TREATMENT OF AUTOIMMUNE DISEASES OF THE CENTRAL NERVOUS SYSTEM OF DOGS

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Several inflammatory, primary central nervous system (CNS) derangements of dogs have been described such as:

1. Granulomatous Meningoencephalomyelitis (GME)
2. Necrotizing Encephalitis of mostly Pug, Maltese and Yorkshire terrier dogs
3. Corticosteroid-Responsive or Neutrophilic Meningitis
4. Eosinophilic Meningoencephalomyelitis
5. Idiopathic Tremor Syndrome or Cerebellitis
6. Pyogranulomatous Meningoencephalitis
7. Meningoencephalomyelitis of undetermined etiology

The two things these conditions have in common are that they are considered to be idiopathic, since no causative agent or infectious organism has been found,[10,17] and they all respond, to some degree, to immune suppressive therapy. Because of this, most people now believe that these diseases are either autoimmune or neoplastic in nature. However, an autoimmune etiology is most likely since in most cases with aggressive immunosuppressive therapy permanent remission can be achieved which would be unlikely if they really were of neoplastic origin.

Depending on where in the brain and spinal cord these diseases start, and how rapidly they progress, they can cause a wide variety of signs. The most common presenting clinical signs are:

1. Progressively worsening central vestibular signs
2. Progressively worsening seizures and behavior abnormalities
3. Progressively worsening neck and or back pain
4. Progressively worsening para or tetraparesis
5. Progressively worsening generalized severe intention tremor
6. Acute onset of blindness

These signs can progress at various rates, but surprisingly they are often acute (1-2 days) to peracute (8-12 hours) in duration on initial presentation. In the peracute form these autoimmune brain and spinal cord diseases can be one of the most serious neurological emergencies. It is possible for a dog with GME involving the brain stem to progress from mild vestibular ataxia to severe violent rolling to opisthotonos, coma and death within 12-24 hours from the first onset of clinical signs. A dog with GME involving the cervical spinal cord may progress from signs of mild ataxia to full tetraplegia in 1-2 days mimicking a cervical disc herniation. Pugs, Maltese terriers and Yorkshire terriers with necrotizing encephalitis commonly present with only 1-2 days or even a few hours of pacing, demented behavior followed by near constant seizure activity and death within 12 to 24 hours.

Although in most cases a neurological patient should be stabilized and diagnostic tests evaluated before treatment is started, a dog with rapidly progressive GME or necrotizing encephalitis may be dead, or permanently neurologically damaged, if treatment is withheld for 8-12 hours so a cerebrospinal fluid (CSF) analysis and advanced imaging can be evaluated before treatment is begun. It is therefore imperative that a high index of suspicion be maintained for autoimmune CNS disease when dogs are presented with unusually rapidly developing seizures, vestibular signs, tetraparesis, violent generalized tremors or blindness. Frequent, accurate neurological examinations will indicate if rapidly progressive or static to improving disease is present. For this reason, it is not a good idea to admit a dog that appears to have acute onset geriatric vestibular disease with plans to re-evaluate the dog the next morning. If the dog has GME death may occur by then. If rapid neurologic deterioration is noted on repeat examination then immediate referral to a 24-hour emergency center or aggressive immune suppressive therapy should be started until a CSF analysis and advanced CNS imaging can be done to confirm the diagnosis. Increased cellularity of a CSF analysis is not likely to be altered by corticosteroid or other immunosuppressive therapy for 12 to perhaps 24 hours; so an accurate diagnosis can still be made after glucocorticoid therapy has begun. However, if CSF is collected after 12-24 hours of glucocorticoid therapy false negative results may be obtained. Therefore it is best to begin, or refer the dog for, diagnostic testing as soon as possible after initiating therapy in such an emergency situation.

High dose, long term, immunosuppression is the key to successful therapy for all autoimmune diseases of the CNS. For this reason it is imperative that infectious causes of CNS inflammation be ruled out by diagnostic testing since immunosuppressive therapy would obviously worsen these conditions. The following therapies have been found to have efficacy in treating CNS autoimmune disease:

1. Corticosteriods in immunosuppressive doses[1,2,3]
2. Azathioprine[20]
3. CCNU (Personal communication March, P, Ohio State University)[4]
4. Cyclosporine Modified by Microemulsion[5,6]
5. Cytarabine[7,18]
6. Leflunomide[15]
7. Procarbazine[7,19]
8. Radiation Therapy[8,3]

Corticosteroids, primarily prednisone, is the drug of first choice and is on rare occasion used as the sole therapy. It is important that immunosuppressive doses be used initially, and therapy be sustained at high doses, very gradually tapered over many months or relapses are likely to occur. A six-month tapering dosage schedule of prednisone that is generally effective is as follows:

1 mg/lb Q 12 hours for 4 days
0.5 mg/lb Q 12 hours for 17 days
0.5 mg/lb Q 24 hours for 35 days
0.25 mg/lb Q 24 hours for 60 days
0.25 mg/lb Q 48 hours for 60 days

Dogs weighing less than 5 kgs are dosed as 5 kg dogs, and dogs weighing 5 to 10 kgs are dosed as 10 kg dogs. Dogs weighing over 35 kg are dosed as 35 kg dogs. Prednisone alone, used in the above dosage schedule, in about 75 percent of cases will cause long-term remission when neutrophilic or eosinophilic meningitis or focal GME of the posterior or rostral fossa of the brain are treated; however the addition of at least leflunomide to prednisone therapy is recommended since it improves the odds of sustained remission.

Prednisone alone or in combination therapy causes many adverse effects. When these adverse effects are severe they may require the prednisone dose to be reduced prematurely or even stopped entirely and another immune suppressive drug used in its place or combined with a reduced prednisone dose. The adverse effects that can occur are:

1. Severe polyuria, polydipsia, polyphagia and panting
2. Urinating in the house or urinary incontinence and weight gain
3. Colitis type diarrhea, vomiting and anorexia
4. Gastrointestinal (especially colonic) ulceration/perforation
5. Life threatening steroid hepatopathy
6. Urinary tract and skin infections and other infections
7. Severe mental depression and lethargy
8. Hyperexcitable, energetic, aggressive
9. Muscle atrophy and weakness
10. Endocrine alopecia
11. Hypertension
12. Calcinosis Cutis

Some of the more common adverse effects listed above can be prevented by some simple instructions to the owner. If the dog has normal renal function, the owner should limit the dog's water consumption to 20 ccs/pound of body weight divided three times a day. This will prevent the excess drinking that causes the dog to urinate in the house and be urinary incontinent. If the dog does start urinating in the house despite this, the dog's urine should be cultured using a cystocentesis urine sample to be sure a urinary tract infection has not developed. The dog should not be fed more than the amount of food he was fed before prednisone therapy. That should be no more than 20 calories of food per pound per day. Feeding a high fiber, low fat food, such as canine or feline RD or feline WD, prevents weight gain and prevents the steroid induced colitis diarrhea that is very common unless this diet is used. The dog should have a 12 hour fasted serum chemistry profile collected in all cases 10 to 14 days after this prednisone schedule is started. If the serum bilirubin is elevated above the normal range, the prednisone dose should be immediately reduced to 0.5 mg/lb once a day and the steroid hepatopathy should gradually start to resolve. In those cases in which the dog becomes severely mentally depressed on prednisone or has severe muscle weakness or an intolerable personality change, prednisone may have to be discontinued permanently or the dose drastically reduced and other immune suppressive drugs considered.

Azathioprine is an immunomodulatory drug that primarily acts by interrupting purine metabolism leading to inhibition of DNA synthesis and mitosis. It is most effective to inhibit cell mediated immunity and is less effective against the humoral response. Azathioprine seemed to have some effectiveness to treat immune mediated CNS disease of dogs in one study.[20] This drug

has been used very effectively to treat many other immune mediated diseases of dogs including myasthenia gravis. The author has used both azathioprine and leflunomide to treat a wide variety of immune mediated diseases of dogs including immune mediated CNS disease, and has found azathioprine generally less effective and more toxic than leflunomide in most cases. The adverse effects of azathioprine include bone marrow suppression, hepatotoxicosis and acute pancreatitis. The bone marrow suppression resulting in leukopenia, thrombocytopenia and anemia are generally dose related and can be resolved with dosage adjustments based on hemogram monitoring. However, the hepatotoxicosis and acute pancreatitis often occur abruptly in the early days of therapy in susceptible dogs, and are not dose related effects. It is impossible to predict before therapy which dogs will experience these often severe hepatic and pancreatic reactions to azathioprine which can be life threatening. In general, the adverse reactions to leflunomide are less severe and can be corrected more rapidly than the adverse reactions to azathioprine. For this reason, leflunomide is the drug of first choice with azathioprine only used if leflunomide is not tolerated due to a drug eruption and other medications such as cytarabine and lomustine in addition to prednisone therapy are not able to maintain remission. Azathioprine is initially administered at 2 mg/kg orally once a day, and in 2 to 4 weeks the dosage is reduced to 2 mg/kg orally every 48 hours. However, this dosage may have to be adjusted to a lower or less frequent interval based on hemogram and serum chemistry profile monitoring. Initially hemograms should be done every 2 weeks then monthly for the duration of therapy. Neutrophil counts less than 3,000/uL warrant a dosage reduction.

CCNU (Lomustine) is a very effective addition to or replacement for prednisone immune suppression in prednisone resistant cases, for cases that relapse off of prednisone or when prednisone adverse effects are too severe. Lomustine is a nitrosourea compound used in the treatment of certain neoplasic diseases and is a potent immune suppressor primarily due to its toxic effect on lymphocytes. It alkylates DNA and RNA but is not cross resistant with other alkylating agents such as Cytoxan. Since the drug has high lipid solubility and it is not ionized at physiological pH, it crosses the blood-brain barrier very well reaching 50 percent or greater than plasma levels. Lomustine is most commonly used to treat brain tumors and lymphosarcoma.

The primary toxicity of the drug is bone marrow suppression causing leukopenia and delayed thrombocytopenia. The toxic effects on the bone marrow are cumulative. The delayed thrombocytopenia is only a problem if the drug is dosed once every three weeks rather than every four weeks. Using every 4-week dosing thrombocytopenia does not occur. Some dogs, toward the end of one year of therapy, start to become too leukopenic on a dose that previously did not cause this. For this reason hemograms should be watched closely toward the end of therapy.
The only other major toxicity is gastrointestinal causing vomiting and diarrhea especially if the dose is high enough to cause excess myelosuppression. If the dog has severe neutropenia and gastrointestinal bleeding from a lomustine overdose, shock, sepsis and death can occur quickly. Lomustine is reported to be hepatoxic in dogs at times when used at high doses of 90 mg/meter squared every 3 to 4 weeks at the same time other hepatotoxic drugs like trimethoprim-sulfadiazine or drugs that interfere with its hepatic metabolism such as cimetidine are given.[14] It is very unlikely this hepatotoxicity will occur at the immunosuppressive doses used for autoimmune disease as long as therapy does not exceed one year. Serum chemistry monitoring for hepatotoxicity can be done after the first treatment then every three months thereafter.

The initial dosage of lomustine for dogs weighing 20 pounds or less is 30 mg/meter squared once a month. For dogs weighing more than 20 pounds the initial dosage is 35 to 40 mg/meter squared once a month. However when the dosage calculation is made the dosage should always be rounded downward to the closest even 2.5 mg increment for dogs weighing 20 pounds or less, and rounded downward to the closest even 10 mg increment for dogs over 20 pounds. Lomustine is supplied as 10 and 40 mg capsules. For small dogs the capsules must be compounded into a smaller size than 10 mg. The capsules should always be handled with gloves by the owner and hospital staff. Some dogs are very sensitive to bone marrow suppression by this drug and others are very resistant. Because of this the first dosage used should be very conservative. A hemogram should be done exactly 6 days after the first treatment. The goal is to have a granulocyte (neutrophil) count nadir of over 1,000/uL and less than 3,000/uL. The dose should be gradually raised each month until this range is achieved. Each time the lomustine dose is increased a hemogram needs to be done 6 days later. Once the correct dose is found and the same dose is being given each month the hemogram 6 days post treatment is no longer needed. A hemogram should also be done 21 to 29 days after each treatment, and it should reflect a neutrophil count at least over 3000/uL to safely give the drug again at 30 days. Lomustine therapy is generally used for one year to treat autoimmune CNS disease.

Lomustine is used initially combined with prednisone, leflunomide and cytarabine in all cases of necrotizing encephalitis, and all cases of GME that involve the spinal cord or that cause blindness since these forms of autoimmune CNS disease seem to almost always relapse or not go into remission at all if prednisone only is used. By adding lomustine initially as part of the treatment combination in these cases, the long-term remission rate approaches 90 percent for GME and 70 to 80% for necrotizing encephalitis.

Cyclosporine is also an effective immunosuppressive drug that can be used in place of, or more often combined with, prednisone, leflunomide, cytarabine and lomustine to achieve maximum immunosuppression. The microemulsified form (Atopcia® Novartis Animal Health US, Inc., Greensboro, NC 27408), or its generic equivalent (cyclosporine modified), should always be used since its dose is less and the blood level achieved is more uniform due to better intestinal absorption than Cyclosporine USP, Sandimmune® (Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936).[9] Cyclosporine acts primarily by strongly suppressing T lymphocyte activation and proliferation. Cyclosporine binds to the cytosol of lymphocytes with cyclosporine-binding proteins and blocks calcium-dependent signal transduction blocking T-cell activation.[9] In addition it prevents synthesis of several cytokines such as interleukin-2, which further inhibits T-cell proliferation.[9] It has been shown by immunohistochemical studies that the bulk of lymphocytes in GME lesions of the brains of dogs are CD3 antigen positive T lymphocytes.[10] The data from these studies strongly suggests that canine GME is a T-cell-mediated delayed-type hypersensitivity, organ-specific autoimmune disease.[10] Therefore, cyclosporine's T-cell specificity makes it a good choice to treat GME. Cyclosporine is lipophilic and has poor blood-brain barrier permeability; however it may be trapped in the endothelial cells and the choroid plexuses of the CNS since it concentrates mostly in intracellular compartments including of erythrocytes and leukocytes.[11] GME primarily creates perivascular lesions in the CNS; so it is likely that cyclosporine would enter the intracellular compartment of the lymphocytes and macrophages in these perivascular granulomas.[6]

Cyclosporine is a very rapidly acting immune suppressor. Effective steady state blood levels can be measured in 24 to 48 hours after starting therapy.[9] In most cases a dosage of 3 mg/kg every 12 hours of Atopica will achieve serum concentrations high enough to be therapeutic for GME.[6] Whole blood concentrations should be measured soon after starting therapy since there is considerable biological variation in absorption of this drug from one patient to the other. Ideally cyclosporine concentrations of 400 - 600 ng/ml would be achieved 12 hours post pill.[9] However it has been shown serum concentrations of only 200 - 400 ng/ml are often effective for GME.[6] It appears from blood level testing the half-life of cyclosporine is short in dogs. Generally blood levels 2 to 3 hours post pill are in the 400 - 600 ng/ml range, but 4 to 8 hours post pill the levels are often 200 - 400 ng/ml and 8-12 hours post pill are often less than 200 ng/ml. When this is found it is sometimes necessary to use 6 mg/kg every 12 hours to achieve consistent serum concentrations of cyclosporine over 200 ng/ml throughout the treatment period in dogs.

In general cyclosporine is a safe drug in dogs with few adverse effects. The most common adverse effect is diarrhea, anorexia or vomiting if the dose is too high for a given individual.[12] Dividing the dose more evenly throughout the day often resolves this. However, on occasion other adverse effects have been seen such as gingival hyperplasia, papillomatosis, hirsutism, excessive shedding, and insulin resistance or inhibition of insulin release which may require the drug to be discontinued.[12] Unlike in humans, the drug is not nephrotoxic or hepatotoxic unless blood levels greater than 3,000 ng/ml are achieved,[9] which would be very difficult to do in dogs. Cyclosporine is metabolized by cytochrome P-450. Since phenobarbital induces this enzyme phenobarbital will decrease cyclosporine blood levels.[12] However, ketoconazole significantly lowers the dose of cyclosporine needed to achieve an effective blood level and seems to make the blood level more even throughout the day.[12] A dose of 10 mg/kg once a day of ketoconazole often allows a 50 to 80 percent reduction in the cyclosporine dose which can result in considerable financial savings since cyclosporine is quite expensive.[12] However, it must be kept in mind that ketoconazole has several adverse effects in some dogs. The most common adverse effects are anorexia, vomiting and diarrhea. On occasion the drug can be hepatotoxic. It is teratrogenic; so it should never be given to pregnant dogs. It also lowers gonadal and steroid hormone levels. For these reasons ketoconazole administration with Atopica should only be considered for an owner that cannot possibly afford Atopica therapy any other way.

Generally Atopica is only used in the most resistant cases such as necrotizing encephalitis and spinal cord or blindness form of GME. It may also be used for GME cases that relapse when steroids are withdrawn or when steroids cause too severe adverse effects. Most commonly Atopica is used in combination with prednisone, leflunomide, cytarabine and lomustine. In this situation the prednisone is used for 6 months, the lomustine and cytarabine for one year and the Atopcia and leflunomide for 1.5 years. Used this way the long-term remission rate for GME is close to 95% and for necrotizing encephalitis 80 to 85%.

Cytarabine (Cytosine Arabinoside) is an antineoplasitc agent mostly used to treat lymphosarcoma of dogs. It has been shown to cross the blood-brain barrier of normal dogs.[7] There are a few reports of its use, combined with other medications, to treat GME successfully in dogs.[7,13,18] The dose recommended is 50 mg/meter squared, subcutaneously, every 12 hours for 2 days every 3 weeks indefinitely.[7] The drug causes a nadir in 7-14 days since it is myeolsuppressive. It can cause vomiting, diarrhea and hair loss. Adverse effects are generally rare and

myelosuppresion is less than with lomustine. The author has used cytarabine at the increased dose of 100 to150 mg/meter squared, subcutaneously, every 12 hours for 2 days every 4 weeks for one year alternated two weeks apart with monthly lomustine as described above. When using cytarabine for the first time the dose should not exceed 100 mg/meter squared. The dose can be increased to 150 mg/meter squared if the 6 days post medication neutrophil nadir is not below 3,000/uL.

Leflunomide is an immunomodulatory drug that has been shown to be effective in treating several autoimmune diseases of dogs, including autoimmune CNS disease, that were unresponsive to conventional therapy.[15] It is leflunomide's active metabolite teriflunomide (A77 1726) that seems to cause the immune suppressive effects.[15] All the effects of this metabolite are not known, but it is thought that teriflunomide inhibits pyrimidine biosynthesis and inhibits cytokine and growth factor receptor associated tyrosine kinase activity thus inhibiting T and B lymphocyte proliferation and function.[15] The effective dose range of leflunomide is 1.5 to 4 mg/kg once a day, but this dose needs to be individually adjusted for each dog base on their teriflunomide blood level measured 24 hours after a dose is given.[15] In humans the peak blood level of the active metabolite is obtained 6 to 12 hours after dosing, and the drug has a very long half-life of about 2 weeks.[16] Therefore, it can take up to two months to reach full steady-state.[16] An initial loading dose could be used to raise the blood level more rapidly, but to date the author has not done this because of the fear of inducing severe, abrupt adverse effects. The primary adverse effects of this drug observed by the author have been thrombocytopenia, hemorrhagic colitis and in about 10% of dogs a rapidly developing cutaneous, ulcerative drug eruption occurs. This drug eruption is most common on the nasal plane, face or food pads, but on occasion will occur on the neck or truncal skin. This drug eruption rapidly resolves if leflunomide therapy is discontinued. In humans hepatotoxicity has been reported[16] but this has not been reported in dogs so far. Currently the author uses prednisone in combination with leflunonmide to treat all autoimmune CNS diseases of dogs. In most cases cytarabine is also added using a three drug combination at the onset of diagnosis. Whenever a relapse occurs or when necrotizing encephalitis is suspected lomustine, and in some cases cyclosporine, is added using the five drugs in combination. Blood levels are measured every 2 to 4 weeks after initiating therapy to adjust blood levels into the safe therapeutic range of 20 to 40 mcg/ml of teriflunomide measured by high-pressure liquid chromatography.[15]

Procarbazine is another antineoplastic alkylating agent used to primarily treat lymphosarcoma. It is lipid-soluble and crosses the blood-brain barrier. It is myelosupressive causing thrombocytopenia and leukopenia. It comes as 50 mg capsules that almost always have to be compounded as an oil base, flavored solution for use in dogs.[7] It is given orally as 25 to 50 mg/meter squared once a day.[7,19] Hemograms are monitored weekly for the first month then monthly thereafter.[7] After the first month, if possible, the dose is reduced to every other day unless disease relapse occurs.[7] It might be possible to use this drug carefully at the same time lomustine or cytosine arabinoside are given, but this has not been tried to date.

Radiation therapy has been used to treat GME of dogs in the past.[8] However, it was not always effective in dogs that relapsed when prednisone therapy was discontinued.[8] With the advent of therapies such as leflunomide, cytarabine, lomustine and cyclosporine there is little indication to use radiation therapy to treat autoimmune CNS disease of dogs since these chemotherapeutic agents seem to be more effective.

Summary: Prednisone alone, in immunosuppressive doses, tapered slowly over 6 months, may be effective in causing permanent remission of neutrophilic and eosinophilic meningitis or focal brainstem or forebrain GME; however a combination of prednisone for 6 months and leflunomide for 1.5 years increases the chance of long term remission and is now always used. If these conditions relapse when prednisone therapy is reduced or discontinued, then adding other chemotherapeutic agents along with the leflunomide such as lomustine and cytarabine (both used for 1 year) can be done to achieve permanent remission. Dogs with GME involving the spinal cord or visual pathways or that have necrotizing encephalitis should be treated with combination therapy of prednisone, leflunomide, cytarabine and lomustine from the outset if they are to survive long-term. Therapy with microemulsion cyclosporine (used for 1.5 years) can also be added to treat resistant cases that relapse despite combination therapy with the four drugs described above.

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