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IMMUNOMODULATORS, IMMUNOSTIMULANTS AND IMMUNOTHERAPIES

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INTRODUCTION

Immunotherapy is a broad term that covers means of either enhancing or suppressing immune function using a variety of novel approaches that are not mainstream pharmacological agents. The goal of immunotherapy is often to selectively modify one aspect of innate or adaptive immunity without having a blanket effect on the entire immune system. The scientific evidence base for immunotherapy is often not robust, but increasing numbers of published studies do now provide mechanistic support for some veterinary immunotherapeutic approaches.

IMMUNOPOTENTIATION

There are relatively few approaches to the non-specific enhancement of immunity in animals. Some of these are historical and no longer recommended. For example, the antiparasitic drug levamisole was once used to attempt to enhance canine immune function (specifically macrophage function) in dogs with deep pyoderma and was used in combination therapy for canine systemic lupus erythematosus. Such treatment sometimes led to the onset of cutaneous drug eruptions (specifically of the erythema multiforme type) and it is no longer recommended. A range of unlicensed bacterial extracts are sometimes used in dogs with deep pyoderma with view to enhancing the anti-bacterial immune response, but the evidence for efficacy is limited.

One product, Zylexis™ (formerly Baypamune™), is licensed in North America and Europe for the management of stress-associated acute respiratory disease in group-housed horses. The product consists of parapoxvirus ovis particles that are suggested to enhance innate immunity and there are now a number of published studies that show variable efficacy in this clinical situation. In some European countries the product is also licensed for use in dogs and cats in group-housed situations and there is a claim for 'reduced severity of symptoms in feline calicivirus infection'.

Domperidone™ is a gastric prokinetic and anti-emetic drug that is now becoming used as an adjunct immunomodulator in the treatment of dogs with leishmaniosis. This effect relates to the action of the drug as a dopamine D2 receptor antagonist which leads to serotonin release and prolactin production. Increased concentrations of serum prolactin are proposed to have a range of immunological effects, specifically in the enhancement of Th1-type immunity over Th2 responsiveness. Another immunomodulator used in the management of canine leishmaniosis is Impromune™, a combination of dietary nucleotides and active hexose correlated compound (AHCC) derived from shiitake mushrooms.

A recent study has evaluated the effect of Reversatrol™ (a phytophenol derived from fruits such as grapes and blueberries) on immune function in healthy dogs. The treatment led to increased neutrophil phagocytosis of bacteria and increased cytokine production by leucocytes stimulated *in vitro*.

ALLERGEN-SPECIFIC IMMUNOTHERAPY

Allergen-specific immunotherapy (ASIT; hyposensitization) for canine atopic dermatitis appears to selectively target allergen-specific lymphocytes. Current research suggests that induction of regulatory T cells may be the major mechanism by which incremental dosage of allergen works. The newest approach to ASIT is sublingual delivery of allergen (sublingual immunotherapy; SLIT) which has been shown to have excellent efficacy. There is currently much research interest in the delivery of antigens (allergens or autoantigens or peptides derived from these molecules) across mucosal barriers (oral or intranasal delivery) with view to inducing immune 'tolerance' to the molecules and providing clinical benefit to patients. The delivery of allergens via 'gene therapy' with bacterial plasmids containing the allergen gene of interest has also been studied experimentally in a canine allergy model. ASIT has also been delivered by intra-lymph nodal injection and this route also shows promising efficacy.

Other immunotherapeutic approaches in canine atopy have involved injection of killed *Mycobacteria* or liposomal bacterial nucleic acids to stimulate Th1 immunity.
Autogenous vaccination with crude *Stapylococcus pseudintermedius* preparations have been used to effect in dogs with deep pyoderma; in attempts to stimulate anti-staphylococcal immune responses.

ANTIGEN-SPECIFIC IMMUNOTHERAPY
Experimental models have been used to demonstrate proof-of-principle for antigen-specific immunotherapy; most often in the context of autoimmune disease. The mucosal delivery of autoantigenic peptides or delivery of such peptides associated with MHC molecules on nanoparticles stimulates regulatory T cells, with the aim of restoring tolerance to autoantigens. One unlicensed veterinary product aimed to exploit the phenomenon of 'oral tolerance' by oral delivery of collagen in an attempt to restore tolerance in immune-mediated polyarthritis in the dog.

In an opposite strategy, the canine melanoma vaccine seeks to induce active effector immune responses to the melanoma-associated antigen tyrosinase in dogs with oral melanoma. The vaccine involves transdermal delivery of bacterial plasmids containing the tyrosinase gene and relies on transduction of cutaneous dendritic cells that subsequently present antigen for stimulation of cytotoxic T-cell responses.

CYTOKINE THERAPY
The use of recombinant cytokines is now well established in human medicine, where a wide range of such products exist. In veterinary medicine, cytokine therapy began with the use of human recombinant colony stimulating factors (e.g. Neupogen™) to enhance leucocyte production in neutropenic animals. Recombinant human anti-viral (type I) interferons have also been widely used parenterally or topically to attempt to treat a variety of feline viral infections (e.g. retroviral infection, FIP, upper respiratory tract viruses), but with limited efficacy. More recently, the licensed recombinant feline interferon omega (Virbagen Omega™) has become available for the treatment of canine parvovirus infection and the adjunct management of feline retroviral infection. In Japan, recombinant canine interferon-gamma (Interdog™) is sold for the treatment of dogs with atopic dermatitis. The same company produces feline recombinant interferon-omega (Intercat™), which has some reported efficacy against FCV-associated stomatitis.

An alternative approach to recombinant cytokine therapy is delivery of the genes encoding target cytokines either by naked DNA transfer (bacterial plasmids) or using a recombinant vector organism. The latter approach is now available in veterinary medicine with the launch of Oncept IL-2™; the canarypox vector carrying the feline IL-2 gene. This product is licensed for the adjunct management of the feline injection site sarcoma and is delivered by repeated intra- and perilesional injection in conjunction with radiotherapy and following surgical excision.

INTRAVENOUS IMMUNOGLOBULIN THERAPY
High dose intravenous human immunoglobulin therapy has been used successfully in the management of challenging cases of canine immune-mediated haemolytic anaemia (IMHA) and thrombocytopenia (IMTP) and in some cases of immune-mediated skin disease. In IMHA and IMTP, the human protein acts by blocking macrophage Fc receptors and inhibiting phagocytosis of antibody-coated erythrocytes or platelets. In other immune-mediated disorders, the mode of action might be by enhancing the activity of regulatory T cells. IVIG is also widely used in human medicine for the management of a spectrum of immune-mediated diseases.

MONOCLONAL ANTIBODY THERAPY
In human medicine there are now numerous monoclonal antibody-based products that are injected intravenously to target specific molecules in cancer or immunological or inflammatory pathways. Monoclonal antibodies may be used as drug or prodrug delivery vehicles ('magic bullets') or to block or delete particular molecules or cells. The most widely used of such products in human medicine is Infliximab™, a monoclonal antibody specific for the cytokine tumour necrosis factor (TNF)-α. The antibody targets and neutralizes this proinflammatory cytokine in patients with a variety of immune-mediated diseases including psoriasis, rheumatoid arthritis, multiple sclerosis and inflammatory enteropathy. Such antibodies are 'humanized' using molecular techniques that enable expression of

murine antigen-binding sites (Fab) on human constant regions (Fc). One study has applied the human product to management of a colony of dogs with cutaneous lupus erythematosus with poor outcome. A feline anti-TNF-α antibody has been produced and used to treat cats with FIP infection with some efficacy.

Several companies are now investing in the production of therapeutic monoclonal antibodies for companion animals. Aratana produced such antibodies for the adjunct therapy of canine T- and B-cell lymphomas, but the first generation of these products did not have the expected efficacy and so further developmental work is being undertaken.

APOQUEL™

This drug acts to inhibit the Janus Kinase (JAK) pathway of signal transduction and thereby block the ability of cells to activate specific genes. The drug is licensed for the treatment of allergic skin disease and the proposed major mode of action is blockade of the ability of lymphocytes to produce the cytokine interleukin (IL)-31. IL-31 is proposed to be one means by which cutaneous nerve endings are activated leading to CNS signalling and induction of the 'itch-scratch cycle'. The clinical effect of the drug is anti-pruritic and there is now a large body of immunological and clinical literature supporting the efficacy and proposed mode of action. One recent in-vitro study has suggested that the drug has other effects on the canine immune system, including the depletion of both $CD4^+$ and $CD8^+$ T cells.

CYTOPOINT™

A further 'caninized' monoclonal antibody therapy is a reagent which targets IL-31, neutralizing it's effect in cutaneous allergy (as above). This treatment need only be given monthly by subcutaneous injection and has rapid onset and prolonged action.

ADJUNCT OR ALTERNATIVE IMMUNOTHERAPY

A wide range of approaches have been studied in attempts to boost immune function in people and animals. There is an entire field of research that aims to identify dietary supplements that might enhance immunity and numerous such studies have been conducted in small animal medicine. The use of prebiotics or probiotics aims to boost the function of regulatory T cells induced via the intestinal mucosa. The most interesting such approach also exploits the intestinal mucosa as a potent means of influencing systemic immunity (and particularly Treg activation). The deliberate establishment of an intestinal parasitic infection to modulate systemic immune function has been the subject of a series of human clinical trials and one reported study examined this approach in the management of dogs with atopic dermatitis.

FURTHER READING

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