

Retrospective evaluation of combined mycophenolate mofetil and prednisone treatment for meningoencephalomyelitis of unknown etiology in dogs: 25 cases (2005–2011)

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Abstract

Objective – To evaluate the use of a combined protocol of prednisone and mycophenolate mofetil (MMF) for the treatment of meningoencephalomyelitis of unknown etiology (MUE) and to describe response, adverse effects, and outcome.

Design – Retrospective study (2005–2011).

Setting – University teaching hospital.

Animals – Twenty-five client-owned dogs with clinical signs, neuroimaging, and cerebrospinal abnormalities consistent with MUE. Five dogs whose MMF treatment was discontinued after 7–14 days due to gastrointestinal clinical signs were evaluated only for adverse effects.

Interventions – Dogs were initially treated with prednisone 2 mg/kg PO every 12 hours and with MMF 20 mg/kg PO or IV every 12 hours. Prednisone was tapered after 4 days to 1 mg/kg every 12 hours for 14 days, then to every 24 hours for 30 days, and again reduced by half every 2–4 months thereafter. When prednisone was tapered completely or to 0.5 mg/kg every 24–48 hours without clinical relapse, MMF was tapered in a similar manner.

Measurements and Main Results – Partial or complete clinical response was achieved in 95% (19/20) of the dogs. Median survival time by the end of the study was 250 days (range 6 to >1,679) with 40% (8/20) of the dogs still alive (336–1,679 days after diagnosis). All Pug dogs (4/20) included in the study died with a median survival time of 14 days. Adverse effects attributed to MMF, which included hemorrhagic diarrhea within the first 2 weeks of treatment, were recorded in 20% (5/25) of the dogs.

Conclusions – MMF can be used as an adjunctive treatment for dogs with MUE. This protocol enables reduction of prednisone treatment or, in some cases, its complete withdrawal. The possibility of intravenous administration is advantageous in cases with severe neurological abnormalities and mentation changes, often seen in MUE. Attention is warranted for gastrointestinal adverse effects, especially in the first 2 weeks of treatment.

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Keywords: canine, CNS disease, inflammatory brain disease, meningoencephalitis, MUE

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Abbreviations

CT	computed tomography
GME	granulomatous meningoencephalomyelitis
IMPDH	inosine monophosphate dehydrogenase
MMF	mycophenolate mofetil
MST	median survival time
MUE	meningoencephalomyelitis of unknown etiology

NLE	necrotizing leukoencephalitis
NME	necrotizing meningoencephalitis

Introduction

Nonsuppurative inflammatory CNS disorders of unknown etiology are relatively common in dogs.¹ The inflammatory process in the CNS may be diffuse, focal, or multifocal, and may present as encephalitis, myelitis, meningitis, or combinations thereof.¹ Granulomatous meningoencephalomyelitis (GME), necrotizing meningoencephalitis (NME), and necrotizing leukoencephalitis (NLE) have been frequently reported among such disorders.²

Diagnosis and classification of the various types of noninfectious meningoencephalitis is challenging. GME has no defined breed or gender specificity. It is characterized by multifocal perivascular angiocentric mononuclear cell accumulations, most often located in the cranial cervical spinal cord, brainstem, cerebellum, and mid-brain and usually with less severe rostral extension into the hemispheric white matter. NME has been reported in various dog breeds, including the Pug and Maltese. It is characterized by multiple bilateral asymmetric foci of either acute encephalitis with mononuclear infiltration and perivascular cuffing, or more chronic malacia and necrosis mainly affecting the hemispheric gray matter, adjacent white matter, and leptomeninges. NLE, which has been described in Yorkshire Terrier, French Bulldog, and Pomeranian dogs, is characterized by multifocal bilateral asymmetric malacic necrotizing lesions in the hemispheric white matter and brainstem, mononuclear infiltration, and perivascular cuffing.³

All of these diseases typically present with an abrupt onset of progressive CNS clinical signs. Young adult toy and other small breed dogs are most commonly affected. Age, sex, and breed cannot be used to differentiate between the diseases. Diagnostically, they share similar characteristics in CSF analysis and advanced imaging.

The term meningoencephalomyelitis of unknown etiology (MUE) refers to a probable meningoencephalomyelitis in which an infectious cause has not been identified and that lacks a histopathological diagnosis.^{1,4-6} This term is broadly used because definitive antemortem diagnosis of the underlying disorder is unlikely without a biopsy, which is infrequently obtained. Although the above-mentioned diseases are classified separately, they are all hypothesized to result from aberrant immune-mediated responses directed against CNS constituents.¹

Aggressive immunosuppression is the current mainstay therapy for these diseases. Various prednisone-based protocols have been reported, either as single-drug

therapy or in combination with other immunosuppressive agents.⁵⁻¹¹ Most of these previous reports are retrospective studies with limited numbers of cases and indefinite diagnoses; therefore, a single, specific therapeutic protocol has not yet been established. Recent studies report inconsistent results regarding the benefit of combined treatment using prednisone and other immunosuppressive drugs, as compared to prednisone alone.^{7,12} However, it is generally accepted that the addition of other immunosuppressive agents to prednisone is beneficial because this allows for reduction of prednisone dose and, consequently, of its adverse effects.^{1,7} As some dogs' clinical signs do not respond to the currently used protocols, the search for other therapeutic options continues.

Mycophenolate mofetil^a (MMF) is an ester prodrug of mycophenolic acid.¹³ It has multiple immunosuppressive effects, the most characterized of which is the selective inhibition of the purine biosynthesis enzyme inosine monophosphate dehydrogenase (IMPDH). This enzyme has 2 isoforms. Type I IMPDH is widely distributed in body tissues, whereas the expression of type II IMPDH dramatically increases in activated T and B lymphocytes. Type II IMPDH has been shown to be nearly 5-fold more sensitive to MMF inhibition relative to type I IMPDH, suggesting that MMF specifically interferes with activated lymphocytes.^{13,14} Lymphocyte specificity is also achieved via the MMF mechanism of action. Purine is generated by 2 primary mechanisms, namely de novo and salvage pathways. The first depends on IMPDH activity, whereas the second does not. Lymphocytes are completely dependent on de novo purine synthesis; therefore, inhibition of IMPDH by MMF results in guanosine nucleotide depletion, mostly in B and T lymphocytes, leading to decreased DNA production and a cytostatic effect.^{13,15,16}

MMF has been used in veterinary medicine for treatment of acquired myasthenia gravis,¹⁵ aplastic anemia,¹⁷ and immune-mediated hemolytic anemia.¹⁸ Its beneficial effect in canine MUE was first suggested by Dewey in 2003,¹⁹ followed by a 5-dog case series,^b but it has yet to be assessed in a larger-scale study. The aims of this study were to assess the use of a combined prednisone-MMF protocol for the treatment of MUE in dogs and document possible MMF-related adverse effects.

Materials and Methods

Case selection and basic design

Medical records of dogs presented to the teaching hospital between 2005 and 2011 were retrospectively reviewed. Dogs with either a presumptive diagnosis of MUE or a histopathological diagnosis of GME, NME, or NLE that were treated with a combined

prednisone-MMF protocol and had complete medical records were included in the study. All dogs were current on their vaccinations for canine distemper and rabies.

The diagnosis of MUE was presumptive and was based on the history, clinical signs (ie, focal or multifocal CNS abnormalities with progressive deterioration), mononuclear pleocytosis (more than 50% mononuclear cells) upon cytological evaluation of CSF samples, and brain computed tomography (CT) imaging findings that were normal or consistent with inflammatory disease. Negative test results for local infectious etiological agents assisted diagnosis, but were not available in all dogs.

The data retrieved from the medical records included signalment, weight, neuroanatomic lesion localization, duration of clinical signs before and after diagnosis and treatment, clinicopathologic results, diagnostic imaging findings, treatment protocol, response to treatment, potentially drug-related adverse effects, results of consecutive CBCs during long-term therapy, and outcome.

Follow-up examinations were conducted in all dogs at 5–7 days, 2–6 weeks, 2–4 months, and 8–14 months from the initiation of steroid-MMF therapy and every 6 months thereafter. Complete blood count and serum biochemistry panels were performed at time of diagnosis and at 2–4 and 8–14 months from initiation of treatment.

Response to therapy was divided into 3 categories: complete, (resolution of neurological signs); partial (improved but unresolved neurological signs); and no response (no improvement or deterioration of neurological signs). Relapse was defined as worsening of neurological signs after initial improvement had been observed. Throughout the reviewed period, monitoring of the clinical and neurological condition in all dogs was performed by board-certified neurologists.

Diagnostic tests

All CT imaging included pre- and postcontrast scans, the latter using intravenous iohexol^c (2 mL/kg). Cerebrospinal fluid samples were obtained from all dogs through cisterna magna puncture. Analysis included total and nucleated cell counts; cytological evaluation including differential nucleated cell counts, presence of blood contamination, and presence of fungi and bacteria; and total protein concentration. Cerebrospinal fluid pleocytosis was determined when cell count was above 6 cells/ μ L. Cytological CSF analysis was conducted on modified Wright's-stained cytocentrifuged slides. Cell types in the CSF were defined as previously described.²⁰

Serological testing for detection of *Toxoplasma gondii*, *Neospora caninum*, and *Ehrlichia canis* in the serum were conducted. Complete blood count and serum biochemistry analyses were performed at presentation and

during treatment. Modified Wright's-stained blood smears were evaluated for evidence of *E. canis* and *Babesia canis*.

Treatment protocol

All dogs began treatment on the day of diagnosis with both prednisone^d 2 mg/kg PO every 12 hours and MMF 20 mg/kg PO or IV every 12 hours. Prednisone was tapered after 4 days to 1 mg/kg every 12 hours and after 14 days to every 24 hours for 30 days. Dose was reduced by half every 2–4 months thereafter. When prednisone was tapered completely or to 0.5 mg/kg every 24–48 hours without clinical relapse, MMF was tapered by reducing the dose by half every 2–4 months. Decisions regarding dosage reduction were based on neurological findings at follow-up examinations. Individually tailored treatment protocols varied and are reported in results; however, the above-mentioned guidelines were followed in all cases.

Statistical methods

Data analysis included descriptive statistics: median, mean, standard deviation, and range as appropriate for continuous variables, and frequency for categorical variables. Normality of data distribution was assessed using the Shapiro–Wilk test. The Mann–Whitney non-parametric test was used to compare CSF cytological variables between complete responders and partial or nonresponders. Kaplan–Meier curves were used to compute survival times of the subgroups. Day 0 was defined as the day of diagnosis, when treatment was initiated. Log-rank test was used to compare the survival curves between complete responders and nonresponders, and between dogs presenting with clinical signs for more than 7 days and those presenting with signs for 7 days or less. All tests applied were two-tailed, and a *P*-value <0.05 was considered statistically significant. All statistical analyses were conducted using statistical software.^e

Results

Signalment and clinical signs

The initial study group included 25 dogs, of which 23 were diagnosed with MUE; GME and NME were diagnosed on postmortem histopathology in 1 dog each. Five dogs developed suspected MMF-related gastrointestinal adverse effects, causing discontinuation of the MMF treatment within 14 days of initiation. These dogs were excluded from the main study group analyzed for descriptive statistics, survival, and response assessment, and were only included in the MMF-related adverse effects analysis.

Breed distribution in the main 20-dog study group was 6 mixed-breed small dogs, 4 Pugs, 2 Chihuahuas, 2 Yorkshire Terriers, and 1 each Maltese, Pekingese, Australian Shepherd, Pomeranian, Toy Poodle, and Dalmatian. There were 8 females (all spayed) and 12 males (4 neutered). Median age was 4.25 years (range 1–12 years) and median weight was 7.5 kg (range 2–25 kg). The median time lag from onset of clinical signs to presentation at the hospital was 7 days (range 1–60 days).

The clinical signs were localized to a single CNS region in 3 dogs and were multifocal in 17 dogs. At presentation, all 20 dogs displayed cerebral clinical signs, mainly altered mental status (18 dogs) or seizures (14). Additional signs included ataxia (12), spinal or cervical hyperesthesia (7), central vestibular dysfunction (5), and cerebellar dysfunction (2).

Brain CT findings

Abnormal findings were detected in 17 dogs (85%) and included ventricular enlargement or asymmetry (15 dogs), mild meningeal enhancement (8), focal areas of mild to moderate contrast enhancement (4), multifocal alterations in brain parenchymal opacity (3), and mild facial deviation (1). In 3 dogs, no abnormal findings were observed.

CSF analysis findings

Cerebrospinal fluid was analyzed in all 20 dogs. Pleocytosis was uniformly detected (median nucleated cell count 110 cells/ μ L, range 16–1,200) and was either mononuclear (12/20, 60%) or mixed (8/20, 40%). Median lymphocyte percentage was 46% (range 14–92%), median monocyte percentage was 25% (range 6–68%), median neutrophil percentage was 20% (range 1–48%), and the median macrophage percentage was 0% (range 0–13%). Reactive macrophages were identified in 7 of 20 of the samples (35%). Cerebrospinal fluid protein concentration was measured in 19 of 20 dogs and was elevated in 17 (89%, median, 54 mg/dL, range 5–359.7, reference interval <25 mg/dL). All samples were cytologically negative for infectious agents. No significant differences were found in total nucleated cell count or in any of the above-mentioned cell types between dogs with complete response to treatment and dogs with partial or no response.

Results of tests for infectious agents

Serological serum tests for *T. gondii* and *N. caninum* were performed in 9 of 20 dogs and for *E. canis* in 1 of 20 dogs and were negative in all dogs tested. Blood smears were evaluated for presence of *E. canis* and *B. canis* in all dogs; no infectious agents were detected.

Treatment variations

The basic prednisone-MMF protocol is described in the Materials and Methods. Ten dogs were administered a single IV methylprednisolone sodium-succinate (MPSS)^f dose (30 mg/kg) prior to initiation of prednisone treatment. Famotidine^g was prescribed to all dogs (1 mg/kg, PO, q 24 h) throughout the entire treatment course. In addition to the MMF-prednisone protocol, clindamycin^h (15 mg/kg, PO, q 12 h) was administered to 9 dogs while serology results were pending, and was ceased when negative results were received. Phenobarbital^{i,j} (2–4 mg/kg, PO, q 12 h) was administered to all dogs that presented with seizures (14/20 dogs), 8 of which received anticonvulsive medication throughout the study period.

In 1 case, the standard treatment protocol described above was modified. At diagnosis of MUE, the dog received only MMF due to concurrent pneumonia. Prednisone was added 21 days later and was tapered as described in the protocol. In this dog, marked improvement was seen before prednisone was initiated.

Response to treatment and survival time

Complete response within 30 days from treatment initiation was recorded in 12 dogs (60%), whereas 7 dogs (35%) partially responded and 1 dog (5%) was unresponsive to therapy. Of the 12 complete responders, 10 (83%) remained neurologically normal for >336 days. By the end of the study, 8 complete responders were still alive with no neurological abnormalities. Three of these 8 survivors were tapered off of all medication after 18 months and were stable without further therapy, 2 were treated with MMF (10 mg/kg, PO, q 48 h) as a single drug, and 3 dogs were treated with prednisone (0.5 mg/kg, PO, q 24–48 h) and MMF (10 mg/kg, PO, q 24–48 h). Two of the 10 dogs that had survived for over 336 days died by the time the study ended. One died of congestive heart failure 3.5 years from treatment initiation, having been off medication for 2 years prior to his death. The other was euthanized due to a relapse of cluster seizures 421 days from treatment initiation. Two complete responders (17%) survived for less than 336 days. Both were euthanized due to a relapse of seizures 4.5 and 5.5 months from the initiation of treatment.

The 7 partial responders died naturally or were euthanized at their owners' request within 7–150 days from treatment initiation, due to relapses of the neurological disease (6/7) or due to preexisting urinary incontinence unrelated to the MUE. Three had relapse seizures without other neurological signs and their owners declined further treatment. One dog was unresponsive to MMF and prednisone therapy and died following a cluster of seizures 6 days after therapy had been initiated.

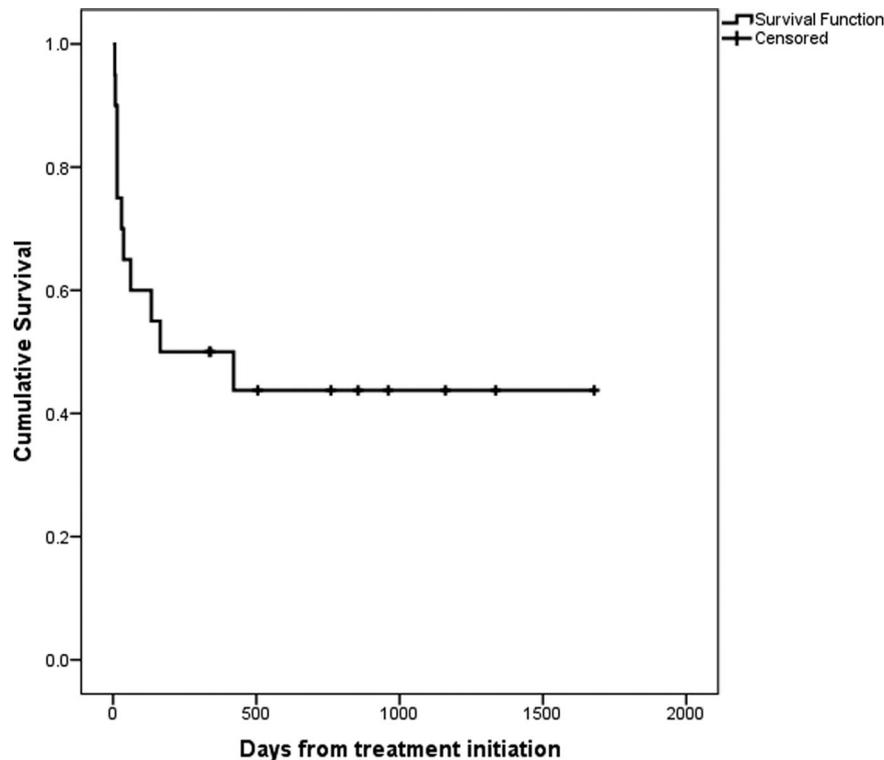


Figure 1: Kaplan–Meier survival curve for 20 dogs treated with mycophenolate mofetil and prednisone for meningoencephalomyelitis of undetermined etiology. The median survival time was 250 days (range 6–1,679).

The median survival time (MST) of all 20 dogs was 250 days (range, 6 to >1,679 days) (Figure 1). Survival time was 14 days (range, 6–165 days) in dogs presented more than 7 days after onset of clinical signs and was significantly shorter ($P = 0.001$) compared to those presented within 7 days from the onset (Figure 2). The median follow-up time of dogs that were presented within 7 days of the onset of clinical signs was 760 days (range, 134–1,679 days). Since fewer than half of the dogs died within the median follow-up time, MST could not be calculated, but would be higher than the median follow-up time. MST of partial responders was 14 days (range, 8–62 days) and was significantly shorter ($P = 0.001$) compared to complete responders (Figure 3). The median follow-up time of complete responders was 633 days (range, 14–1,679 days). MST could not be calculated for complete responders but it would have been higher than the median follow-up time. All Pug dogs in this study (4/20) survived less than 165 days. Their MST was 14 days and was significantly shorter ($P = 0.008$) than other breeds.

Treatment-related adverse effects

Acute hemorrhagic gastroenteritis was recorded within the first 2 weeks of treatment initiation in 5 of 25 dogs (20%), which necessitated discontinuation of MMF therapy. These dogs presented with hemorrhagic

diarrhea (5/5, 100%), anorexia (5/5, 100%), and vomiting (2/5, 40%) that required supportive treatment and resolved upon withdrawal of MMF. We cannot exclude that the gastrointestinal signs in these dogs could have been related to MPSS or high-dose prednisone treatment. During the initial phase of therapy, hematological findings in these 5 dogs were unremarkable with the exception of thrombocytopenia in 1 dog that had concurrent monocytic ehrlichiosis; GME was histopathologically confirmed in this dog.

The long-term adverse effects in the 20 dogs that continued treatment included sporadic infections attributed to long-term immunosuppression, such as pyelonephritis, cystitis, septic arthritis of a single joint, demodectic mange, and *Staphylococcus pseudintermedius* dermatitis, each diagnosed in 1 dog. Acute gastritis due to dietary indiscretion was reported in 2 dogs several months after treatment initiation, and was resolved with supportive care without reduction in MMF or prednisone. Polyuria and polydipsia attributed to prednisone were recorded in all dogs and improved during tapering.

Long-term hematologic abnormalities included mild leukocytosis ($17\text{--}22 \times 10^9$ cells/L, reference interval, $6\text{--}17 \times 10^9$ cells/L) with absence of left shift or cytoplasmic toxicity (5 dogs) related to steroid treatment, or severe leukocytosis ($>25 \times 10^9$ cells/L) that was

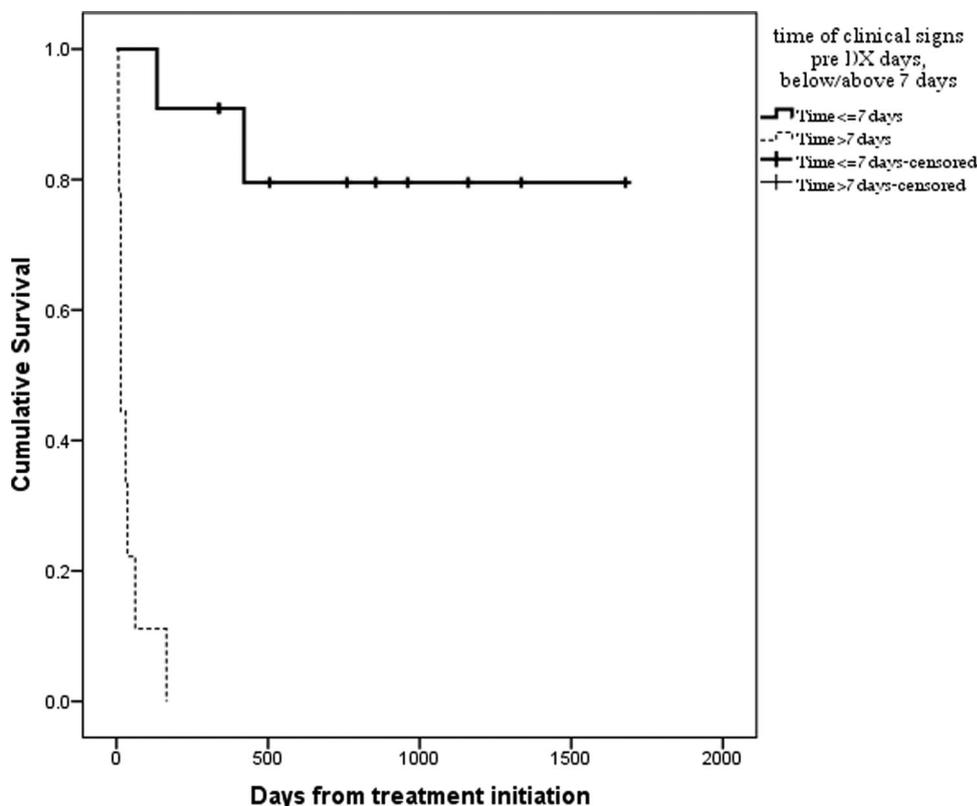


Figure 2: Kaplan–Meier survival curve for 20 dogs treated with mycophenolate mofetil and prednisone for meningoencephalomyelitis of undetermined etiology. Dogs that underwent diagnosis and treatment more than 7 days after the onset of clinical signs of ($N = 9$, dotted line) were compared to dogs that began treatment 7 days or less after the onset ($N = 11$, continuous line). Survival times differed significantly between the groups ($P = 0.001$).

related to concurrent bacterial infections and resolved with antibiotic therapy (3 dogs). Changes in the leukogram were deemed unrelated to MMF therapy. Serum biochemistry abnormalities included increased alanine aminotransferase and alkaline phosphatase activity (10 dogs) and hypertriglyceridemia (3 dogs), which were attributed to long-term steroid therapy. Lymphopenia, bone marrow suppression, or acute hepatotoxicity was not observed in any dog during the study period.

Discussion

The results presented here show that combined prednisone-MMF therapeutic protocol can be used as a long-term treatment for MUE in dogs. Most dogs in this study responded either partially or completely to treatment, with 60% of them displaying complete clinical response. The MST in our study was 250 days, but 8 of 20 (40%) of dogs were alive at the end of the study 336–1,679 days from diagnosis, with an average follow-up time of 871 days. Previous reports reveal that dogs treated with prednisone combined with lomustine⁷ had a MST of 457 (GME) and 323 (NME) days; combined with

procarbazine⁵ had a MST of 425 days; combined with cytosine arabinoside had a MST of 531¹¹ and 26 days;²¹ combined with cyclosporine⁴ had a MST of 930 days; and combined with azathioprine had a MST of 1,834 days.¹⁰ These studies are difficult to compare to one another due to their retrospective natures, differences in case selection, and lack of histologic confirmation of disease. Thus, conclusive establishment of an optimal treatment regime is currently impossible.

In the present study, a combined prednisone-MMF therapeutic protocol was initiated immediately upon diagnosis of MUE. In previous studies,^{4,5,10} immunosuppressive medications were withheld until negative results were obtained for infectious agents, which sometimes delayed therapy for up to a week. In such circumstances, dogs that did not survive the intermediate period were not included in survival analyses, which might have accounted for longer MST's reported. In the present study, 8 of 20 dogs (40%) were still alive 336–1,679 days from diagnosis, suggesting that addition of MMF to prednisone in MUE has a similar beneficial effect to other immunosuppressive medications reported.^{4–6,10,11}

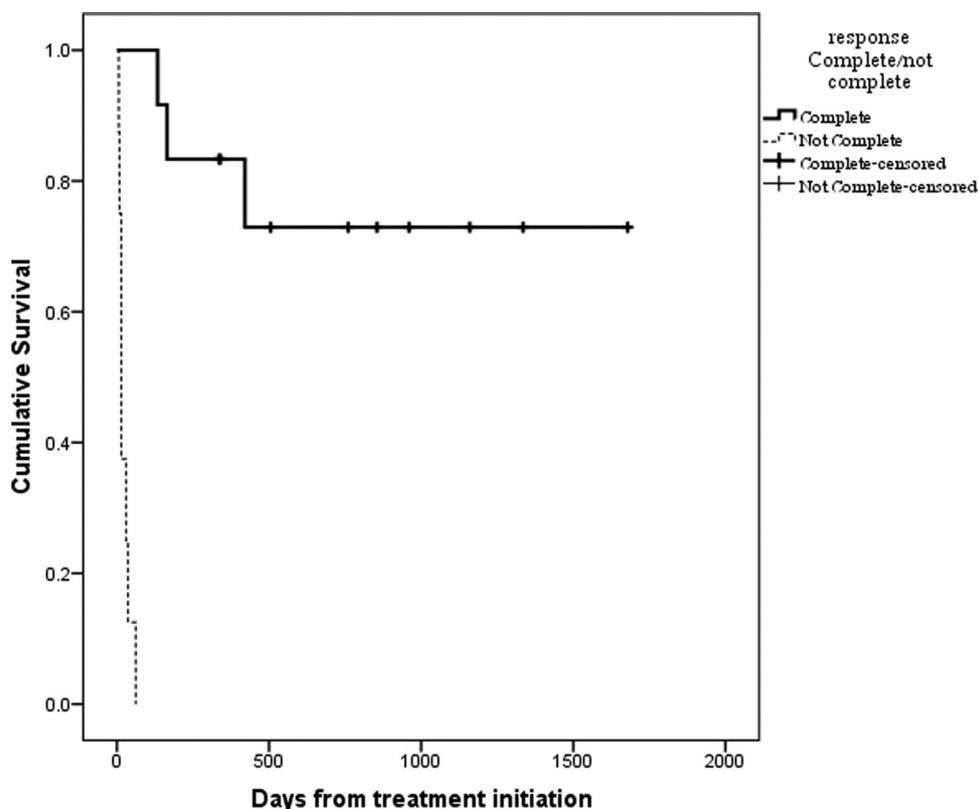


Figure 3: Kaplan–Meier survival curve for 20 dogs treated with mycophenolate mofetil prednisone for meningoencephalomyelitis of undetermined etiology. Dogs that showed a complete response to treatment ($N = 12$, continuous line) were compared to dogs that had partial or no response ($N = 8$, dotted line). Survival times differed significantly between the groups ($P < 0.001$).

MST was significantly longer for complete responders compared to incomplete and nonresponders, in agreement with previous findings of dogs with MUE treated with a combined prednisone-azathioprine protocol.¹⁰ The first 2 months of therapy were critical for survival in the present study, as 8 of 10 dogs (80%) that survived <1 year were euthanized or died during that period. Similar observations were made in 2 other studies of MUE in dogs.^{7,9} Additionally, significantly longer MST was recorded in dogs that were presented within 7 days of onset of clinical signs, relative to those presented after more than 7 days, suggesting that early diagnosis and treatment might influence survival time. It thus seems that the critical period for successful outcome in dogs with MUE extends from the onset of clinical signs to the first few weeks following treatment initiation. Efforts should be made to provide early diagnosis and treatment and, in cases of incomplete or no response, additional therapeutic measures should be considered in order to improve survival.

The initial MMF dose used in this study was 20 mg/kg every 12 hours, based on the current literature.^{1,b} Pharmacokinetic data of oral MMF therapy in dogs are somewhat limited. Results from 1 study showed that

wide interpatient and interdose variations exist, which might explain why certain dogs are adversely affected while others are not when similar MMF doses are administered.²² In another study, the half-life of MMF was 8 hours at doses of 20 and 40 mg/kg, suggesting that a dosing interval of 8–12 hours effectively maintains inhibition of IMPDH activity by MMF.²³ Because MMF is increasingly used in dogs, additional pharmacokinetic and pharmacodynamic studies of MMF in dogs are warranted to establish effective and safe administration protocols.

Although gastrointestinal adverse effects necessitated discontinuation of MMF in 5 of 25 dogs, there were no life-threatening MMF-related adverse reactions noted in this study. The adverse effects, which occurred within the first 14 days of treatment, were all reversible and subsided upon MMF discontinuation and with standard supportive therapy. These results suggest that the currently used prednisone-MMF protocol is relatively safe with proper monitoring for gastrointestinal signs. These findings are in agreement with previous reports, in which MMF was used in dogs.^{23–25,b} However, when high MMF doses (60 mg/kg/day) were used, it led to gastrointestinal erosion and necrosis.²⁶ Because dogs

treated for MUE are immunosuppressed, they are generally prone to opportunistic infections, including of the intestinal tract. When MMF-related gastrointestinal insult occurs, these dogs should be treated aggressively and carefully monitored. Data from MMF-treated human patients suggest that gastrointestinal adverse effects of the drug are mainly related to its peak serum concentration (C_{max}), whereas its immunosuppressive efficacy seems to depend on the cumulative dose over time.²⁶ This suggests that lower MMF dose combined with decreased dosing interval may retain high efficacy while reducing occurrence of adverse effects. Given the high incidence (20%) of MMF-treated dogs that developed short-term adverse effects that required discontinuation of the drug, reducing the initial dose to 10 mg/kg every 8–12 hours should be evaluated by further studies.

This study has several limitations. The number of available cases was small, thereby weakening the statistical analyses and increasing the chance of errors. A definitive diagnosis was absent in most cases, as is often the case in immune-mediated diseases. Therefore, this study probably included dogs with several different inflammatory disorders, thereby introducing variance. Furthermore, although the inclusion criteria in this study were similar to other studies,^{5,10,11} they could not ensure total exclusion of infiltrative neoplastic disorders. Also, an infectious etiology of inflammatory CNS disease was incompletely ruled out in most of the dogs. However, such diseases are uncommon in our region and were less likely to show dramatic improvement with immunosuppressive therapy, as was observed in this study.

Technically, the CT beam-hardening artifact can obscure lesions involving the brainstem or cerebellum, which would result in misinterpreted findings. This limitation probably had little influence on case selection, since solid masses in this area are not overlooked. Magnetic resonance imaging would have been a better diagnostic tool to characterize brain inflammatory diseases and to differentiate them from other CNS pathologies. However, despite the limited soft tissue detail provided by CT, when coupled with CSF analysis it can provide evidence for meningoencephalitis. In addition, in most cases this combination can rule out a neoplastic mass, which is the most frequent differential diagnosis for dogs with progressive focal or multifocal CNS signs. The retrospective design of the study has innate limitations. The therapeutic protocol varied among dogs with regards to the time lag from clinical signs onset to initiation of therapy, types and doses of additional drugs used, tapering of both prednisone and MMF, and time of follow-up visits, thereby introducing further variance. Lastly, as in previous works,^{4,6,11} a considerable number of dogs

in this study were still alive when the survival analysis was completed. Since exact MST could not be established, comprehensive comparisons and interpretations are limited.

In conclusion, this study shows that MMF can be used as an adjunctive therapy in dogs with MUE. Attention for occurrence of gastrointestinal adverse effects is warranted, particularly within the first 2 weeks of treatment. The beneficial effects of MMF included good control of clinical signs and allowing significant reduction or even discontinuation of prednisone. The possibility of IV dosing is advantageous in cases with severe neurological abnormalities and mentation changes often seen in MUE. Early treatment and a favorable initial response were associated with longer MST. These results warrant larger-scale, controlled, prospective studies to provide better assessment of the efficacy of MMF as an adjunct immunosuppressive agent in dogs with MUE.

Footnotes

- ^a Cellcept, Roche Laboratories, Nutley, NJ.
- ^b Feliu-Pascual AL, Matiasek L, de Stefani A, et al. Efficacy of Mycophenolate Mofetil for the treatment of presumptive granulomatous meningoencephalomyelitis. In: Annual Symposium of the European College of Veterinary Neurology; 2007: Bern, Switzerland. p. 509.
- ^c Omnipaque, GE Healthcare Pharmaceuticals Inc, Wayne, NJ.
- ^d Prednisone, Watson Pharma, Verna, India.
- ^e PASW statistics 18, SPSS Inc, Chicago, IL.
- ^f Solu-Medrol, Pfizer Inc, New York, NY.
- ^g Gastro, Unipharm Ltd, Tel-Aviv, Israel.
- ^h Dalacin, Pfizer Inc, Poce-sur-Cisse, France.
- ⁱ Phenobarbital, West-Ward Pharmaceuticals, Eatontown, NJ.
- ^j Cytarabine, Hospira Inc, Lake Forest, IL.

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