A New Treatment for Autoimmune Blistering Diseases: Efficacy of the Bruton’s Tyrosine Kinase (BTK) Inhibitor PRN473 in Canine Pemphigus Foliaceus

Introduction

Although it is a relatively rare disease, pemphigus foliaceus (PF) is the most common form of pemphigus and probably the most common cutaneous autoimmune disease in the dog. PF usually presents in one of two forms, a mucocutaneous and encrusted pustular disease or a generalized and encrusted (often pruritic) dermatosis, with the latter form associated with systemic signs such as fever or lethargy. Most commonly affected areas include the dorsal muzzle, nasal planum, pinnae, periorbital skin, and the paw pads; dermatis is often present. Nasal planum and hardened dorsal muzzle will typically be affected concurrently. BTK drugs act by inhibiting BTK in non-T cell white blood cells, reducing downstream signaling from the B-cell receptor (Figure 1), as well as that of the FcγR (surface IgG receptor), and thus modulating inflammation mediated via these receptors. The effects of a BTK in canine PF should be generalizable beyond veterinary treatment to human pemphigus foliaceus and pemphigus vulgaris, due to the common autoimmune mechanisms shared by these diseases.

PRN473- A Potent and Selective BTK Inhibitor

PRN473 is a novel investigational drug that inhibits B-cell receptor and FcγR signaling through highly selective inhibition of BTK. It has a high degree of affinity for the ATP binding site of BTK without significant or durable potency on most undesired, off-target kinases (Table 1). PRN473 is an irreversible inhibitor, with a long duration of action on BTK due to its slow off-rate kinetics, resulting in prolonged occupancy after a single dose. This profile offers the potential for efficacy due to full target occupancy without adverse side effects from off-target binding. PRN473 has undergone extensive toxicology testing in healthy beagle dogs, including a 12-week Good Laboratory Practice (GLP) study of very high doses. In that study, minimal findings were attributed to PRN473 at doses up to 400mg/kg/day other than reduced activity and weight loss, seen particularly in females. Substantial plasma exposures were confirmed and were drug-like.

In this study, PRN473 was dosed orally at approximately 15 mg/kg once daily, or as the tablets fed orally or crushed into food. This dose was estimated to be the ideal therapeutic dose based on PK and BTK occupancy in healthy beagle dogs.

Study Design

The design of this pilot study was an open label, cohort of newly presenting and chronic cases of immunosuppressive-dependent companion dogs with PF. Treatment-naïve dogs were given monotherapy with PRN473, with a subset subject dose adjustment based on clinical response and BTK occupancy level. If pretreated, combination treatment with PRN473 and continued immunosuppressive therapy was used initially and the immunosuppressive therapy tapered and/or halted. After 12 weeks, dose reduction by approximately 50% was done if clinically acceptable, as Monday, Wednesday, Friday dosing of the same prior daily dose, or as a 50% dose reduction, before ceasing the drug completely at 14-16 weeks. If the dog subsequently relapsed, retreatment with PRN473 therapy was available as an option for owners. Dogs were hospitalized for the first 24 hours of treatment during which the first dose of study medication was supervised, and blood was drawn for PK and PD measurements at subsequent time points.

Results

To date eight dogs have been enrolled into the trial with new onset PF, seven with follow up data. All had an initially positive clinical response to PRN473 treatment, showing a pronounced reduction in skin disease activity in the first weeks of therapy (Figures 3 & 4). Four dogs continued to improve and obtained good disease control by four weeks, with sustained full or near-complete remission through the end of the study. Three cases required conventional immunosuppressive intervention. In case #2 prednisolone/azathioprine rescue was necessary at week 4, and subsequently took several months to achieve good control of disease. In case #7 low dose prednisolone was added to PRN473 with no obvious improvement. In that case twice daily PRN473 treatment was added without greater effect. The duration of remission in two dogs was 4 months and 9 days. Both were retreated upon relapse and again responded quickly and fully to repeat PRN473 therapy. PRN473 achieved target BTK occupancy at trough (pre-dose) of 50% or greater with once daily doses (Figure 5), suggesting that this level of BTK inhibition is sufficient for substantial clinical activity. Tolerability of PRN473 was good with no changes in laboratory parameters or clinical safety signals, with the caveat that the number of cases was limited (n=7).

Discussion and Conclusions

BTK inhibition with PRN473 monotherapy shows promise as a rapidly effective treatment for canine PF, potentially abrogating the need for usual medical care with high dose corticosteroids in a significant proportion of dogs.

Average BTK inhibition of approximately 75-85% over the day appears adequate for full clinical effect.

We believe this study is the first to report the rapid and effective anti-inflammatory effects of BTK inhibition in a naturally occurring autoimmune disease. BTK inhibition should be further studied in canine and human blistering, and other autoimmune, diseases.

References

PBM1 BTK Occupancy

PBMC

BTK

PRN473-

Significant Clinical Effects

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References

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