyfylline, a well-known inhibitor of phosphodiesterase, is a trimethylated xanthine derivative, which triggers an increase in intracellular cyclic adenosine monophosphate, causing the dilatation of blood vessels and the improvement of microcirculation. It has been used to improve peripheral blood vessel disease for many years (Windmeier & Gressner, 1997; Schuppan *et al*., 2000). A rise in intracellular cAMP has been suggested as a pentoxyfylline-mediated inhibitory effect on the respiratory burst of neutrophils (Besler *et al*., 1986). Furthermore, pentoxyfylline has been shown to inhibit the synthesis of glycosaminoglycan, the production of fibronectin in cultured fibroblasts, the activity of collagenase and TNF-α (Berman & Duncan, 1989; Chang *et al*., 1993).

Methylprednisolone, an anti-inflammatory and immune suppressive agent, is a synthetic adrenocortical derivative, which inhibits TNF-α (Pitzalis *et al*., 1997; Xu *et al*., 1998), IL-2 (Wandinger *et al*., 1998), IL-6 (Stanton *et al*., 1999), IL-10 (Hodge *et al*., 1999) and the synthesis of glycosaminoglycans in rats (Laato *et al*., 1989).

Our previous study (Sevimli *et al*., 2004) showed that vitamin A increased the severity of *E. faecalis*-induced amyloid arthropathy. The aim of this study was therefore to determine the effects of high vitamin A added feeding on Freund's adjuvant-induced amyloid arthropathy and the effects of pentoxyfylline and methylprednisolone on amyloid arthropathy treatment.

Materials and Methods

Ethics. The experimental protocols were approved by the Animal Care and Use Committee at Uludag University and are in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals.

Animals and experimental design. One hundred and seventy-five 1-day-old brown layer chicks were used. The chicks had been vaccinated against avian influenza, infectious bronchitis and Marek's disease, Newcastle disease and Gumboro disease. The light schedule was 14 h light and 10 h dark. The chicks were allocated into five groups. Group I (negative control, $n=35$), Group III (positive control, $n=35$), Group IV (pentoxyfylline, $n=35$), Group V (methylprednisolone, $n=35$) were fed *ad libitum* with a commercial diet containing normal levels of vitamin A (5000 IU/kg) while Group II (vitamin A, $n=35$) were fed *ad libitum* with a commercial diet containing high levels of vitamin A (75 000 IU/kg). To induce amyloid arthropathy in Groups II, III, IV and V, the birds were injected with 0.25 ml complete Freund's adjuvant into the left inter-tarsal joint at the fifth week of the experiment as described by Landman *et al*. (1998), while Group I was injected intra-articularly with 0.9% NaCl (0.25 ml). On the same day, chicks in Group IV and Group V were. injected intramuscularly with 10 mg/kg pentoxyfylline and methylprednisolone, respectively, to induce immunosuppression. Four chickens in Group III and one chicken in Group IV died of pneumonia at the sixth week. All pullets were necropsied at 13 weeks post-injection.

Tissue sampling and processing. The whole inoculated hock joints (including the synovial membrane and joint capsule) collected during necropsy were fixed in 10% phosphate-buffered formaldehyde solution for 24 h and processed to paraffin, sectioned at 5 μm and stained with haematoxylin and eosin and Congo red stain (Lee & Luna, 1968). Immunohistochemistry was done to identify amyloid using the streptavidin–biotin–peroxidase method (True, 1990). Goat anti-mouse Amyloid A Ab-1 (mc1) antibody was used as supplied (Neomarkers-Freemont, USA) to demonstrate amyloid deposition in synovial membrane. AEC was used as chromogen in all tissue sections. Tissue sections were examined for amyloid occurrence rates and inflammatory cell infiltration rates.

The amount of amyloid deposition in synovial membrane was scored semiquantitatively in the Congo red and immunohistochemically stained slides (True, 1990). Congo red-stained slides were examined in polarized light for the characteristic green birefringence of amyloid while immunohistochemically stained slides were examined under light microscopy. Scores (– to +++) were given based on the amount of amyloid. The presence of amyloid was graded according to the intensity and dissemination of staining as negative (–), mild (+), moderate (++), severe (+++) under light microscopy with 10 × magnification. The type of inflammatory cells was investigated in sections stained with haematoxylin and eosin under light microscopy at 20 × magnification. The presence of heterophils, lymphocytes, plasmocytes and macrophages seen in the area with 20 × magnification under a light microscope were also graded. The absence of cells was graded as negative (–); the presence of three to six cells graded as mild (+); seven to 10 cells graded as moderate (++); above 10 cells was graded as severe (+++).

Serological studies. Blood samples of 12 randomly selected birds per group were taken from the carotid artery into disodium ethylenediamine tetraacetic acid-coated tubes before necropsy and were used for SAA and serum retinol measurements.

SAA measurement. A commercial enzyme-linked immunosorbent assay kit (TP-802M; Tridelta, Maynooth Co. Kildare, Ireland) was used to detect SAA. In this study, a murine kit and its standards were used because a kit for chicken SAA was not available. However, the producer of the murine kit recommended the use of the murine kit since there is a cross-reactivity between chicken and mouse antibody (Tridelta). The Tridelta phase™ range SAA kit is a solid-phase sandwich enzyme-linked immunosorbent assay. A monoclonal antibody specific for SAA had been coated onto the wells of the microtitre strips provided.

Test reagents and samples were allowed to reach room temperature prior to use. The number of eight-well strips needed for the assay was determined. Fifty microlitres of diluted biotinylated anti-SAA were added into each well. The serum samples were vortexed and diluted 1:500 in 1 × diluent buffer. Fifty microlitres ere added, in duplicate, of diluted sample into each well. The plates were covered with a dust cover. The plates were incubated for 1 h at 37°C. After incubation, aspiration was performed and the plates were washed four times with diluted wash buffer. After the last wash, the plates were dried on absorbent paper. One-hundred microlitres of streptavidin–peroxidase was added into each well. The plates were covered and incubated at room temperature in the dark for 30 min. The wells were aspirated and then washed four times. The plate was dried after the last wash and 100 microlitres tetramethyl benzidine substrate, which was provided with the kit, was added. The plates were covered and incubated in the dark at room temperature for 30 min. Fifty microlitres of the stop solution was added. The absorbance of each well was read at 450 nm using 630 nm as reference. The mean absorbance for each sample was calculated as standard. The absorbance of the standards was plotted against the standard concentration on semi-logarithmic graph paper.

Serum retinol measurement. The assessment of retinol levels in serum was made using a spectrophotometer (Mert, 1996).

Haematological study. The previously mentioned disodium ethylenediamine tetraacetic acid blood samples of 12 birds per group were examined for the heterophil/lymphocyte (H/L) ratio. H/L ratios were calculated on a blood smear stained with the May–Grünwald and Giemsa methods (Lee & Luna, 1968).

Statistical analysis. The values of the SAA and serum retinol levels were evaluated with variance analysis and Tukey tests, and the scores of the

microscopic examinations were assessed with chi-square tests (SAS Institute Inc., 1991).

Results

Clinical findings. In all experimental groups, swelling in the inoculated left inter-tarsal joints resulting in lameness was observed on days 5 to 7 after the injections (p.i.) and these findings were more apparent in birds of Groups II and III than in Groups IV and V. No swelling of the inoculated joints or lameness was seen in the birds of Group I.

Necropsy findings. In all experimental groups, especially in Groups II and III, the inoculated left inter tarsal joints were swollen. Macroscopically, in the amyloid-positive pullets, the amyloid appeared as multifocal orange-coloured thickenings in the periarticular region.

Microscopical findings. The findings of amyloid arthropathy and its severity in the joints are given in Table 1. The highest rate of amyloid arthropathy found was 100% in Group II, while the frequency of amyloid arthropathy was 87%, 76%, and 66% in Groups III, IV and V, respectively (Figure 1). The differences between the five groups were significant ($P < 0.001$). Amyloid arthropathy with the most severe amyloid deposition (+++) was also seen in Group II (54.28%), whereas the incidence of severe deposition (+++) was 32%, 29.41% and 23% in Groups III, IV and V, respectively (Table 1).

The degree of differential cell infiltration in synovial membranes are presented in Table 2. Severe (+++) heterophil infiltration was seen in 87% of birds in Group III, followed by Group II with 77%, Group IV with 70% and Group V with 63%. The highest rate of severe macrophage infiltration was observed in 51% of birds in Group II, followed by Group IV with a rate of 41%, Group III with a rate of 39% and Group V with a rate of 6%. Severe (+++) lymphocyte and plasma cell infiltration was seen in 68% of birds in Group III and the lowest rate of severe (+++) lymphocyte and plasma cell infiltration was seen in Group IV where 44% of birds were affected. The comparison of the incidence of amyloid arthropathy with severe heterophil infiltration severe macrophage infiltration and severe lymphocyte and plasma cell infiltration are presented in Figures 2–4, respectively.

Serological findings. *SAA findings.* The SAA levels were increased in all groups when compared with the negative control group (166 ± 17 ng/ml). The highest levels were observed in Group II (607 ± 40 ng/ml), followed by Group III (423 ± 39 ng/ml), Group IV (342 ± 27 ng/ml) and Group V (293 ± 22 ng/ml), respectively.

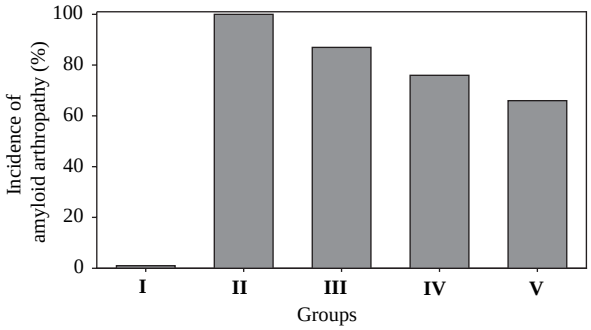

Figure 1. *Amyloid arthropathy occurrence rate (%) according to congo red stain and immunohistochemistry by light microscopy in five groups. I, negative control group; II, vitamin A group; III, positive control group; IV, pentoxyffline group; V, methylprednisolone group.*

Serum retinol findings. A decrease in serum retinol levels was detected in Group II (42.72 ± 3 μg/dl) when compared with Group I (59.75 ± 3.8 μg/dl) and Group III (59.24 ± 3.6 μg/dl), while an increase was detected in both Group IV (102 ± 9.1 μg/dl) and Group V (101.3 ± 12.3 μg/dl)

The comparison of the incidence of amyloid arthropathy occurrence with SAA levels (Figure 5) and serum retinol levels (Figure 6) are presented in Figures 5 and 6.

Haematological findings. An increase in the H/L ratio was observed both in Groups II (0.75) and III (0.75) when compared with the negative control group (0.504), while a decrease in the H/L ratio was observed in Groups IV (0.087) and V (0.44). Figure 7 compares the incidence of amyloid arthropathy with the H/L ratio.

Discussion

There are publications about the possible role of retinol and its active metabolite retinoic acid on transthyretin-related and β-amyloid precursor-related amyloidosis (Lahiri & Nall, 1995; Yang *et al*., 1998; White & Kelly, 2001). On the other hand, there has been only one report examining the role of chronic hypervitaminosis A in type AA amylodosis of animals. The study examined six cats (Clark & Seawright, 1968).

Table 1. *The frequency and severity of amyloid arthropathy in chickens of five groups*[a]

Group	Number of chickens	Amyloid deposition rates			Total
		Mild (+)	Moderate (++)	Severe (+++)	
I, negative control group	35	0/35 (0%)*	0/35 (0%)*	0/35 (0%)*	0/35 (0%)*
II, vitamin A group	35	5/35 (14.28%)*	11/35 (31.42%)**	19/35 (54.28%)*	35/35 (100%)*
III, positive control group	31	5/31 (16%)*	12/31 (39%)*	10/31 (32%)**	27/31 (87%)*
IV, pentoxyfylline group	34	9/34 (26.47%)*	7/34 (21%)*	10/34 (29.41%)**	26/34 (76%)*
V, methylprednisolone group	35	6/35 (17.14%)*	9/35 (26%)**	8/35 (23%)*	23/35 (66%)*

[a]The differences between the groups were calculated for each column separately, and between every two values the statistical significance of the difference is indicated: * – * and * – ** $P < 0.001$ (chi-square), ** – **: $P < 0.05$ (chi-square).

Table 2. *Distribution of different inflammatory cell infiltration in synovial membranes and severity in five groups (%)*[a]

Group	Number of chickens	Heterophil infiltration (%)			Mononuclear cell infiltration					
					Lymhocyte and plasma cell infiltration (%)			Macrophage infiltration (%)		
		Mild (+)	Moderate (++)	Severe (+++)	Mild (+)	Moderate (++)	Severe (+++)	Mild (+)	Moderate (++)	Severe (+++)
I, negative control group	35	0/35 (0%)	0/35 (0%)	0/35 (0%)*	0/35 (0%)	0/35 (0%)	0/35 (0%)*	0/35 (0%)	0/35 (0%)	0/35 (0%)**
II, vitamin A group	35	2/35 (6%)	6/35 (17%)	27/35 (77%)**	4/35 (11%)	9/35 (26%)	22/35 (63%)**	6/35 (17%)	11/35 (31%)	18/35 (51%)*
III, positive control group	31	1/31 (3%)	3/31 (10%)	27/31 (87%)*	0/31 (0%)	10/31 (32%)	21/31 (68%)**	0/31 (0%)	19/31 (61%)	12/31 (39%)*
IV, pentoxyfylline group	34	5/34 (15%)	5/34 (15%)	24/34 (70%)**	0/34 (0%)	19/34 (56%)	15/34 (44%)*	0/34 (0%)	20/34 (59%)	14/34 (41%)*
V, methylprednisolone group	35	7/35 (20%)	6/35 (17%)	22/35 (63%)*	1/35 (3%)	13/35 (37%)	21/35 (60%)*	5/35 (14%)	28/35 (80%)	2/35 (6%)**

[a]Statistical analysis was carried out only for the severe infiltration values. The differences among the groups were calculated for each column separately, and between every two values the statistical significance of the difference is indicated: * – * and * – ** $P < 0.001$ (chi-square), ** – ** $P < 0.05$ (chi-square).

Figure 2. *Occurrence of severe heterophil infiltration (●) and amyloid arthropathy (□) in joints in five groups. I, negative control group; II, vitamin A group; III, positive control group; IV, pentoxyfllline group; V, methylprednisolone group.*

In the present study, the most frequent and the most severe amyloid arthropathy was observed in the vitamin A-treated groups when compared with the positive control group (Table 1). This finding confirmed our previous report (Sevimli *et al*., 2004) that vitamin A increases the severity of *E. faecalis*-induced amyloid arthropathy in brown layer chickens.

It was also observed that the incidence and the severity of amyloid arthropathy was reduced in the pentoxyfilline-treated and methylprednisolone-treated groups when compared with the positive control group (Table 1). Methylprednisolone was found to be more successful in reducing the amyloid arthropathy. There are no previous reports on the use of pentoxyfilline or methylprednisolone for the prevention of amyloid formation.

It has been reported that an increase in serum levels of SAA precedes the formation of amyloidosis (Tape *et al*., 1988). Although SAA-dependent amyloidosis has been studied in a wide variety of mammalian species (Hol & Gruys, 1984), only a few studies have been conducted in chickens to date (Landman *et al*., 1996).

Our results indicated that the serum levels of SAA in experimental groups were significantly higher when compared with the negative control group ($P < 0.001$) and this supports the suggestion that there is a positive correlation between the serum SAA levels and the formation of amyloid arthropathy. It has been demonstrated that retinoids and vitamin A induce cytokines such as IL-1 and TNF-α (Dillahay *et al*., 1988; Turpin *et al*., 1990). Cytokines including IL-1, IL-2, IL-6, TNF-α and M-CSF have been reported to induce

Figure 3. *Occurrence of severe macrophage infiltrations (●) and amyloid arthropathy (□) in joints in five groups. I, negative control group; II, vitamin A group; III, positive control group; IV, pentoxyfllline group; V, methylprednisolone group.*

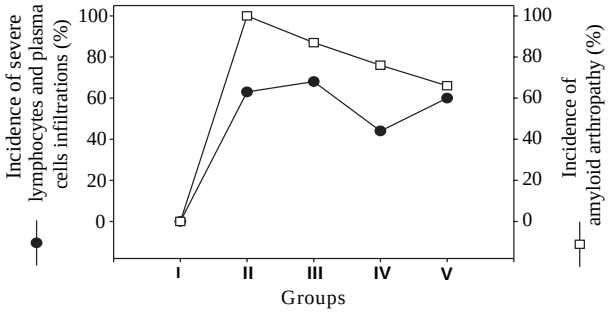

Figure 4. *Lymphocytes and plasma cells infiltration rates (●) and amyloid arthropathy occurrence rates (□) in joints in five groups. I, negative control group; II, vitamin A group; III, positive control group; IV, pentoxyfllline group; V, methylprednisolone group.*

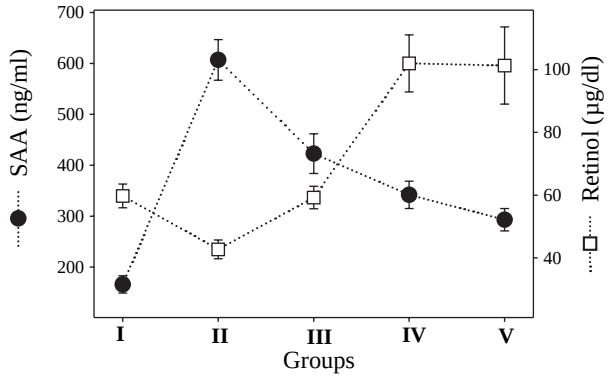

Figure 6. *Serum amyloid A (●) and serum retinol levels (□) in five groups. I, negative control group; II, vitamin A group; III, positive control group; IV, pentoxyfllline group; V, methylprednisolone group.*

hepatic or extrahepatic synthesis of SAA (Rivas *et al*., 1992; Rysava *et al*., 1992; Ray *et al*., 1999). Conversely, the synthesis of cytokines could be inhibited by anti-inflammatory agents. For example, pentoxyfylline has inhibitory effects on TNF-α and lymphokines (Haslet, 1998), whereas methylprednisolone has inhibitory effects on IL-1, IL-2, IL-4, IL-6, IL-10, interferon γ and interferon α, and TNF-α (Pitzalis *et al*., 1997; Wandinger *et al*., 1998; Xu *et al*., 1998; Hodge *et al*., 1999; Stanton *et al*., 1999; Ou *et al*., 2001).

In the present study, the most severe amyloid arthropathy and the highest SAA values were observed in the vitamin A-treated group. The severity of amyloid arthropathy was reduced and the increase in SAA, compared with the negative controls, was not marked in the pentoxyfylline-treated and methylprednisolone-treated groups (Figure 5). The methylprednisolone-dependent decrease in serum SAA level was significantly greater than that of the pentoxyfylline-dependent decrease in serum SAA levels. This might suggest that a wide spectrum of cytokine inhibitors could be effective in preventing amyloidosis.

Some researchers suggest that neutrophils and macrophages play a very important role in the formation of amyloid fibrils (Skogen *et al*., 1980; Hawkins *et al*., 1993; Yamada *et al*., 1996; Zekerias *et al*., 2000). The present study confirmed that there was an association between the intensity and the type of leukocyte infiltration and the incidence and severity of amyloidosis. As shown in Table 2, the highest numbers of macrophages were found in the vitamin A-treated groups and

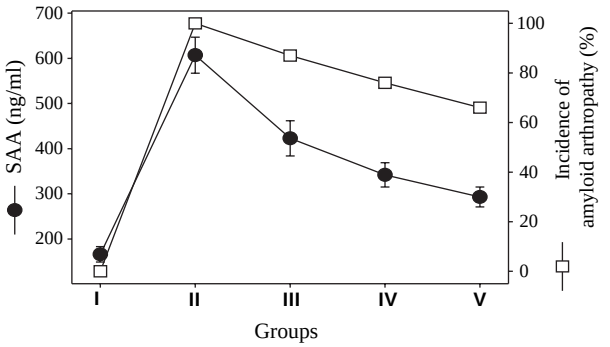

Figure 5. *Serum amyloid A levels (●) and the incidence of amyloid arthropathy occurrence (□) in joints in five groups. I, negative control group; II, vitamin A group; III, positive control group; IV, pentoxyfllline group; V, methylprednisolone group.*

the highest numbers of heterophils were found in the positive control group and vitamin A-treated group, respectively, while the lowest number of macrophages and heterophils were found in methylprednisolone-treated groups. These findings support the involvement of macrophages (Skogen *et al*., 1980) and neutrophils (Phillips *et al*., 1993) in fibrillogenesis.

The findings of the present study support the findings of Turpin *et al*. (1990) who demonstrated that vitamin A increases the number and the activity of macrophages. Furthermore, this study also confirmed that methylprednisolone inhibits the mononuclear cell infiltration (Ou *et al*., 2001) and suppresses the migration of neutrophils (Pitzalis *et al*., 1997; Hodge *et al*., 1999).

There have been conflicting reports about the effects of pentoxyfylline on the migration of neutrophils into tissues (Besler *et al*., 1986; Boogaerts *et al.*, 1990; Elferink *et al*., 1997; Hodge *et al*., 1999). In the present study, it was found that the number of heterophils was significantly lower in the pentoxyfylline-treated group than in the positive control group.

Thus, findings in this study were in agreement with the findings of Boogaerts *et al*. (1990) and Elferink *et al*. (1997), whereas they were not in agreement with the findings of Besler *et al*. (1986) and Hodge *et al*. (1999) regarding the effect of pentoxyfylline on heterophils.

When pentoxyfylline and methylprednisolone were compared, it was found that methyprednisolone significantly inhibits fibrillogenesis by lowering both heterophil and macrophage infiltration, while pentoxyfylline failed to prevent fibrillogenesis and migration of macrophages, although it inhibited heterophil infiltration into the tissues.

In this study, the role of lymphocyte and plasma cell infiltration into the joints was investigated but no correlation was found between the formation of amyloid and the presence of lymphocytes or plasma cells.

It is widely known that the number of heterophil leucocytes and monocytes increase in a bacterial infection and that these cells synthesize cytokines (Latimer *et al*., 1988; Andreasen *et al*., 1991; Kogut *et al*., 1994). In this study, the findings of high H/L ratio and its association with the formation of amyloid in both vitamin A and positive control groups supported the findings of Zekerias *et al*. (2000), who found a positive correlation between the numbers of heterophils in peripheral blood and amyloid occurrence.

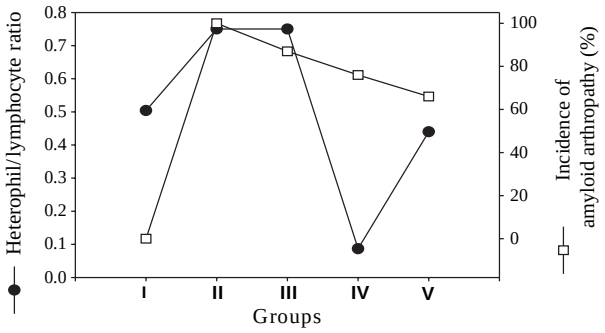

Figure 7. *H/L ratio (●) and amyloid arthropathy occurrence rates (□) in joints in five groups. I, negative control group; II, vitamin A group; III, positive control group; IV, pentoxyfilline group; V, methylprednisolone group.*

Some researchers observed that low plasma retinol concentrations were associated with elevated acute-phase protein concentration, especially with that of serum amyloid A (Thurnham *et al*., 2003). In this study, it was indicated that there was a negative association between the serum retinol levels and SAA levels and also amyloid deposition in tissues. Therefore, it is suggested that as tissue amyloid deposits form, vitamin A passes into the tissues and integrates into the amyloid. Landman *et al*. (1994) suggested that coloration of amyloid in the joints is because of retinoids in the amyloid.

It has also been reported that pentoxyfylline (Berman & Duncan, 1989; Aulthouse *et al*., 1992; Chang *et al*., 1993) and methylprednisolone (Laato *et al*., 1989) have inhibitory effects on the synthesis of proteoglycans, glycosaminoglycans, collagen IV and fibronectin determined in amyloid (Skogen *et al*., 1980; Lyon *et al*., 1991; Gallo *et al*., 1994; Ancsin & Kisilevsky, 1997; Landman *et al*., 1998b).The role of pentoxyfylline and methylprednisolone in the prevention of amyloidosis should further be investigated.

The findings of this study and the reports by Aulthouse *et al*. (1992) and Margis *et al*. (1992) suggest that the effects of vitamin A on the synthesis of glycosaminglycan and fibronectin and its relationship with amyloidosis should further be investigated.

In conclusion, vitamin A increased the development and severity of Freund's adjuvant-stimulated amyloid arthropathy by increasing the levels of SAA, and there is a positive association between the severity of amyloidosis and the rate of macrophage and heterophil migration into the tissue. On the other hand, methylprednisolone and pentoxyfylline suppressed amyloidosis by decreasing serum SAA levels. Methylprednisolone suppressed amyloidosis better than pentoxyfylline.

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Translations of the abstract in French, German and Spanish are available on the *Avian Pathology* website.

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Non-English Abstracts

The effects of vitamin A, pentoxyfylline and methylprednisolone on experimentally induced amyloid arthropathy in brown layer chicks

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Il a été étudié les effets de la vitamine A, de la pentoxyfylline et de la méthylprednisolone sur l'arthropathie amyloïde induite expérimentalement. Pour cette étude, 175 futures pondeuses rousses âgées d'un jour ont été utilisées. Tout au long de l'étude, le groupe II (vitamine A) a reçu des doses élevées en vitamine A (75,000 IU/kg), alors que les groupes I (témoin négatif), III (témoin positif), IV (pentoxyfylline) et V (méthylprednisolone) recevaient des niveaux normaux de vitamine A dans l'alimentation. A la cinquième semaine, les groupes expérimentaux II, III, IV et V ont reçu par voie intra articulaire de l'adjuvant de Freund pour induire l'arthropathie amyloïde. Le groupe IV a reçu de la pentoxyfylline et le groupe V a reçu une fois de la methylprednisolone [10 mg/kg, par voie intramusculaire (i.m.)]. Des échantillons d'articulation et de sang ont été étudiés 13 semaines après les injections. Les valeurs obtenues dans les groupes I, II, III, IV et V ont été respectivement les suivantes : - formation d'arthropathie amyloïde (en %) 0, 100, 87, 76, 66; - sérum amyloïde A (SAA) (ng/ml) 166 ± 17, 607 ± 40, 423 ± 39, 342 ± 27, 293 ± 22; - les teneurs du sérum en rétinol (μg/dl): 59,75 ± 3,8, 42,72 ± 3, 59,24 ± 3,6, 102 ± 9,1, 101,3 ± 12,3; - rapport hétérophiles/lymphocytes (H/L) 0,504, 0,75, 0,75, 0,087, 0,44.
En conclusion, il a été observé que la vitamine A augmentait le développement de l'arthropathie amyloïde et qu'il y avait des associations positives entre l'amyloïdose, les niveaux élevés du SAA et l'augmentation des nombres de tissus infiltrés par les macrophages. La méthylprednisolone a eu un effet plus satisfaisant sur l'arthropathie amyloïde que la pentoxyfylline.

Es wurden die Wirkungen von Vitamin A, Pentoxyfyllin und Methylprednisolon auf eine experimentell induzierte amyloide Gelenkserkrankung untersucht. In dieser Studie wurden 175 braune Legehennen-Eintagsküken verwendet. Während der Untersuchungen erhielt Gruppe II (Vitamin A) hohe Dosen von Vitamin A (75.000 IU/kg), wohingegen die Gruppen I (Negativkontrolle), III (Positivkontrolle,) IV (Pentoxyfyllin) und V (Methylprednisolon) normale Vitamin A-Gehalte im Futter hatten. In der fünften Woche wurde den Versuchsgruppen II, III, IV und V zur Auslösung einer amyloiden Arthropathy Freundsches Adjuvans intraartikular injiziert. Einmalig erhielten Gruppe IV Pentoxyfyllin und Gruppe V Methylprednisolon (10 mg/kg intramuskulär (i.m.)). 13 Wochen nach den Injektionen wurden Gelenks- und Blutproben untersucht. Die Werte in den Gruppen I, II, III, IV und V waren folgendermaßen: Ausbildung amyloider Gelenksveränderungen (%): 0, 100, 87, 76, 66; Serumamyloid A (SAA) (ng/ml): 166 ± 17, 607 ± 40, 423 ± 39, 342 ± 27, 293 ± 27, 293 ± 22; Serumretinol (g/dl: 59,75 ± 3,8, 42,72 ± 3, 59,24 ± 3,6, 102 ± 9,1, 101,3 ± 12,3; Verhältnis von Heterophilen/Lymphozyten (H/L): 0.504, 0.75, 0.75, 0.087, 0.44.
Zusamenfassend kann festgestellt werden, dass Vitamin A die Entwicklung einer amyloiden Arthropathy verstärkte und dass es einen positiven Zusammenhang zwischen Amyloidose, erhöhter SSA-Werte und erhöhter Anzahl Gewebe infiltrierender Makrophagen gab. Methylprednisolon hatte einen stärkeren inhibitorischen Effekt auf die amyloide Arthropathy als Pentoxyfyllin.

Se investigaron los efectos de la vitamina A, la pentoxifilina y la metilprednisolona en una artropatía amiloidea inducida experimentalmente. En este estudio, se utilizaron 175 pollitas rubias de un día de edad. A lo largo del estudio, el Grupo II (vitamina A) recibió altas dosis de vitamina A (75,000 IU/kg), mientras que los Grupos I (control negativo), III (control positivo), IV (pentoxifilina) y V (metilprednisolona) recibieron

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niveles normales de vitamina A en la dieta. A la quinta semana, los grupos experimentales II, III, IV y V fueron inyectados con adyuvante de Freund's intra-articularmente para inducir artropatía amiloidea. El Grupo IV recibió pentoxifilina y el Grupo V recibió metilpredinisolona [10 mg/kg, intramuscularmente (i.m.)] una vez. Se examinaron muestras de articulación y sangre a las 13 semanas. Los valores de los Grupos I, II, III, IV y V, respectivamente fueron los siguientes: desarrollo de artropatía amiloidea (%): 0, 100, 87, 76, 66; amiloide sérico A (SAA) (ng/ml): 166 ± 17, 607 ± 40, 423 ± 39, 342 ± 27, 293 ± 22; retinol sérico (μg/dl): 59.75 ± 3.8, 42.72 ± 3, 59.24 ± 3.6, 102 ± 9.1, 101.3 ± 12.3; proporción heterófilo/linfocito (H/L): 0.504, 0.75, 0.75, 0.087, 0.44. En conclusión, se observó que la vitamina A favorecía el desarrollo de artropatía amiloidea y hubo una asociación positiva entre amiloidosis, niveles de SAA incrementados e incremento de los números de los macrófagos infiltrando el tejido. La metilprednisolona tuvo un efecto inhibitorio mucho mayor que la pentoxifilina en la artropatía amiloidea.