Papers

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Contents

1 Allergies

1.1 Allergen Specific Immunotherapy

1.1.1 2022 Efficacy of subcutaneous allergen immunotherapy in atopic dogs: A retrospective study of 664 cases

- cAD affects around 10% of dogs
- Dogs treated with steroids showed poorer response

- Sucessful ASIT results in modulation of T- and B-cell responses, increased T-regs, skewing of specific-antibody isotopes from IgE to IgG, as well as inhibition of migration of eosinophils, basophils and mast cells to tissues and release of their mediators.
- Largest study investigating efficacy in atopic dogs
- For ASIT to be successful, an early desensitisation of mast cells and basophils, a reduction of type 2 helper T-cells and an induction of interleukin (IL)-10-secreting inducible regulatory T and B cells seems to be necessary.

1.2 Canine Atopic Dermatitis

1.2.1 2023 Update on the role of genetic factors, environmental factors and allergens in canine atopic dermatitis 2023 ICADA

Current evidence on the role of genetic and environmental factors and allergic sensitisation since last review update since last review 2015

1. Genetics Canine atopic dermatitis (cAD) is a hereditary, generally pruritic and predominantly T-cell-driven inflammatory skin disease, involving an interplay between skin barrier abnormalities, allergen sensitisation and microbial dysbiosis 7 GWAS (genome wide linkage and association studies) and one candidate genere study Filaggrin mutations not detected in three studies of WHWT but it was implicated in a group of Labrador retrievers in the UK but not from other locations. A GWAS identified two SNPs associated with AD GSD gene sequence on plakophilin 2 but followup study disputed because no diff between AD and control dogs Only two GWAs since ICADA 2015 WHWTs genes

2. Environment Protective factors - growing up in a rural environment with contact to farm animals, a diet rich in dietary fibre, high food diversity and early contact with siblings and peers. Parasites Two recent studies invetsigated the relationship between Toxocara canis and cAD - T. canis infections may helpd against development of cAD? lab beagles - 6 controls and 6 infected with T. canis - experimentally sensitised to D. farinae - Infected dogs higher decrease lesional scores and shorted pruritus after D. farinae challenge - suggests T. canis infections may have protective effect against D. farinae-induced cAD flares

3. Allergens House dust mite the most common. High rate of cross reactivity between house dust mitr and storage mites, ectoparasites and sarcoptic mites may explain false positives in allergy testing.

4. Summary Although five breeds (boxer, bulldog, Labrador retriever, pug and WHWT) are considered as predisposed worldwide prevalent varies Several miRNAs have been identified in recent years that have been shown to play a role in the regulation of gene expression in immune

1.2.2 2015 Treatment of canine atopic dermatitis: 2015 updated guidelines from the International Committee on Allergic Diseases of Animals (ICADA)

1. Acute

   Oral type 1 antihistamines might provide a small and limited benefit in some dogs with AD (SOR B). Due to their mode of action and for an optimal benefit, oral type 1 antihistamines should preferably be given before a flare occurs to block the effects of histamine (SOR C). Clinical benefit might also occur due to the sedative effect of first generation type 1 antihistamines (e.g. diphenhydramine, chlorpheniramine...) (SOR C). Due to their limited efficacy, type 1 antihistamines are likely to be more beneficial in dogs with mild AD (SOR C). There is no evidence supporting the use of topical type 1 antihistamine formulations to treat canine AD (SOR C). Oral EFAs are not useful to treat acute flares of AD due to the length of time needed for any possible beneficial effect to occur.

2. Chronic Dogs with AD should be treated year-round with an effective flea control regimen. Supplementation with oral EFAs Summary of 2010 guidelines: The oral intake of EFAs, especially those rich in omega-6 EFAs either as supplement or in enriched diets can influence superficial skin lipids and improve the gloss and quality of the coat. Oral EFAs might also provide some small benefit in reducing clinical signs of AD in dogs, but the limited degree of improvement expected makes it unlikely that EFA supplementation would be suitable for monotherapy of canine AD. The benefit of EFAs, if any, might not be seen before two months of supplementation. At this time, there is no evidence of superiority for any particular EFA combination, dosage, ratio or formulation (including enriched diets) to improve skin and coat

quality in dogs with AD. In general, EFA-enriched diets provide higher amounts of EFAs than oral administration. Topical lipid formulations can help normalize existing stratum corneum lipid barrier defects in dogs with AD (SOR C). Because of inconsistency in outcomes of clinical trials, there is still insufficient evidence for the benefit of lipid-containing topical formulations to recommend these as monotherapy for canine AD (SOR B). The benefit, cost and ease of use of topical EFA-containing formulations as adjuvant therapy for canine AD must be weighed against those of feeding oral EFA supplements or enriched diets (SOR C). The benefit of topical EFA- containing formulations is likely minimal in dogs already fed EFA-rich diets or EFA supplements (SOR C). As orally administered EFAs can normalize stratum corneum lipid in the same way as a topical lipid mixture (QOE 3) [36–38], the addition of topical EFA-containing formulations to dogs already fed high levels of EFAs is likely to provide little added benefit. In a 12-week RCT, a hydrocortisone aceponate spray (Cortavance, Virbac) showed a similar efficacy and tolerance compared to oral ciclosporin (Atopica, Elanco Animal Health) (QOE 1). Masitinib (Masivet/Kinavet, AB Science) appears to offer some benefit in dogs with chronic AD, but this effect must be weighed against the risk of severe renal adverse drug events that requires the performance of periodic urinalyses to detect developing proteinuria (SOR A). Masitinib might be a useful alternative for atopic dogs with signs not responding to other approved drugs (SOR C). A large RCT confirmed that masitinib at 12.5 mg/kg once daily was moderately effective in reducing clinical signs in atopic dogs. The development of a protein-losing nephropathy in some dogs, which, if unrecognized could be potentially fatal, is a limitation of masitinib treatment. An open RCT study evaluating pentoxifylline at the high dose of 20 mg/kg three times daily, either alone or in combination with oral EFA supplementation, reported a significantly greater improvement in skin lesions and pruritus of these interventions over placebo; the effect seemed highest for dogs treated with the combination of pentoxifylline and EFAs (QOE 2). Updated 2015 recommendations: There is currently insufficient evidence supporting the use of oral probiotics as nonspecific immunotherapy for prevention.

1.3 Feline Atopic Syndrome

1.3.1 2021 Treatment of the feline atopic syndrome – a systematic review Ralf Mueller, Tim Nuttall et al

In this review, there was good evidence for the efficacy of systemic glucocorticoids and ciclosporin, and limited evidence for the efficacy of topical glucocorticoids, oclacitinib and allergen-specific immunotherapy in feline atopic skin syndrome.

Evidence pointed to low-to-moderate efficacy for antihis-tamines, fatty acids and palmitoyl ethanolamide. Feline asthma, there was good evidence for the efficacy of oral and inhaled glucocorticoids, and limited evidence of moderate efficacy for allergen-specific immunotherapy. reaction patterns include miliary dermatitis, self-induced alopecia/hypotrichosis, the eosinophilic granuloma complex (eosinophilic granuloma, eosinophilic plaque, indolent ulcer) and/or excoriations-ulcers on the head and neck. **ASIT** Recommendations seems to be an efficacious therapy for FASS (QOE 2; SOR B). However, some studies were presented only as abstracts with very limited information,23,25 none of the studies were controlled or randomised, and all were characterised by unclear outcome measures, making final assessment difficult. By contrast, there is evidence of moderate-to-good efficacy of ASIT in naturally occurring feline asthma (QOE 2; SOR B) and moderate efficacy of RIT in cats with experimental asthma. **Systemic glucocorticoids** Recommendations are rapid and effective in most cats with FASS (QOE 1; SOR A). Treatment with 1.4–1.5 mg/kg once daily of methylprednisolone-induced remission in 33 of 36 cats within 14 days. By contrast, 1 mg/kg once daily of prednisolone (approximately 50% of the above dosages) was much less effective. Once in remis-sion, treatment can be tapered to the lowest and least frequent dosage that maintains remission (QOE 1; SOR A). On average, this equated to 20–25% of the starting dosage. Feline asthma - good evidence for clinical efficacy of glucocorticoids - based on experiementaly sensitised cats Topical (HCA) rapidly effective in some cats Recommendations **ciclosporin** - GI signs most common +/- anorexcia and weight loss. Gingival hyperplasia rare. Based on the available evidence in a large number of cats with FASS, ciclosporin at a dose of 7 mg/kg once daily is efficacious in the treatment of reaction patterns caused by FASS (QOE 1; SOR A). Insuffience evidence for asthma. If get *Toxoplasma Gondii* while on treatment can get more severe signs. Recommendations **Oclacitinib** - overall good response with 1 mg/kg once or twice daily - limited evidence for asthma Recommendations **Bronchodilators** - frequently mentioned but no evidence. Recommendations

H1-receptor blocking antihistamines - well tolerated - 2.37 sedation with chlorphenamine,. Advised effects in 11 of 10 with cyprohepatadine. Oral antihistamines could provide a small and limited benefit in some cats with FASS and this is not likely to result in good-to-excellent response in most cases (QOE 2; SOR B). The available evidence supports the use of chlorphenamine as a first-line H1R-antihis-tamine (QOE 2; SOR B). No evidence for use in cats with asthma Recommendations **Essential fatty acids and palmitoylethanolamide** - limited evidence for moderate efficacy of EFA supplmentation in cats with milary dermatitis. Moderate devidence for PEAum in FASS. Insufficient evidence for both in feline asthma. Recommendations **Maropitant** - one study 2mg/kg orally SID for 4 weeks. Increase salivation. Limited evidence of good efficacy in FASS. No evidence in asthma. **Antibiotics** - amoxiclav significantly reduced mean lesion size of eosinophilic plaques (96%) and indolent ulcers (43%) compared to placebo. These cats diagnosed with secondary bacterial infections. In cats with asthma 4 days of doxycycline did not influence asthamtic response. Guidelines recommend topical over systemic were possible. **Inhaled lidocaine** - one study, lidocaine may serve as adjunctive therapy in feline asthmatics with mild beneficial effects on airflow obstruction (QOE2; SOR B). **Mesenchymal stem cell therapy** - limited evidence of mild-to-moderate long-term efficacy of MSC in the treatment of feline asthma (QOE2; SOR B).

2 Drugs

2.1 2024 Pharmacology of drugs used in autoimmune dermatopathies in cats and dogs: A narrative review

- Glucocorticoids (GC) are synthesised from cholesterol through steroidogenesis. Predominantly in the adrenal cortex, although local GC production also has been reported in the lungs, intestine and skin.

- Glucocorticoids are lipophilic and diffuse easily through the cell membranes. Once in the cell cytosol, GCs bind to glucocorticoid receptors (GR) and translocate into the nucleus as GC–GR complexes via binding to proteins known as importins. In the nucleus, the GR interacts with DNA and proteins to alter gene expression.

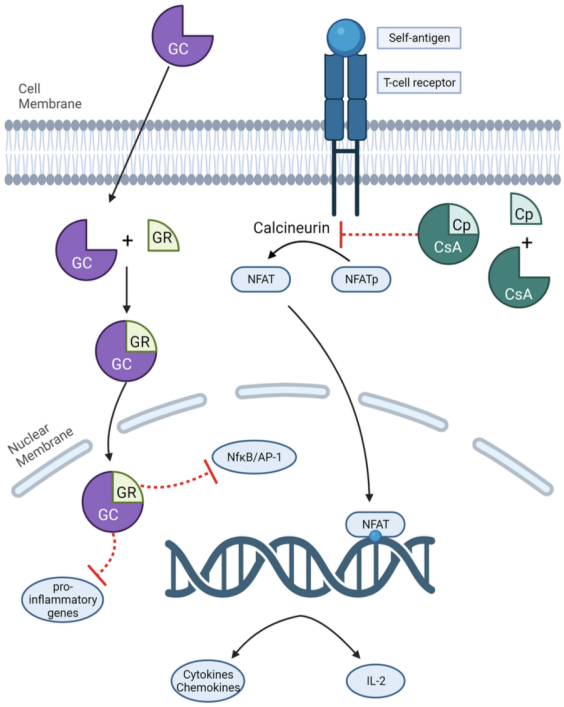

FIGURE 1 Schematic drawing of the mechanism of action of glucocorticoids and ciclosporin A. AP-1, activator protein-1; Cp, cyclophilin; CsA, ciclosporin; GC, glucocorticoid; GR, glucocorticoid receptor; IL-2, interleukin-2; NFAT, nuclear factor of activated T cells; NFκB, nuclear factor-κB.

- Following oral administration of prednisone, prednisolone concentrations in the plasma of healthy dogs are approximately sixfold higher than the concentrations of prednisone
- Ciclosporin A (CsA) is derived from the soil fungus *Beauveria nivea*
- Ciclosporin A is classified as a calcineurin inhibitor; its primary immunosuppressive effect is the inhibition of T-lymphocyte function
- Activated calcineurin dephosphorylates nuclear factor of activated T cells (NFAT), thereby allowing its translocation into the nucleus, which sub- sequently upregulates transcription of genes important for innate and adaptive immunity such as interleukin (IL)-2, IL-4, tumour necrosis factor (TNF)- and TNF- . Interleukin-2 in particular, is a potent T-lymphocyte stimulator: it induces proliferation and differentiation of naïve CD8+ T cells into effector T cells by promoting secretion of granzyme B and perforins; it stimulates the proinflammatory activity

of T helper (Th)-dependent B cells, antigen-presenting cells, mast cells, basophils and eosinophils; and it influences the differentiation of CD4+ T cells into Th1 or Th2, and subsequently affects the proliferation and differentiation of natural killer (NK) cells and B cells

- Ciclosporin A acts by binding to intracellular cyclophilin, which creates a complex that has a high affinity for calcineurin. The binding of the ciclosporin–cyclophilin complex with calcineurin inhibits its function of dephosphorylating NFAT and thus prevents the translocation of NFAT into the nucleus. Without NFAT in the nucleus, the aforementioned inflammatory cytokines are not transcribed and full T-lymphocyte activation is impaired.

- Ciclosporin is primarily metabolised in the liver by the cytochrome P450 3A (CPY3A) family of metabolising enzymes. Several drugs that also are metabolised by this enzyme will affect the blood concentration of CsA if given concurrently. Of these drugs, azole anti- fungals (e.g. ketoconazole and fluconazole) are often used along with CsA (especially in large dogs) because they decrease the metabolism of CsA, and therefore increase blood and skin CsA concentrations. This enables a CsA dose reduction of 50%–70%,45 which reduces the overall cost of therapy.

- The most common adverse effect reported with CsA is gastrointestinal (GI) upset, with vomiting (28%) and diarrhoea (14%) the most frequently reported clinical signs in dogs Gastrointestinal upset is usually transient and resolves with dose reduction. Anecdotally, storing CsA capsules (Atopica) in the freezer for 30–60min before oral administration reduces the incidence of vomiting, and the author has found this beneficial in preventing vomiting in some dogs. When stored in a –20°C freezer for one month, the stability and absorption of CsA in dogs is not impacted.

- Other adverse effects include gingival hyperplasia, cutaneous papillomatosis and op- portunistic infections. Opportunistic bacterial (Nocardia spp., Burkholderia cepacian complex)81–83 and fungal (Alternaria spp., Curvularia spp. and Aspergillus spp.)

Similar to dogs, the most common adverse effects of oral CsA in cats are diarrhoea and vomiting. In cats that were previously infected with feline herpesvirus-1 (FHV-1), administration of oral CsA at the dose of 7mg/

kg/day for 42days could result in reactivation of FHV-1 yet the clinical signs were mild and self-limiting. Acute fatal toxoplasmosis secondary to CsA therapy has been reported in cats yet is still considered rare.

Azothioprine It is a pro-drug of 6-mercaptopurine (6-MP) that exerts its immunosuppressive effects by interfering with nucleotide synthesis. Because AZA is a cytotoxic drug, it should be used with caution with other alkylating agents that interfere with DNA synthesis (e.g. cyclophosphamide) as it may lead to profound myelosuppression. There is some evidence that concurrent use of GC and AZA may increase the risk of acute pancreatitis.

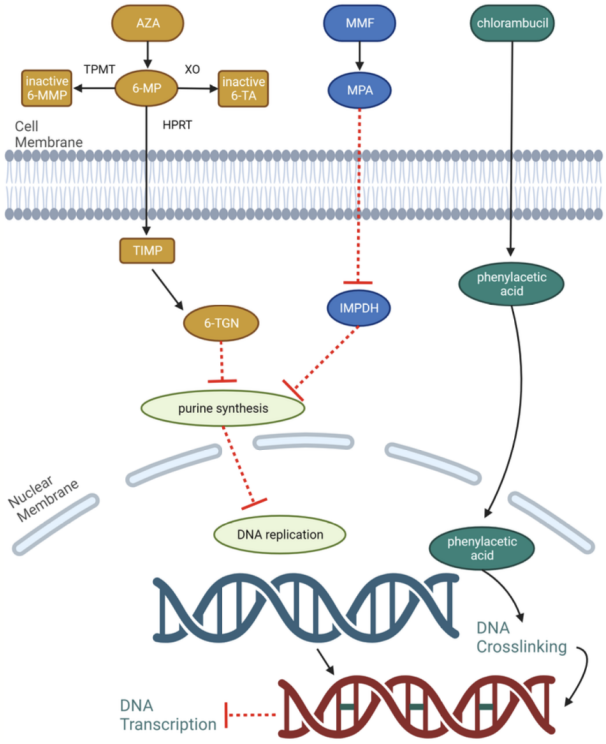

FIGURE 2 Schematic drawing of the mechanism of action of azathioprine, mycophenolate mofetil and chlorambucil. 6-MMP, 6-methylmercaptopurine; 6-MP, 6-mercaptopurine; 6-TA, 6-thiouric acid; 6-TGN, 6-thioguanine; AZA, azathioprine; HPRT, hypoxanthine-guanine phosphoribosyltransferase; IMPDH, inosine monophosphate dehydrogenase; MMF, mycophenolate mofetil; MPA, mycophenolic acid; TIMP, 6-thioinosine monophosphate; TPMT, thiopurine *S*-methyltransferase; XO, xanthine oxidase.

CHLORAMBUCIL Chlorambucil is an anticancer drug from the nitrogen mustard group. Chlorambucil is generally well-tolerated in cats and dogs, although GI effects such as inappetence, vomiting and diarrhoea may be seen. However, cytotoxic myelosuppression can occur 7–14days after initiation of

treatment. Other less common adverse effects include reversible myoclonus and Fanconi syndrome, both of which were reported only in cats.

MYCOPHENOLATE MOFETIL Mycophenolate mofetil (MMF) is a pro-drug that is converted to mycophenolic acid (MPA), where it exerts its pharmacological activity. Interestingly, MPA was first isolated from Penicillium stonoliferum in 1913 where it was discovered to possess antibiotic, antiviral and anti- inflammatory properties.

Mycophenolate mofetil exerts its immunosuppressive effect by inhibiting the formation of guanine nucleotides.

OCLACITINIB Oclacitinib is a Janus kinase (JAK) inhibitor Janus kinases are intracellular, nonreceptor tyrosine kinases. They reside in the cytoplasm of cells and are attached to the intracellular/proximal portion of Type I and Type II cytokine receptors. There are four family members of the JAKs—JAK1, JAK2, JAK3 and TYK2— and they play an important role in the transduction of cytokine-mediated signals through the JAK–signal transducers and activators of transcription (JAK–STAT) pathway. Upon binding of a ligand (e.g. cytokines and growth factors) to the receptor, the JAKs are activated and phosphorylate the intracellular domain of the receptor, thereby creating docking sites for the STAT molecules, which are signalling proteins. Once docked, the STAT molecules are further phosphorylated by the JAKs and then released back into the cytoplasm, where they form dimers with other phosphorylated STAT molecules. The dimerised STAT molecules translocate into the nucleus and bind with the DNA to transcript genes that regulate immunity, inflammation and haematopoiesis. Cytokine receptors can be grouped based on which JAKs are associated with the receptor complex.

While cytokines involved in allergy, inflammation and pruritus bind receptor complexes that utilise JAK1, the binding of other cytokines or growth factors involved in haematopoiesis (e.g. erythropoietin) and innate immunity (e.g. IL-12) activate receptors which are associated with the pairing of JAK2/JAK2 or JAK2/TYK2.156 Higher extra-label doses of oclacitinib are associated with immunosuppressive activity. Lymphocyte- enriched cells treated with 10M of oclacitinib (equivalent to 3–4mg/kg twice daily) resulted in reduced secretion of IL-2, IL-15, IL-18 and IFN-, which inhibits the proliferation of T cells. Higher doses of oclacitinib also have been shown to induce apoptosis of canine CD4+ and CD8+ T cells in vitro. In a more recent study, oclacitinib prevented the generation (rather than inducing depletion) of regulatory T cells and the production of IL-10, which are important to maintain immune tolerance. Taken together, higher doses ofoclacitinib or doses used concurrently with another immunosuppressive drug can have immunosup-

pressive effects on the immune system.

Pharmacokinetics and pharmacodynamics Adverse effects Owing to the MoA, higher doses of oclacitinib could lead to impaired T-cell proliferation and increased risk of infection. Indeed, during the initial safety study, oclacitinib induced cutaneous papillomas, demodicosis and bacterial pneumonia in several 6- and 12-month-old dogs (package insert; Apoquel, Zoetis). In a retrospective study of 53 dogs with AD treated with prolonged twice-daily administration of oclacitinib (0.4–0.6mg/ kg twice daily), pyoderma, gastrointestinal signs and otitis externa were the most common adverse effect reported; only three dogs developed mild neutropaenia. In an feline immunodeficiency virus (FIV)-positive cat, treatment with oclacitinib (1mg/kg twice daily) for feline atopic skin syndrome resulted in fatal disseminated toxoplasmosis; the clinical signs developed fivemonths after initiation of this therapy. In cats, doses of 1–2 mg/kg every 12 h for 28 days were shown to be safe and well-tolerated, although the higher doses did result in gastrointestinal signs in two of 10 cats. Long-term studies with a large number of cats have not been performed and therefore, the long-term safety of oclacitinib in cats is as yet unknown. At present, oclacitinib is not licensed for use in cats.

BRUTON'S TYROSINE KINASE INHIBITOR Bruton's tyrosine kinase (BTK) is an important signalling protein that serves as a link between the B-cell receptor (BCR) and B-cell proliferation and survival. Adverse effects reported from the study involving dogs with PF treated with PRN473 included immune-mediated polyarthritis (n = 1; Week 12), mast cell tumour (n = 1; Week 4), peripheral lymphad- enopathy (n = 2) and pancreatitis (n = 1). Of the four dogs that received PRN1008 for canine PF, only one dog had pyometra, and increased ALT and aspartate aminotransferase. In tolerability studies using an unrelated BTKi (G278), hepatotoxicity was reported in dogs.