



Practical Approach to IMHA

DRIP 3

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Immunomodulation

So we've got to treat it. And we have lots of drugs at our disposal.

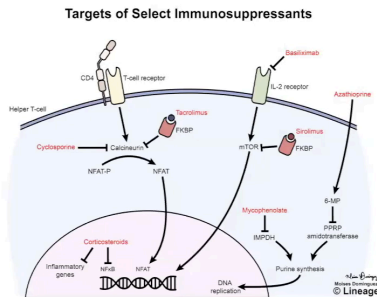
CORTICOSTEROIDS

CYCLOSPORINE

MYCOPHENOLATE

AZATHIOPRINE

LEFLUNOMIDE



If you attended this lecture tonight with the hopes of learning the best immunomodulatory protocol, I'm going to sadly disappoint you, because we don't know it. I wish I knew it. It would be fantastic, but we don't. And so I'm going to share with you experience. I'm going to share with you some published data when it's appropriate.

CORTICOSTEROIDS

Side Effects



Dose

CYCLOSPORINE

MYCOPHENOLATE

AZATHIOPRINE

LEFLUNOMIDE

- 2019 ACVIM Consensus Statement (dogs only)
 - Prednisone
 - 2-3 mg/kg/day if <25 kg
 - 50-60 mg/m²/day if >25 kg
 - Dexamethasone
 - 0.2-0.4 mg/kg/day
 - If starting prednisone dose >2 mg/kg/day
 - Decreased to ≤2 mg/kg/day within 1-2 weeks of treatment if PCV/HCT stable
- My Approach
 - Dogs
 - Prednisone @ 1-2 mg/kg/day or 40 mg/m²/day
 - Dexamethasone @ 0.14-0.28 mg/kg/day
 - Cats
 - Prednisolone @ 2-4 mg/kg/day or 40 mg/m²/day
 - Dexamethasone @ 0.28-0.4 mg/kg/day

Without question, the quintessential drug used to treat immune-mediated disease are your corticosteroids. And in 2019, the American College of Veterinary Internal Medicine released a consensus statement on the diagnosis and treatment of IMHA, and their prednisone dose and dexamethasone doses are listed on your screen.

I understand where these doses came from, but quite honestly, I think they're too high. I don't tend to need to use such high doses as was recommended in the ACVIM consensus statement. I do agree with their recommendation to dose our large and giant breed dogs on a body surface area strategy. It's just that when I do that, I use a slightly lower dose. Cats need more than dogs. So while I might use 1 to 2 milligrams per kilogram per day in a dog of prednisolone, in my cat friends, it's at least 2, and potentially up to 4 milligrams per kilogram per day.

CORTICOSTEROIDS

CYCLOSPORINE

MYCOPHENOLATE

AZATHIOPRINE

LEFLUNOMIDE

- Dose
 - Dogs: 5-10 mg/kg PO q12 hr
 - Cats: 3-7 mg/kg PO q12 hr
- Measure pharmacokinetic & pharmacodynamic data within 1-2 weeks of starting therapy
- Side Effects
 - GI upset
 - Idiosyncratic hepatotoxicity
 - Hypertrichosis
 - Gingival hyperplasia
 - Predisposition to neoplasia (chronic therapy)
 - PLT activation?



Cyclosporine is perhaps my second most favorite immunomodulatory medication. We do need to use lower doses in cats. Their drug levels tend to go into the toxic level quite a lot. They don't always have clinical signs of toxicity, which makes them a little bit more challenging.

But I like this drug because not only can we measure drug levels. We can actually measure what cyclosporine is doing in the body. So remember, it's a calcineurin inhibitor. And that means that ultimately we get a reduction in the production of interleukin-2 and interferon-gamma. And so we can actually submit a blood test. You can submit a blood test to Mississippi State to Dr. Andy Mackin and Todd Archer's laboratory. And they'll measure interleukin-2 and interferon-gamma in your canine samples.

And what you want with an effective cyclosporine dosing protocol is that you have near maximal suppression. And so it's nice. If you have a patient that's not responding the way that you would like them to, you can measure this pharmacodynamic data. And if you have maximal suppression, it doesn't really make sense to increase that cyclosporine dose. You want to look at a different therapy.

Alternatively, if I get a result back that says I'm only mildly suppressed, now I'm justified in combination with my patients' lack of clinical control of increasing the dose. It doesn't always work. And that's why there's not a perfect immunomodulatory protocol. I just like cyclosporine because at least in my canine patients, I can see what that drug is doing at a molecular level.



CORTICOSTEROIDS

CYCLOSPORINE

- Dose
 - Dogs/Cats: 10 mg/kg PO q12 hr

MYCOPHENOLATE

- Side effects
 - GI upset
 - Myelosuppression
 - Multifocal leukoencephalopathy

AZATHIOPRINE

LEFLUNOMIDE

I also like mycophenolate for my large breed dogs. Why? Because, honestly, for the average pet owner using cyclosporine at the high doses that are needed, it's just not-- it's cost-prohibitive a lot of the time. So mycophenolate for a 25-kilo dog dosed at 10 milligrams per kilogram twice a day is 250 milligrams, which is the size of the commonly available commercial tablet.

It does tend to cause gastrointestinal upset. So sometimes concurrently treating with an antiemetic can be helpful. You do need to monitor the complete blood count quite frequently for potential myelosuppression. I have had patients on mycophenolate not fully rebound, because the drug was actually preventing the bone marrow from fully rebounding.

CORTICOSTEROIDS



CYCLOSPORINE

- Side effects
 - GI upset
 - Anemia
- Myelosuppression
- Severe hepatotoxicity
- Idiosyncratic pancreatitis?

MYCOPHENOLATE

AZATHIOPRINE

- Dose (dogs only)
 - 2 mg/kg PO q24 hr initially

LEFLUNOMIDE

We also have azathioprine. This is my least favorite. And I only say that because I never can get it to work in my hands. And my own dog, when he was living with ITP, he developed idiosyncratic pancreatitis from it. So I've never been a fan of it. But one of my dearest mentors, this was her preferred immunomodulatory drug. And she hated cyclosporine. So again, it serves the point that there is no perfect immunomodulatory protocol.

CORTICOSTEROIDS



CYCLOSPORINE

- Side effects
 - GI upset
 - Myelosuppression
 - Cutaneous drug reactions
 - Hepatotoxicity

MYCOPHENOLATE

AZATHIOPRINE

- Dose
 - Dogs: 2-4 mg/kg PO q24 hr
 - Cats: 2-3 mg/kg PO q24 hr; 10 mg/cat PO q24 hr

LEFLUNOMIDE

And you've probably heard of leflunomide as well. This can be effective. It has documented efficacy against immune-mediated polyarthropathy, and then there's subsequent reports, and many anecdotal reports of effective use of leflunomide. It can cause gastrointestinal upset. It can cause pretty potent myelosuppression at certain doses. And unfortunately, even using the generic form, it's expensive.



IVIg

- MOA
 - Inhibit pathologic Abs
 - Block Fc receptors on phagocytes
 - Modulate complement activation
 - Interfere with activation of cytotoxic T cells
- Adverse Effects
 - Volume overload & dyspnea
 - Increased BP
 - Thromboembolic events
- Dose
 - 0.5-1.5 g/kg IV over 4-12 hours
 - 0.5 g/kg IV over 4 hours x 3 days

Even more expensive is intravenous immunoglobulin-G, which basically slows down the immune-mediated process, because you're infusing a vat of IVIg. And so there are volume overload issues, sometimes through a propensity for hypercoagulation thromboembolic, events have been documented. It's exceedingly expensive, and based on the literature,...



- 2009 *J Vet Emerg Crit Care* clinical trial of 28 IMHA dogs
 - Prednisone + IVIg or placebo
- 13/14 with IVIg discharged
 - 6 died/euthanized within 40 days
 - 5 in remission 5 months later
- No statistical difference in survival, length of hospitalization, lag time to HCT stabilization or transfusion requirements

Use of human immunoglobulin in addition to glucocorticoids for the initial treatment of dogs with immune-mediated hemolytic anemia

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... it didn't really do anything significant. It didn't seem to hurt, but there was no significant difference with IVIg infusion.



Poll Question #2

True or false? Dogs with IMHA should be treated with more than one immunomodulatory medication.