Case Report

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Evaluation of Treatment with a Combination of Prednisolone and Mycophenolate Mofetil for Dogs with Immune-Mediated Polyarthritis

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Abstract Immune-mediated polyarthritis (IMPA) is an inflammatory, noninfectious disease that affects two or more joints in dogs. Immunosuppressive doses of prednisolone are considered the initial treatment choice for dogs with IMPA. However, few reports have described the combination of mycophenolate mofetil and prednisolone for treating dogs with IMPA. In this report, we described the cases of three dogs treated with a combination of mycophenolate mofetil and prednisolone. The clinical signs were alleviated in all cases, and C-reactive protein levels were reduced after treatment. Our results show that combination therapy of mycophenolate mofetil and prednisolone is effective in managing IMPA. However, careful monitoring of the potential adverse effects, including sporadic infections and metabolic diseases, is necessary. In addition, screening tests and appropriate treatments are necessary for proteinuria, a common complication in dogs with IMPA.

Key words dog, immune-mediated polyarthritis, mycophenolate mofetil, prednisolone, lameness.

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Introduction

Immune-mediated polyarthritis (IMPA) is an inflammatory, non-infectious disease that affects two or more joints in dogs (6,17). The underlying pathology of IMPA is considered a type III hypersensitivity reaction in which immune complexes are formed and deposited in the synovial joint in response to immunological stimulation (3,6,12). Immunosuppressive doses of prednisolone (PDS) are commonly used as the standard treatment for primary IMPA (12,17). A previous study reported that the immunosuppressive dose of PDS induced an initial response in 81% of dogs with primary IMPA (3). However, long-term and high-dose PDS may cause adverse effects, which may debilitate animals and reduce their quality of life (17). Therefore, alternative immunosuppressive therapy for IMPA has been studied (4,5,22). Leflunomide, an alternative immunosuppressive drug, monotherapy was evaluated in 14 dogs; eight dogs achieved complete resolution (CR) and five dogs achieved partial resolution (4). Cyclosporine with PDS was also evaluated in 10 dogs, among which seven achieved CR (22). Two studies have reported that the combination of PDS with cyclosporine or leflunomide monotherapy had similar efficacy to PDS monotherapy (4,22). Mycophenolate mofetil (MMF), a prodrug of mycophenolic acid, an inhibitor of inosine 5′-monophosphate dehydrogenase, is a widely used immunosuppressive agent in veterinary medicine (13). The most common adverse effects of MMF are gastrointestinal diseases, including diarrhea, anorexia, and vomiting (8). To the best of our knowledge, there has been only one case report of successful treatment with a combination of MMF and PDS in a dog with IMPA (5). This report describes the clinical course of three dogs diagnosed with IMPA and treated with a combination of PDS and MMF.

Case Report

Case 1

A 10-year-old neutered female Maltese dog presented with a 7-day history of abdominal pain, hyporexia and reluctant to walk. Physical examination revealed systemic hypertension (180 mmHg), fever (39.4°C), and sticky mucous membrane. There were no clinical signs and symptoms of joint inflammation such as heat, pain, or swelling during palpation of thoracic and pelvic limb joints. Complete blood cell count (CBC; IDEXX ProcyteDx, IDEXX Laboratories, Inc., Westbrook, ME, USA) results were all within the reference range, except for non-regenerative anemia (hematocrit of 34.7%, reference interval [RI]: 37.3-61.7; reticulocyte of 47.7 $\times$ 10^9/L, RI: 10-110 $\times$ 10^9/L). Serum biochemistry (IDEXX Catalyst One chemistry analyzer, IDEXX Laboratories, Inc., Westbrook, ME, USA) and blood gas analysis (pHOxUltra, Nova Biomedical, USA) revealed no abnormalities, except for an elevated C-reactive protein (CRP) level (5.9 mg/dL, RI: 0.1-1). Urinalysis revealed an increased urine protein creatinine (UPC) ratio (0.59; RI <0.2). Radiography (XPLRER-900, Medien International Co. Ltd., Anyang, Korea) and ultrasonography (Philips Ultrasound, Bothell, WA, USA) revealed no abnormalities. In all performed tests, the cause of the patient's elevated CRP and clinical signs could not be determined. Therefore, arthrocentesis was performed initially to rule out the cause of fever of unknown origin. Synovial fluid samples were obtained from bilateral elbow, stifle, and carpal joints. Although there were no clinical symptoms of joint inflammation on physical examination, synovial fluid from right stifle and bilateral carpal joints appeared to have slightly decreased viscosity and exhibited a yellowish, cloudy appearance. In the cytologic examination of the affected synovial fluid, the average number of cells per field at 400x was 33 cells (RI <3 cells) and the average proportion of non-degenerative neutrophil was 94% (RI <10%) (Fig. 1A).

The results of synovial fluid culture and polymerase chain reaction (PCR), antinuclear antibody titers, and rheumatoid factor test were negative. Based on these findings, the dog was diagnosed with IMPA. PDS (Solondo®, Yuhan, Seoul, Korea; 1 mg/kg, q 12 h, PO), MMF (CellCept®, Roche, Seoul, Korea; 10 mg/kg, q 12 h, PO), and benazepril (Benacil® Ashish Life Science, Thane, India; 0.25 mg/kg, q 24 h, PO) were prescribed for medical management of IMPA and proteinuria. The abdominal pain and lameness gradually improved and resolved on day 9. The dog underwent a physical examination and serum chemistry

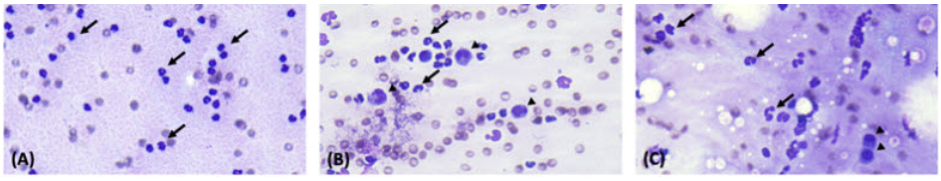


Fig. 1. Images of microscopic examination of synovial fluid. Neutrophilic pleocytosis is observed in case 1 (A), case 2 (B), and case 3 (C) with Diff-Quik ×100. Neutrophils (arrows) and monocytes (arrowheads) are identified on the synovial fluid smear.

recheck after 14 days. CRP levels declined to the normal reference range (Fig. 2A). After achieving CR, the PDS dose was gradually reduced by approximately 25% every 3 weeks. Tapering started on day 62, and on day 147, the PDS dose was decreased to 0.3 mg/kg PO q 24 h. Despite the resolution of IMPA, the UPC ratio gradually increased, benazepril dose was increased to 0.5 mg/kg PO q 24 h on day 91, and telmisartan (Telmisartan Ilyang, Gyeonggi, Korea; 0.5 mg/kg, q 24 h, PO) was added on day 174 (Fig. 3A). The UPC ratio normalized after combining these two drugs on day 219 and no longer increased during the follow-up period. The dog neither showed clinical signs of IMPA nor experienced a relapse during the 11-month follow-up period. At the last follow-up, the dog was receiving PDS at a dosage of 0.3 mg/kg PO every other day and MMF at a dosage of 10 mg/kg PO q 12 h for the management of IMPA. In addition, for the management of proteinuria, the dog was taking benazepril at a dosage of 0.5 mg/kg PO q 24 h and telmisartan at a dosage of 0.5 mg/kg PO q 24 h.

Case 2

A 13-year-old neutered male Shit-Tzu dog presented with a 6-month history of lameness. There were clinical signs and symptoms of joint inflammation such as heat, pain, and swelling during palpation of the bilateral carpal, elbow, and left tarsal joints. CBC results were all within the reference range, except for thrombocytosis (450×10^9/L, RI, 143.3-400). Serum biochemistry and blood gas analysis revealed no abnormalities except for an elevated CRP level (4 mg/L). The complete urinalysis results were normal. Radiography and ultrasonography revealed no abnormalities except bilateral carpal, elbow, and left tarsal joint swelling. Synovial fluid samples obtained from the bilateral elbow, carpal, tarsal, and stifle joints were analyzed using a smear examination. The synovial fluid in the bilateral carpal and left tarsal joints appeared to have slightly decreased viscosity and exhibited a white, cloudy appearance. In the cytologic examination of the affected synovial fluid, the average number of cells per field at 400x was 30 cells (RI <3 cells) and the average proportion of non-degenerative neutrophil was 90% (RI <10%) (Fig. 1B). The results of synovial fluid culture and PCR, antinuclear antibody titers, and rheumatoid factor test were negative. Based on these findings, the dog was diagnosed with IMPA. PDS (1 mg/kg, q 12 h, PO) and MMF (10 mg/kg, q 12 h, PO) were initially prescribed.

The lameness resolved, and CRP levels declined to the normal reference range 28 days after the initial presentation (Fig. 2B). After achieving CR, the PDS dose was gradually reduced by approximately 25% every 3 weeks. Tapering started on day 87, and on day 114, the PDS dose was decreased to 0.25 mg/kg PO q 24 h. 209 days after the initial diagnosis, the patient was diagnosed with diabetic ketoacidosis (DKA). The patient discontinued PDS and managed IMPA solely with MMF. On day 304, bacterial skin infections and demodicosis were newly diagnosed and managed with appropriate treatment. During the 20-month follow-up period, no clinical signs of IMPA were observed, and no relapse occurred. At the last follow-up, the dog was receiving MMF at a dosage of 10 mg/kg PO q 12 h for the management of IMPA.

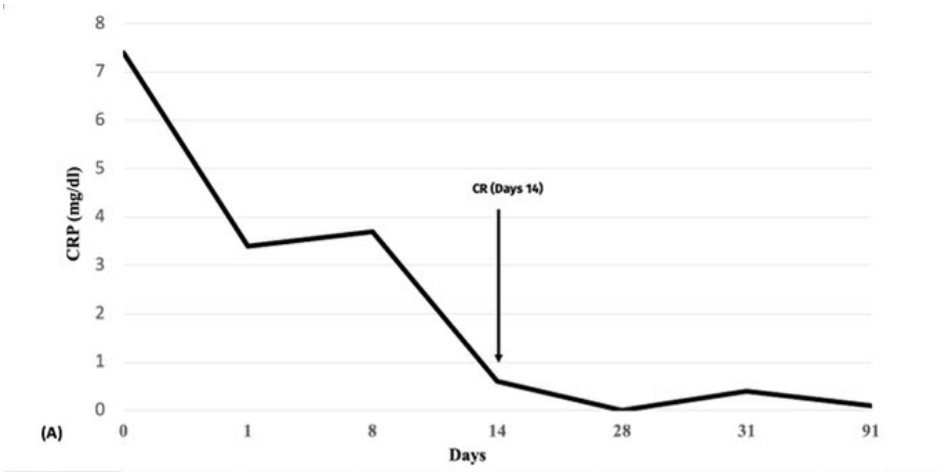
Case 3

A 7-year-old neutered female poodle dog presented with a 5-day history of hyporexia, lethargy, and lameness. Physical examination revealed enlarged prescapular and popliteal lymph nodes. There were clinical signs and symptoms of joint inflammation such as pain and swelling during palpation of the bilateral stifle and right carpal joints. CBC results were all within the reference range, except for thrombocytopenia (143×10^9/L). Serum biochemistry and blood gas analysis revealed no abnormalities except for an elevated CRP level (9.8 mg/L). Urinalysis was not performed during the initial presentation. Radiography and ultrasonography revealed no abnormalities except bilateral stifle and right carpal joint swelling.

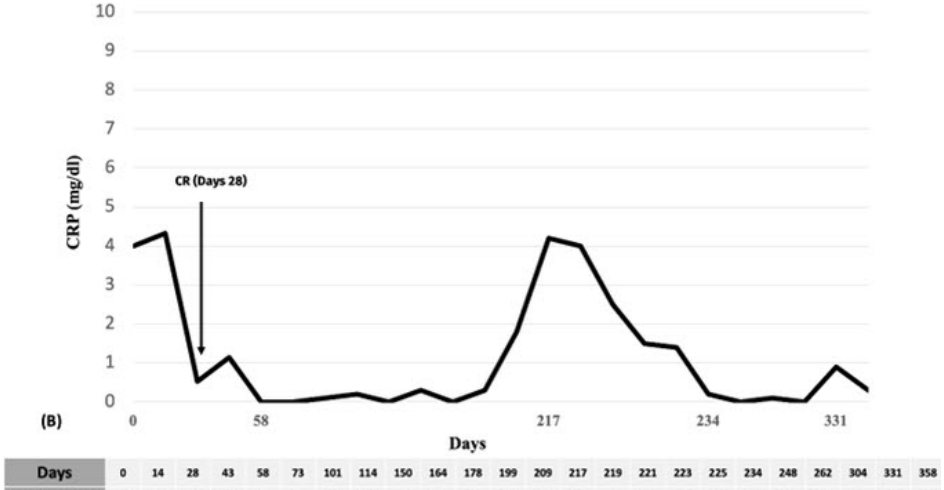
Complete urinalysis performed on day 109 showed an elevated UPC ratio of 1.12. Synovial fluid samples obtained from the bilateral shoulder, carpal, elbow, and stifle joints were analyzed using a smear examination. The synovial fluid in the carpal and stifle joints appeared to have slightly decreased viscosity and exhibited a white, cloudy appearance. In the cytologic examination of the affected synovial fluid, the average number of cells per field at 400x was 18 cells (RI <3 cells) and the average proportion of non-degenerative neutrophils was 88% (RI <10%) (Fig. 1C). The results of synovial fluid culture and PCR, antinuclear antibody titers, and rheumatoid factor test were negative. Based on these findings, the dog was diagnosed with IMPA.

PDS (1 mg/kg, q 12 h, PO), MMF (10 mg/kg, q 12 h, PO), and benazepril (0.5 mg/kg, q 24 h, PO) were prescribed for medical management of IMPA and proteinuria. After 11 days of treatment, the CRP level declined to the normal reference range, and the lameness completely resolved (Fig. 2C). However, on day 53, mild elevation of the CRP level (2.4 mg/L) and slight lameness were observed. Melatonin (Circadin®, KUHNIL, Seoul, Korea; 2 mg/kg, q 12 h, PO) was added to the treatment, and the CRP level returned to normal, while the lameness resolved within 2 weeks.

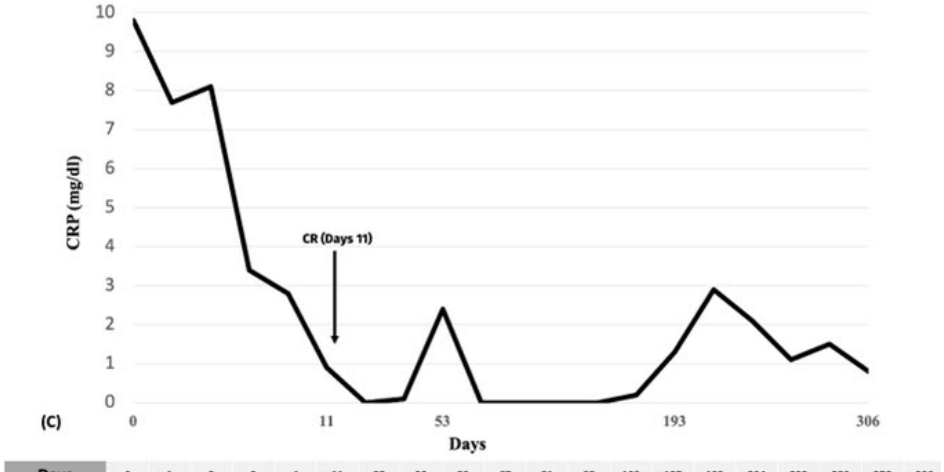
After achieving CR, the PDS dose was gradually reduced by approximately 25% every 4 weeks. Tapering started on day 81, and on day 137, the PDS dose was decreased to 0.25 mg/kg PO



Days	0	1	8	14	28	31	91
CRP(mg/dl)	7.4	3.4	3.7	0.6	0	0.4	0.1

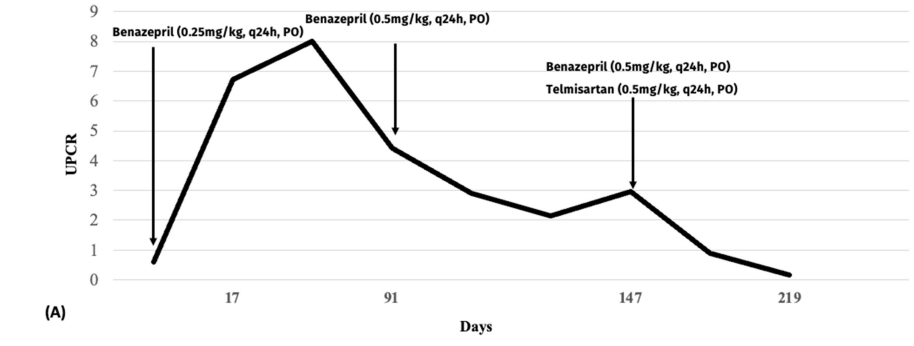


Days	0	14	28	43	58	73	101	114	150	164	178	199	209	217	219	221	223	225	234	248	262	304	331	358
CRP(mg/dl)	4	4.33	0.53	1.14	0	0	0.1	0.2	0	0.3	0	0.3	1.8	4.2	4	2.5	1.5	1.4	0.2	0	0.1	0	0.9	0.3

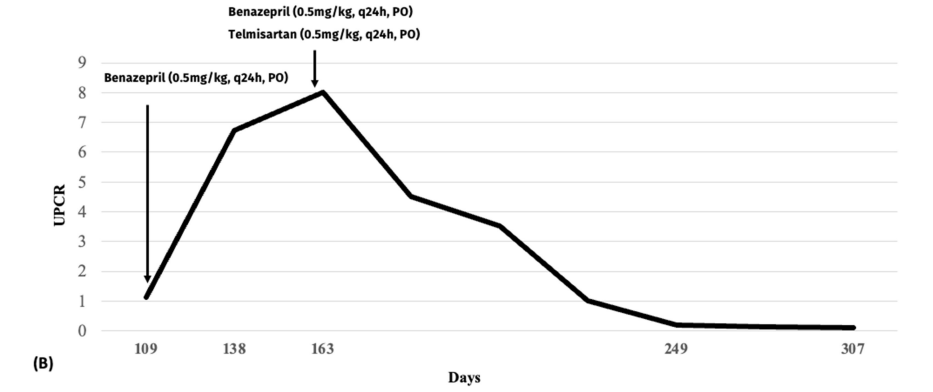


Days	0	1	2	3	4	11	25	39	53	67	81	95	109	137	193	204	222	250	278	306
CRP(mg/dl)	9.8	7.7	8.1	3.4	2.8	0.9	0	0.1	2.4	0	0	0	0	0.2	1.3	2.9	2.1	1.1	1.5	0.8

Fig. 2. Changes in CRP levels after treatment with PDS and MMF in case 1 (A), case 2 (B), and case 3 (C). The median time to CR was 14 days (range, 11-28 days).



Days	0	17	31	91	113	127	147	197	219
UPCR	0.59	6.72	8	4.43	2.91	2.14	2.97	0.89	0.17



Days	109	138	163	181	195	206	249	279	307
UPCR	1.12	6.72	8	4.5	3.53	1.01	0.19	0.15	0.12

Fig. 3. Changes in UPC ratio after treatment with benazepril or telmisartan in case 1 (A), and case 3 (B). The combination of benazepril and telmisartan achieved CR of proteinuria in both cases.

q 24 h. Despite the prescription of benazepril, the UPC ratio increased to 8 on day 163, likely due to IMPA or glucocorticoid-related proteinuria (Fig. 3B). Telmisartan (0.5 mg/kg, q 24 h, PO) was added to the treatment on day 163. Proteinuria resolved after administration of the combination of the two drugs on day 249. The dog neither showed clinical signs of IMPA nor experienced a relapse during the 17-month follow-up period. At the last follow-up, the dog was receiving PDS at a dosage of 0.3 mg/kg PO q 24 h and MMF at a dosage of 10 mg/kg PO q 12 h for the management of IMPA. In addition, for the management of proteinuria, the dog was taking benazepril at a dosage of 0.5 mg/kg PO q 24 h and telmisartan at a dosage of 0.5 mg/kg PO q 24 h.

Discussion

IMPA is characterized by synovial inflammation and failure to identify a microbial etiology in the routine culture of synovial fluid and clinical response to immunosuppressive therapy (6,7). IMPA is diagnosed based on medical history, blood analysis, synovial fluid analysis, urinalysis, and diagnostic imaging (6,7,12,17). Elevated CRP levels are commonly observed in blood analyses (7,12,17,24). As in the previous study, the increase and decrease of CRP were associated with clinical signs of IMPA (19). Synovial fluid may be turbid, with decreased viscosity and increased volume. Cytological evaluation reveals neutrophilic inflammation without any evidence of infection (7,14,17). All dogs in the present report were diagnosed with primary IMPA by ruling out underlying diseases that cause reactive polyarthritis.

In general, adjuvant immunosuppressant therapy is initiated due to a patient's lack of response to treatment, to reduce adverse effects of PDS therapy, or due to a patient's severe clinical presentation (18,25). In the present report, a combination of PDS and MMF was administered to manage primary IMPA. Responses to treatment can be evaluated through

the alleviation of clinical signs, reduction of inflammatory cells in the synovial fluid, and a decline in CRP level (3,6,12,18). In this case report, CR was defined as the sustained alleviation of clinical signs and normalization of CRP levels. The treatment response was evaluated based on the decrease in CRP levels and the alleviation of clinical signs. No repetitive arthrocentesis was performed. All three dogs treated with a combination of PDS and MMF showed CR of IMPA. The duration to achieve CR in the three dogs was 14, 28, and 11 days, respectively. PDS tapering was initiated on days 62, 87, and 81, respectively. All three dogs achieved CR during the treatment period, and appropriate management was provided during the follow-up period. Based on these findings, it was confirmed that combination therapy of MMF and PDS is effective in treating IMPA.

During the treatment period, few adverse effects were observed. In the present report, sporadic infections occurred in cases 2 and 3, and DKA occurred in case 2. It is well-known that long-term immunosuppressive therapy increases the risk of spontaneous infections (17,25). Urinary tract infection and skin infection are commonly associated with immunosuppressive therapy (11,15). Additionally, long-term use of PDS is known to increase insulin resistance (16). In case 2 of the present report, the clinical signs of DM were masked by the polyuria, polydipsia, and polyphagia associated with PDS therapy (16). Thus the diagnosis of DM was delayed, leading to the progression of the condition to DKA. However, successful recovery without recurrence of IMPA was achieved through discontinuation of PDS and appropriate management for diabetes. Thus, regular check-up and immediate management for sporadic infections and metabolic derangements during multi-agents immunosuppressive therapy in IMPA patients appear to be of utmost importance.

In case 3 in the present report, the elevation of CRP levels and lameness, suspected of relapse, occurred during the PDS tapering period. The increase in CRP levels and lameness was mild. The PDS dose was not increased owing to concerns of PDS-induced polyuria and polydipsia, and melatonin was prescribed to manage the relapse. The relapse was successfully managed by adding melatonin without increasing the PDS dose. In this case, melatonin was used as an immune modulator to manage the IMPA relapse. Melatonin is important in the immune response to diseases (2). Previous studies have reported conflicting data on melatonin's mechanism of action (2). One study reported that melatonin upregulates the production of proinflammatory cytokines, such as interleukin-2 (IL-2) and interferon-γ (INF-γ) (9). However, another study reported a decreased production of these cytokines (23). Recently, a study that evaluated melatonin administration in dogs reported that melatonin therapy does not affect IL-2 or IFN-γ expression in healthy dogs (20). The use of melatonin is controversial because consistent evidence for its clinical efficacy in dogs is lacking (2,20,21). In case 3 in the present report, the addition of melatonin seemed to modulate IMPA effectively. However, a large-scale case-control study is required to demonstrate melatonin's effectiveness in treating IMPA.

Proteinuria is common in dogs with IMPA (24). The cause of proteinuria in dogs with IMPA is not fully understood. However, it is believed to be associated with a type III hypersensitivity reaction, where immune complexes deposit within the nephrons leading to glomerular nephropathy. This process is similar to the pathogenesis of immune complexes forming within the joints in IMPA (3). However, it should be noted that PDS, which is commonly used for the treatment of IMPA, can induce proteinuria and glomerular changes in dogs (26). Recent studies have shown that proteinuria occurs more frequently in dogs with IMPA, and significant proteinuria is completely resolved after resolution of IMPA despite PDS treatment (1,24). This suggested that PDS therapy might worsen proteinuria but resolves it by treating the underlying diseases (1,10). However, in this report, none of the two dogs with proteinuria responded to treatment for IMPA and proteinuria was successfully resolved with additional medications, and it was well managed until the last follow-up. Therefore, in the management of proteinuria in dogs with IMPA, regular monitoring and the addition of appropriate drugs for proteinuria such as benazepril and telmisartan might be helpful.

Conclusions

This report shows that combination therapy with PDS and MMF significantly affects IMPA. However, given the occurrence of adverse effects in two of the three cases, careful monitoring of potential adverse effects is necessary when using this combination therapy. Further studies are required to compare the superiority of combination therapy over PDS monotherapy.

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Conflicts of Interest

The authors have no conflicting interests.

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