New drugs in dermatology

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A new class of insecticides: Isoxazoline

Isoxazoline is a new class of potent insecticides including Fluralaner, afoxolaner and sarolaner amongs others [1-3].

The mode of action studies of this class of drugs demonstrated that these compounds control insects by inhibiting GABA-gated chloride ions channels [1]. All these compounds are acting against fleas and ticks in a similar way. GABA-gated chloride ion channels are the target of several ectoparasites such as ivermectin, fipronil or cyclodienes [4]. However, ivermectin binds a distinct site and activates rather than blocks GAGA-gated chloride ion channels [5]. That is the reason why, it is very unlikely that insects which exhibit resistance to commonly used insecticide compounds will also show cross-resistance to this class of drug [4].

The safety profile of this class of drug is excellent, as demonstrated in several studies [6, 7].

Another very interesting feature of this group of ectoparasitic compounds is the length of activity. In example, Fluralaner has been shown to be active against ticks and fleas for three months[8]. The activity of Afoxolaner is more limited but still very long, one month[2].

Interestingly, these drugs demonstrated a wide spectrum of activity against acarids and insects [9]. Studies have shown efficacy to sarcoptes, otodectes and even demodex [10, 11]. For this latter indication, even though the first results are encouraging, additional studies on various form of canine demodicosis are warranted. In fact, all studies published yet have been carried out on juvenile demodicosis, a form of the disease often associated with spontaneous cure.

Fluralaner can also be used in cats and in spot-on[12, 13].

Last but not least several studies have shown a possible and safe association with other drugs, especially endoparasitic drugs [14-16].

IL31, the new target for atopic patients

Oclacinitib is not really a new drug as the first studies mentioning its efficiency for the control of allergic pruritus were published a few years ago [17-19]. However, this drug was not widely distributed and many practionners are still not very familiar with its use.

Oclacitinib belongs to a large family of so-called JAK inhibitors but this specific compounds exhibits the unique property of blocking IL31 [17, 20]. This cytokines belongs to the group of Th2 cytokines and specifically induces prutitus in carnivores. Interestingly, it has been recently shown that IL31 is one of the first activated gene in a model of allergic dogs. As pruritus is not only the consequence but also one of the most important inducer of development of AD, oclacitinib is a very potent anti-allergic drug. In fact, pruritus induced stratum corneum impairment, which, in turn, facilitates allergen and microbe penetration in the living epidermis. One of the most fascinating feature of oclacitinib is the speed of activity. This drug alleviates pruritus within a few minutes, which is sometimes mandatory, especially in patients which have very severe itch behaviour. After several weeks of use, Oclacitinib demonstrates a similar efficacy when compared with references drugs such as glucocorticoids or Cyclopsorine[21]. Some studies have shown that it could be associated with these drugs [22]. This latter feature allows combinations that are sometimes very helpful for patients. The safety profile of this drug is good and short-term use is associated with less side-effects

than cyclosporine or glucocorticoids. Its however worth mentioning that very long- term studies and data of the pharmacovigilance are still lacking.

Oclacitinib has however some limitations. It cannot be used in dogs under one year, mainly because it could induce demodicosis in some patients. As well, it has been observed that some dogs may have a deep rebound of the pruritus when the drug is discontinued. It is also difficult to taper or discontinue the treatment. In some rarer occasions, dogs responding well initially seem to respond more modestly after a few weeks of treatment. Efficacy in cats not yet well documented[23]

Oclacitinib is certainly not the drug that will solve all problems associated with the treatment of atopic dogs but it definitively belongs to the arsenal, that practionners should get, to treat adequately our allergic patients

Lokivetmab is a very recently registred anti-IL31 antibody. The target of this drug is IL31 and the drug should control on a longer term the clinical signs of atopy[24, 25] . The injectable compound is administered once monthly and could adequately complete a symptomatic treatment with none of the drug mentioned above. Studies on the efficacy, especially long-term efficacy, are still missing and further independent studies are warranted.

It is also wort recalling that the first trials with anti IgE monoclonal antibodies were conducted recently in allergic dogs [26].

New routes for allergen-specific immunotherapy

Allergen-specific immunotherapy is the only etiologic treatment of the allergic disease. In this regard, every improvement is welcome [27]. During decades, ASIT has been applied subcutaneously and success rates ranges from 50% to 75% depending on the authors. In humans new routes for ASIT have been tested, especially transdermal, sublingual and intralymphatic. In veterinary allergology, some recent studies demonstrated that sublingual or intralymphatic may be, at the least, as effective as the subcutaneous route [28-30]. More importantly, it seems that these routes are safe and may lead, at least in some patients, to more rapid and more pronounced improvement. It has also been shown that some patients not responding to regular subcutaneous IT responded better to another route.

Some other progress have been made in this domain. In particular, a Japanese group recently presented fascinating data showing a remarkable improvement of DF sensitized atopic dogs when treated with an ASIT solution composed with Derf2 allergens and adjuvant pullulan [31]. A Spanish group presented recently safety data on the use of allergoids for ASIT[32]. Allergoids are modified allergens. Results in human allergology are very promising. The same group also presented data on another adjuvant (mannan), while data coming from Hungary suggested that associating lactobacillus strains improve the efficacy of ASIT [32-34].

Last but not least a first successful attempt was recently made to desensitized food allergic dogs [35].

New drugs for AD: why not trying Palmitoylethanolamine?

Palmitoylethanolamine is a naturally-occuring bioactive lipid with anti-itch, -pain and –inflammation properties. It has recently been shown that an ultra-micronized solution administered orally improves significantly the pruritus and lesions of about 60% of the treated atopic dogs. This open study is very encouraging especially because only a minority of treated dogs experienced side-effect, generally mild [36].

1. Ozoe, Y., et al., *The antiparasitic isoxazoline A1443 is a potent blocker of insect ligand-gated chloride channels.* Biochem Biophys Res Commun, 2010. **391**(1): p. 744-9.
2. Dryden, M.W., et al., *Evaluation of fluralaner and afoxolaner treatments to control flea populations, reduce pruritus and minimize dermatologic lesions in naturally infested dogs in private residences in west central Florida USA.* Parasit Vectors, 2016. **9**(1): p. 365.
3. McTier, T.L., et al., *Discovery of sarolaner: A novel, orally administered, broad-spectrum, isoxazoline ectoparasiticide for dogs.* Vet Parasitol, 2016. **222**: p. 3-11.
4. Shoop, W.L., et al., *Discovery and mode of action of afoxolaner, a new isoxazoline parasiticide for dogs.* Vet Parasitol, 2014. **201**(3-4): p. 179-89.
5. Asahi, M., et al., *Differential mechanisms of action of the novel gamma-aminobutyric acid receptor antagonist ectoparasiticides fluralaner (A1443) and fipronil.* Pest Manag Sci, 2015. **71**(1): p. 91-5.
6. Walther, F.M., et al., *Safety of fluralaner chewable tablets (Bravecto), a novel systemic antiparasitic drug, in dogs after oral administration.* Parasit Vectors, 2014. **7**: p. 87.
7. Walther, F.M., et al., *Safety of concurrent treatment of dogs with fluralaner (Bravecto) and milbemycin oxime-praziquantel.* Parasit Vectors, 2014. **7**: p. 481.
8. Kilp, S., et al., *Comparative pharmacokinetics of fluralaner in dogs and cats following single topical or intravenous administration.* Parasit Vectors, 2016. **9**(1): p. 296.
9. Rohdich, N., R.K. Roepke, and E. Zschiesche, *A randomized, blinded, controlled and multi-centered field study comparing the efficacy and safety of Bravecto (fluralaner) against Frontline (fipronil) in flea- and tick-infested dogs.* Parasit Vectors, 2014. **7**: p. 83.
10. Beugnet, F., et al., *Efficacy of afoxolaner in a clinical field study in dogs naturally infested with Sarcoptes scabiei.* Parasite, 2016. **23**: p. 26.
11. Beugnet, F., et al., *Efficacy of oral afoxolaner for the treatment of canine generalised demodicosis.* Parasite, 2016. **23**: p. 14.
12. Fourie, J.J., et al., *Efficacy of orally administered fluralaner (Bravecto) or topically applied imidacloprid/moxidectin (Advocate(R)) against generalized demodicosis in dogs.* Parasit Vectors, 2015. **8**: p. 187.
13. Walther, F.M., M.J. Allan, and R.K. Roepke, *Safety of concurrent treatment of cats with fluralaner and emodepsid-praziquantel.* Parasit Vectors, 2016. **9**(1): p. 322.
14. Rehbein, S., et al., *Efficacy of afoxolaner plus milbemycin oxime chewable tablets against naturally acquired intestinal nematodes in dogs.* Vet Parasitol, 2016. **217**: p. 29-35.
15. Foy, J.M., A.M. Rashmir-Raven, and M.K. Brashier, *Common equine skin tumors.* Compend Cont Educ Pract Vet, 2002. **24**(3): p. 242+.
16. Walther, F.M., et al., *Safety of the concurrent treatment of dogs with Bravecto (fluralaner) and Scalibor protectorband (deltamethrin).* Parasit Vectors, 2014. **7**: p. 105.
17. Gonzales, A.J., et al., *Oclacitinib (APOQUEL((R))) is a novel Janus kinase inhibitor with activity against cytokines involved in allergy.* J Vet Pharmacol Ther, 2014. **37**(4): p. 317-24.
18. Cosgrove, S.B., et al., *Efficacy and safety of oclacitinib for the control of pruritus and associated skin lesions in dogs with canine allergic dermatitis.* Vet Dermatol, 2013. **24**(5): p. 479-e114.
19. Cosgrove, S.B., et al., *A blinded, randomized, placebo-controlled trial of the efficacy and safety of the Janus kinase inhibitor oclacitinib (Apoquel(R)) in client-owned dogs with atopic dermatitis.* Vet Dermatol, 2013. **24**(6): p. 587-97, e141-2.
20. Collard, W.T., et al., *The pharmacokinetics of oclacitinib maleate, a Janus kinase inhibitor, in the dog.* J Vet Pharmacol Ther, 2014. **37**(3): p. 279-85.
21. Gadeyne, C., et al., *Efficacy of oclacitinib (Apoquel(R)) compared with prednisolone for the control of pruritus and clinical signs associated with allergic dermatitis in client-owned dogs in Australia.* Vet Dermatol, 2014. **25**(6): p. 512-8, e86.

22. Little, P.R., et al., *A blinded, randomized clinical trial comparing the efficacy and safety of oclacitinib and ciclosporin for the control of atopic dermatitis in client-owned dogs.* Vet Dermatol, 2015. **26**(1): p. 23-30, e7-8.
23. Ortalda, C., et al., *Oclacitinib in feline nonflea-, nonfood-induced hypersensitivity dermatitis: results of a small prospective pilot study of client-owned cats.* Vet Dermatol, 2015. **26**(4): p. 235-e52.
24. Michels, G.M., et al., *A blinded, randomized, placebo-controlled trial investigating three dose levels of lokivetmab (ZTS-00103289), a caninized anti-canine IL31 monoclonal antibody, for the reduction of pruritus and associted skin lesions in dogs with atopic dermatitis.* Veterinary Dermatology, 2016. **27 (suppl.1)**: p. 55.
25. Michels, G.M., et al., *A minimally restricted blinded, randomized, placebo-controlled trial of the safety of lokivetmab (ZTS-00103289), a caninized anti-canine Il31 monoclonal antibody, in client-owned dogs with atopic dermatitis.* Veterinary Dermatology, 2016. **27 (Suppl.1)**: p. 56.
26. Hammerberg, B. and S. Eguiluz-Hernandez, *Therapeutic anti-IgE monoclonal antibody single chain variable fragment (scFv) safety and immunomodulatory effects after one time injection in four dogs.* Vet Dermatol, 2016.
27. DeBoer, D.J., *The future of immunotherapy for canine atopic dermatitis.* Veterinary Dermatology, 2016. **27 (suppl.1)**: p. 8.
28. Fischer, N., et al., *Intralymphatic immunotherapy: An effective and safe route for canine atopic dermatitis.* Veterinary Dermatology, 2016. **27 (Supll.1)**: p. 56.
29. Timm, K., R. Mueller, and C.S. Nett, *Evaluationof the long term effect of intralymphatic immunotherapy in the management of canine atopic dermatitis.* Veterinary Dermatology, 2016. **27 (Suppl.1)**: p. 56.
30. DeBoer, D.J., M. Verbrugge, and M. Morris, *Clinical and immunological responses of dust mite sensitive, atopic dogs to treatment with sublingual immunotherapy (SLIT).* Vet Dermatol, 2016. **27**(2): p. 82-7e23.
31. Kawano, K. and T. Mizuno, *The effects of next generation allergen-specific immunotherpay (Allermune HDM) in canine atopic dermatitis.* Veterinary Dermatology, 2016. **27 (suppl.1)**: p. 9.
32. Casanovas, M. and V. Zalve, *Safety evaluation study of specific immunotherapy based on allergoids adsorbed onto aluminium hydroxide in dogs.* Veterinary Dermatology, 2016. **27 (Suppl.1)**: p. 73.
33. Gonzales, J.L., M. Casanovas, and V. Zalve, *Safety and the efficacy of immunotherapy based on mannan-conjugated polymerised extracts in allergic dogs sensitized to mites.* Veterinary Dermatology, 2016. **27 (Suppl.1)**: p. 75.
34. Tarpataki, N., B. Buranski, and M. Terenyi, *The effect of allergen specific immunotherapy and Gynevac injection on the clinical signs and blood CD4/CD8 lymphocyte ratio of atopic dogs, a pilot study.* Veterinary Dermatology, 2016. **27 (Suppl.1)**: p. 79.
35. Maina, E. and E. Cox, *A double blinded, randomized, placebo-controlled trial of the efficacy, quality of life, tolerability and safety of food allergy specific sublingual immunotherapy in client-owned dogs with food allergy: results of a small pilot study.* Veterinary Dermatology, 2016. **27 (Suppl.1)**: p. 77.
36. Noli, C., et al., *Efficacy of ultra-micronized palmitoylethanolamide in canine atopic dermatitis: an open-label multi-centre study.* Vet Dermatol, 2015. **26**(6): p. 432-40, e101.