Evidence-Based Therapy

By Wayne Rosenkrantz, DVM, DACVD

Despite progress in relying on evidence-based medicine in veterinary dermatology, there is a need for further evaluation, especially when we look at clinical trials regarding treatment interventions for pemphigus foliaceus. The most effective and safest therapies remain unknown.

A recent human review to assess interventions for efficacy and safety in the management of pemphigus vulgaris and pemphigus foliaceus found that for the majority of interventions, results were inconclusive. Further research is required, especially to assess the optimal glucocorticoid dose, the role of adjuvant immunosuppressive medications, and long-term adverse events to improve harm: benefit analyses.

When reviewing the veterinary literature for treatment interventions in canine and feline pemphigus foliaceus, all recommendations were made based on interventions used in human disease and no controlled prospective clinical trials have been reported regarding treatments in animals. Nevertheless, the following is what is currently being used as interventions for pemphigus foliaceus in dogs and cats.

**Glucocorticoids**

Localized forms of pemphigus foliaceus and pemphigus erythematosus can be treated with topical glucocorticoids. Occasionally topical therapy in conjunction with systemic therapy can be used in more persistent focal lesions. A potent glucocorticoid is often needed initially and if adequate response is seen, switching to a less potent topical glucocorticoid is then recommended.

Common options used include 0.1% amcinonide cream or mometasone. Less potent formulations can also be effective and options would include 0.015% triamcinolone acetonide solution or hydrocortisone aceponate. These can be used daily for seven days then EOD for seven days, and if an adequate response is seen an even less potent formulation can be tried (1–2% hydrocortisone sprays, gels, creams, ointments) as needed.

The most common form of therapy used in pemphigus foliaceus management is systemic glucocorticoids. In my specialty referral practices, approximately 35% of the pemphigus foliaceus cases are adequately controlled with only glucocorticoid therapy. The form of oral glucocorticoid therapy selected depends on the individual case response and the side effects seen in that particular patient. I prefer methylprednisolone to prednisone or prednisolone due to the reduced mineralocorticoid effects resulting in less polyuria and polydipsia. It is also the preferred form to use in cats, as oral prednisone is not very well absorbed and/or converted to prednisolone. Other more potent oral glucocorticoids such as triamcinolone or dexamethasone can also be utilized in more refractory cases. However these glucocorticoids need to be used at lower dosages and also suppress the hypothalamic-pituitary-adrenal axis for 24-48 hours, and it is optimal to give these drugs every 72 hours for longer term maintenance. In severe cases of pemphigus foliaceus, shock dosages of prednisolone sodium succinate (10mg/kg/IV) or dexamethasone (1mg/kg/IV) can be utilized for short term immediate effects. Monitoring should include semiannual complete blood counts, chemistry profiles, urinalysis and urine cultures.

**Azathioprine Therapy**

Azathioprine is my first choice immunosuppressive to add to glucocorticoids or use as an option to glucocorticoids in canine pemphigus cases. It can be used as a glucocorticoid-sparing agent in cases when glucocorticoids cannot be reduced to safe long-term levels, used in combination with glucocorticoids or other immunosuppressives in more refractory cases, or as a sole therapy. Even though it is effective in the cat, it is generally contraindicated in cats due to its more profound myelosuppression and potential for fatal reactions in cats thought to be due to lower

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in Pemphigus Foliaceus

thiopurine methyltransferase levels. Adverse reactions primarily include myelosuppression (lymphopenia, anemia and leukopenia) diarrhea and increased susceptibility to opportunistic infections when used long-term (pyoderma, demodicosis and dermatophytosis). Less common complications include vomiting, hepatotoxicity and possible pancreatitis. Dosage adjustments can be made based on the results of lab monitoring and clinical improvement. Complete blood counts with platelet counts are recommended every two-three weeks for the first three months of therapy. Initially periodic (every two-three months) monitoring of chemistry profiles is also recommended. Once cases are in remission monitoring can be reduced to every six months.

Chlorambucil
Chlorambucil is an alkylating agent that functions by affecting the cross linking of DNA. It is considered less toxic and slower acting than other alkylating agents. It is available in a two mg non-scored coated tablet, making dosing in small dogs and cats easier. Myelosuppression is a concern and similar monitoring as listed with azathioprine should be performed. Other side effects include vomiting, diarrhea and anorexia.

Tetracycline and Niacinamide
I will occasionally use this therapy but usually find it an adjunctive therapy at best for the pemphigus complex. It may be more successful in localized cases such as pemphigus foliaceus limited to the face or in cases of pemphigus erythematosus. Adverse reactions include vomiting, diarrhea, anorexia and increased liver enzymes.

Cyclosporine and Tacrolimus
Cyclosporine (Atopica, Novartis) and tacrolimus (Prograf oral formulation and 0.03% and 0.1% Protopic topical preparation, Fujisawa USA, Inc) are immunosuppressant agents that have been evaluated for the treatment of autoimmune diseases. Both of these drugs work similarly, however tacrolimus is much more potent and the oral formulations appear toxic in the canine and systemic administration is not recommended in canine clinical cases. The initial studies of cyclosporine in the treatment of pemphigus and other cutaneous autoimmune diseases have not been impressive and only limited responses have been seen. I have seen individual case responses utilizing the microemulsion formulation (Atopica, Novartis). It is dosed at 7-10mg/kg q 24h often with ketoconazole 5mg/kg q 24h to aid in increasing relative serum levels of the cyclosporine. I have also recently used cyclosporine in conjunction with azathioprine in more refractory cases of pemphigus with good success. Localized pemphigus may respond favorably to topical tacrolimus, with no adverse reactions reported in one study.

Mycophenolate Mofetil
Mycophenolate mofetil (CellCept, Roche Pharmaceuticals) inhibits de novo purine (guanine) synthesis. B and T lymphocytes are dependent upon guanosine synthesis because they are unable to use the salvage guanosine synthesis pathway. This unique aspect of lymphocytes allows mycophenolate mofetil to inhibit the proliferation of lymphocytes and the production of antibodies relatively selectively with minimal effects on other tissues. Canine studies show success rates of approximately 50% with some dogs weaned completely off prednisone while others have relapsed when the glucocorticoids were dropped too low.

Conclusion
Prospective controlled studies are needed to determine the optimal therapy for pemphigus foliaceus. Specifically, a prospective study with randomization comparing a glucocorticoid only group to glucocorticoids combined with other immunosuppressives needs to be performed.

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