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Review

Sublingual Immunotherapy in Human and Canine Atopic Dermatitis: A Mini Review

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Abstract: Atopic Dermatitis (AD) is a prevalent disease that affects both humans and animals. Dogs share similar environments with the owners and spontaneously develop a disease that is clinically and immunologically identical to AD in humans. In past decades AD has become more and more common in both dogs and humans, possibly due to the increased exposure to indoor allergens and decreased exposure to parasites and beneficial bacteria. The allergic component plays an important role in both species. Allergen specific immunotherapy (ASIT) has been used with great success in veterinary medicine for decades for the treatment of AD and traditionally has been accomplished with subcutaneous injections. In human medicine, ASIT has been traditionally used for respiratory manifestations of atopic disease and only recently considered for the therapy of AD. Interestingly, dogs primarily express cutaneous manifestations of atopic disease and only rarely progress from cutaneous into respiratory disease, a process referred in human medicine as "atopic march". Recently, sublingual immunotherapy has been replacing subcutaneous immunotherapy both in human and veterinary medicine due to its ease and safety, leading to increased compliance. The purpose of this mini review is to focus on the use of sublingual immunotherapy for AD highlighting similarities and differences between humans and dogs.

Keywords: immunotherapy; sublingual; atopic dermatitis; dog; human

1. Introduction

Allergies are becoming increasingly common in westernized countries both in humans and dogs, possibly due to changes in life style conditions and decreased exposure to beneficial bacteria and parasites that help modulate the immune system. Allergies are chronic and progressive and can significantly impact the quality of life of affected individuals. It is very common for both humans and animals to build an allergic response to an increasing number of allergens over a lifetime requiring strategies to control symptoms in the long-term. In most individuals allergic disease is linked to some type of environmental exposure such as pollens, dust mites, molds, or food. While some allergens can be avoided (e.g., foods), others are difficult to avoid completely (e.g., dust or pollens). Due to the chronic nature, long-term sustainable alternatives are needed.

Many drugs that are effective in decreasing the symptoms also have undesirable long-term adverse effects (e.g., glucocorticoids). The concept of administering increasing doses of allergens with the intent of "re-educating" the immune system to shift from an "over-reactive" (or allergic response) to a more tolerant response is old and it is the base for allergen specific immunotherapy. Over the years many attempts have been done to refine this concept and to identify the most effective dosing regimen and the safest, least invasive, yet effective route of administration. Researchers have also tried to answer the question of threshold of allergens both in terms of number and amounts in order to obtain a clinical response thus trying to find a compromise between science and application of immunotherapy. Despite the multitude of studies and protocols, immunotherapy is still considered an art rather than an exact science and many controversies still exist.

Immunotherapy has been used in both veterinary medicine and human medicine for decades. The original route of administration has been the subcutaneous route with the idea of injecting progressively increasing doses of allergens. With this route of administration adverse effects are described and could be life-threatening such as anaphylactic reactions. The frequency of adverse systemic reactions varies between studies [1] and can range from 3.4% of patients [2] to one per 1600 visits or one per 47 patients [3]. One of the most recently published reports described a rate of 0.1% systemic reactions [4]. The need for increased safety while not jeopardizing efficacy, has led to the exploration of alternative routes of allergen administration. The sublingual route has gained interest in recent years thus the focus of this mini review is to selectively focus on sublingual immunotherapy in a comparative fashion highlighting similarities and differences between the experience in human medicine and the one in veterinary medicine.

2. The Experience in Human Medicine

Atopic dermatitis (AD) is a common, chronic, inflammatory, pruritic skin disease affecting flexural surfaces. The prevalence of AD ranges between 15% and 30% in children and 2%–10% in adults. Secondary Staphylococcal infections are common in atopic patients and further aggravate the severity of clinical signs. Dry skin due to genetically inherited epidermal barrier dysfunction is the main characteristic of the disease. Impaired epidermal barrier function can lead to penetration of allergens, susceptibility to infections and chronic inflammation [5]. Although AD is not considered as a typical allergic disorder, aeroallergens, food allergens, and house dust mites are known facilitating or

aggravating factors of eczematous skin lesions in most of the patients [6]. It is also known that some of the patients with AD may manifest other signs of atopic disease besides skin and may experience an "atopic march" during their life. They may start with cutaneous disease (eczema) at young age and later develop allergic asthma and allergic rhinoconjunctivitis [7]. In about 80% of adult patients with AD, the disease may be associated with positive skin prick test, atopy patch test results, and increased serum IgE levels against specific allergens and concomitant allergic asthma and rhinitis [8]. These patients are described as having an allergic component to their eczema and are more amenable to treatments focused on control of allergen exposure as an allergic trigger is identifiable. Besides allergen avoidance, these patients are also ideal candidates for immunotherapy as their disease results from a combination of skin barrier defect and allergic sensitization.

Allergy treatment includes avoidance measures, pharmacotherapy and allergen-specific immunotherapy (ASIT). ASIT was first described by Noon in 1911 and remains the only treatment directed at the cause of IgE-mediated allergic diseases [9]. The main goal of ASIT is to induce allergen specific tolerance and stimulate T regulatory response. Peripheral T-cell tolerance is crucial for this [10]. ASIT induces important immunomodulatory effects, including induction of Treg with increased production of IL-10 and Transforming Growth Factor beta (TGF-β), Th1 and IgG. A decrease of IgE, Th2, and increase of blocking allergen specific IgG1 and IgG4 antibodies has been observed with ASIT although a decrease of IgE does not necessarily correlate with improvement of clinical signs. Decreased mediator release by mast cells and basophils and impaired IgE-facilitated antigen presentation by dendritic cells have been described after ASIT [11].

Unmodified or modified allergen extracts (allergoids) can be used in ASIT. Allergoids are produced by treating allergens with formaldehyde or glutaraldehyde, and these modified proteins are thought to have a reduced IgE-binding capacity. In most commercial allergens, aluminum serves as an adsorbent for delaying the release of extract. Some of the products contain adjuvants to increase the immunogenicity.

Allergen-specific immunotherapy induces not only symptomatic relief during the treatment, but also provides long-term clinical remission after discontinuation [12]. In addition to the clinical and cost-benefits during and after treatment, ASIT has been shown to prevent the development of asthma and new allergen sensitivities [13] thus it is the only treatment currently available that has the ability to halt the progression of the disease and have a protective effect from future worsening particularly when started at young age [14,15]. Currently ASIT is indicated for the treatment of allergic rhinitis, allergic asthma, and hymenoptera-induced anaphylaxis. Based on these clinical considerations ASIT was initiated to be used in the treatment of AD with limited data [5]. The traditional administration of allergens has been parenteral, and initial attempts to deliver allergens through other routes (e.g., orally) have provided unsatisfactory results [16,17]. As subcutaneous immunotherapy (SCIT) can induce severe adverse effects resulting in anaphylaxis and death, the interest in developing alternative, safer, and yet effective routes of allergen deliveries has grown over the past two decades. The investigation of the sublingual route (SLIT) was started due to the ease of administration. Some allergens, such as grass pollen and house dust mite (HDM) can be delivered through either route, whereas some, such as venoms, are only delivered subcutaneously [10]. Mucosal epithelium has no vasculature and yet contains dendritic cells, so the dendritic cells could be pulsed with less risk for systemic adverse reactions [13]. Thus, SLIT has a better safety profile than SCIT, which makes SLIT also useful for home administration [10]. The immunologic changes associated with SLIT are complex but reported to

be similar to those of SCIT, ranging from modulation of cellular immunity, humoral response, and cytokine profile to promote tolerance.

SLIT has been commercially available and used in Europe with a satisfactory safety profile [8]. In 2014 a few SLIT formulations have been approved by the Federal Drug Administration (FDA) in the United States. Even before the official FDA approval of SLIT formulations, SLIT prescribers had already significantly increased from 5.9% in 2007 to 11.3% in 2011 [18]. The three approved formulations are Oralair® (a mix of five different grasses) produced by Greer, and Grastek® (timothy grass) and Ragwitek® (ragweed) both produced by Merck.

Based on the literature, SLIT is used in allergic rhinitis and asthma, which is associated with rhinitis in both adults and children [19]. Atopic dermatitis is being considered as a promising field of use of SLIT [19]. SLIT is currently accepted as an alternative to injections because of its satisfactory safety profile. Adverse effects are typically limited to itching in the oral cavity and, rarely, gastrointestinal effects. Systemic life-threatening adverse effects have been rarely reported with SLIT although they are still possible. SLIT's efficacy and safety in rhinitis and asthma in children has been confirmed in clinical trials [20]. Most of the clinical trials have focused on the efficacy and safety of SLIT for grass allergies, and fewer studies have been done to investigate other allergens. Based on the data available, the highest level of evidence for effectiveness of SLIT is given with grass pollen extract [12].

A meta-analysis was performed by Bae *et al*. [9], to assess the long-term efficacy of ASIT in patients with AD. They analyzed eight randomized controlled studies, six of which were performed with SCIT and two with SLIT. They demonstrated that ASIT has a significant positive effect on AD, also in long-term treatment for patients with severe AD when administered subcutaneously. Subgroup analyses of ASIT for children and of SLIT did not demonstrate significant effects. They explained these controversial results with the small number of studies and subjects [9].

Mastrandrea *et al*. [21], reported the results of a retrospective study with the treatment of SLIT in 35 patients with AD. Sixteen patients suffered from AD without respiratory allergic symptoms and 19 had AD associated with mild asthma and/or rhinitis. Allergy to respiratory allergens was diagnosed with a skin prick test. Allergens were prepared in a glycerol-saline solution and administered three times a week for 3 years. Only the complete disappearance of skin lesions was considered to indicate effectiveness. In the group without respiratory symptoms, complete remission of skin disease was demonstrated in 12.6% after 6 months, 31.2% after 12 months, and 68.8% of patients after 24 months. One patient developed asthma in this group 3 years after immunotherapy ended. In the group with AD associated to asthma or rhinitis complete remission of skin disease was seen in 0% after 6 months, 36.8% after 12 months and 73.7% of patients, respectively, after 24 months. The authors commented that SLIT was a safe treatment modality in AD and might favorably prevent the progression of atopic march [21]. Pajno *et al*. [6], designed a double-blind, placebo controlled (DBPC) study to assess the effect of SLIT in HDM sensitized children with AD. Patients were treated with SLIT or placebo for 18 months in addition to standard atopic dermatitis therapy. SLIT proved effective in reducing symptoms as presented by significant reduction of SCORAD (Scoring Atopic Dermatitis) index and use of standard medications [6]. However, SLIT did not demonstrate significant clinical benefits in patients with severe AD. The authors concluded that SLIT with a standardized mite extract could be considered safe and effective in children with mild to moderate AD.

In another open non-controlled trial pilot study, 86 patients with AD and IgE-proved HDM sensitization treated with SLIT (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* extracts) for one year. At the end of 12 months a significant improvement, defined as a SCORAD reduction of >30%, was observed in 51 out of 86 patients (59%). In five patients (5.8%) SCORAD values did not change at the end of the observation period. Total and specific IgE levels were significantly decreased after SLIT [8]. The authors also reported that SLIT had allowed a gradual or complete withdrawal of concomitant therapies.

Zheng reported a study with 96 children suffering from AD. The patients were randomized into two treatment groups receiving HDM-SLIT drops or conventional therapy including antihistamines and topical medications. Clinical improvement and complete remission rates were significantly higher in the immunotherapy group than the medication group [22]. Limitations of this study included the lack of a control group and the lack of an objective definition of what was considered clinical improvement. Vanbervliet *et al*. [23], have tested the efficacy of SLIT against HDM in a mouse model of AD, as a proof of concept of using ASIT in type IV skin allergy. Mice were sensitized on the ear by application of HDM and they developed a specific ear inflammation and also distant challenge. After sensitization they were treated either with SLIT or placebo. Mice treated with SLIT did not develop HDM-induced skin inflammation in contrast to placebo [23].

A recently published study specifically addressed the efficacy and safety of SLIT with *Dermatophagoides farinae* drops in patients with AD and investigated related factors influencing the patients' compliance [24]. This was a randomized controlled study in which both groups were allowed pharmacotherapy, and the control group was allowed to receive medication and no vaccine. As there was no vehicle vaccine group the patients were aware of allocation to groups. Authors recorded the daily drug scores of the two groups, compliance and visual analogue scale (VAS) scores, and IgG4 level at various time points. Therapeutic efficacy was estimated by the change in SCORAD index. The reduction ratio of the SCORAD index was calculated by the score decrease from the first month divided by the first month. Patients with a reduction ratio of the SCORAD index ≥90% were considered cured, between 60% and 89% were deemed to gain a marked effect, between 20% and 59% were seen to improve, and ≤19% were believed to be ineffective. The authors defined the total effective rate of treatment as the ratio of cured cases plus cases with marked effect to total cases in each group. The total effective rate in the treatment group (77.78%) was significantly higher than the control group (53.85%) ($p < 0.05$). The treatment group was significantly reduced in daily drug scores and VAS scores compared with the control group at a 12-month follow-up. It is important to note that statistical significance may not always equate to clinically appreciable difference. For example in this study the control group had a VAS at the end of the study of 7.2 while the active ingredient group had a VAS of 6.1, a difference that is most likely not clinically appreciable. More importantly the amount of medications needed to control symptoms was different between the two groups. The authors reported that starting after the first month a significant different in drug scores was recorded between with two groups with the patients on SLIT needing fewer medications to control their clinical signs. Also, the SLIT group had a higher level of serum-specific IgG4 than the control group at 6 and 12 month of treatment ($p < 0.05$). In this report the authors concluded that *Dermatophagoides farinae* drops were a safe and effective SLIT for patients with AD, which was proven to reduce the need for rescue medications. The fact that significant improvement was noted after just the first month of therapy is considered a particularly encouraging result.

SLIT is also an effective treatment modality in food allergies. There have been three DBPC studies with hazelnut, peach, and peanut that suggest that SLIT represents a significant tolerance in allergic response of these foods [13].The potential use for food allergies is of great importance as currently there are no valid alternatives for patients with food allergies other than avoidance. Most recently both oral IT and SLIT have been evaluated for peanut allergy [25]. Peanut allergy is becoming increasingly common in children in westernized countries. Contrary to other food allergies, peanut allergy is rarely outgrown and can have fatal consequences. Thus it is crucial to identify safe and effective therapies for this allergy. In a recently published meta-analysis there was no difference in efficacy between the oral IT or SLIT group. Studies showed a statistically significant benefit of peanut IT in patients with peanut allergy. The main limitation is that these findings are based on an analysis of a small number of randomized controlled studies. It is important to emphasize that failure to demonstrate differences between different therapies is not necessarily the same as proving that there is no difference particularly when the power of the studies is low. In these types of situations all that can be stated is that the results are not conclusive either way. Thus controversy exists on whether there is already sufficient evidence to recommend this form of therapy in the clinics and on the risks for this type of recommendation. In order to make final recommendations, additional larger, well-designed and double-blinded randomized controlled studies are needed.

The preventive effects of SLIT on atopic march are also being studied [26] and it is currently hypothesized that early implementation of SLIT can halt the progression of allergic disease [27]. The preventative effect of SLIT was investigated [28] and showed that during the follow-up period, only 1% of non-asthma patients reported an onset of respiratory symptoms, and only 9.6% of patients undergoing new skin tests showed new sensitizations. It was also found that the clinical benefits were strongly linked to the length of treatment. The authors reported that patients with long-lasting benefits were treated for a mean length of over 2 years while patients that regressed to clinical signs similar to pre-SLIT condition had been treated for approximately 1 year. Thus it was concluded that it was beneficial to prolong SLIT and that the longer SLIT was done, the more likely it was that it could halt the progression of the disease and the development of new sensitizations. Although these findings were limited to the investigation of respiratory disease, they represent very encouraging results to help individuals that would be otherwise genetically predisposed to severe and progressive allergies.

Another longitudinal study evaluated the long lasting effect of SLIT over a 15-year period [29]. The authors reported that in the patients receiving SLIT for 3 years, clinical benefits persisted for 7 years. Patients receiving SLIT for 4 or 5 years showed clinical benefits for 8 years. Thus the authors concluded that a 4-year duration for SLIT was the optimal length of therapy. In terms of new sensitizations, they were reported in all the control subjects over a 15-year period and in less than a quarter of the patients receiving SLIT, thus confirming a positive effect to decrease the development of new allergies.

Effective SLIT doses for many allergens have not been established yet. The effective cumulative SLIT dose with grass pollen is 20 to 30 times higher than the SCIT dose. Most commonly SLIT is used in patients with a single allergen, and multi-allergen SLIT has not been well studied yet [10]. The safety of SLIT is reported to be superior to SCIT although systemic adverse effects can still occur. There are some rare reports of anaphylaxis with SLIT, and the most frequently reported side effects are oral itching, mild local edema, and throat irritation which generally occur within the few days of treatment and resolve spontaneously [17]. Only the first intake needs doctoral supervision. Patients in

SLIT treatment must have an intact oral mucosa and the treatment should not be carried out immediately after teeth brushing [12].

SLIT represents a significant advance because of its efficacy, safety, and convenience [30]. Very few small, randomized trials directly compared efficacy of SLIT with SCIT and could not demonstrate a significant difference in efficacy between the two routes [31]. Many clinical trials on SLIT and AD are ongoing to determine the most appropriate dosing regimen and provide high quality evidence of efficacy for AD [32]. It is important to remember that AD is a multifactorial disease, which includes complex genetic modifications, responsible for skin barrier impairment, and combinations of environmental and endogenous factors that can direct the disease course. For these reasons, we need more controlled and long-term studies to be able to assess the efficacy of SLIT in the treatment of human AD and disease-modifying potential on atopic march.

A recently published review [33] reviewed 266 articles to retrieve data on SLIT for a variety of allergies. One of the challenges in comparing the results of the various studies is that great variation in doses and protocol exists across studies making a direct comparison impossible. SLIT was reported to be effective at a wide range of doses, much larger than the doses used for SCIT. These doses range from the 5–300-fold of those for SCIT. SLIT was found to be very efficacious and the efficacy is sustained for a long time even after discontinuation. Clinical efficacy was maintained for at least one year after discontinuation and immunologic changes were detectable for up to 3 years after [34,35].

3. The Experience in Veterinary Medicine

Dogs are affected with a natural homologue of human AD that has striking clinical, immunologic, and skin barrier impairment similarities with the human counterpart [36,37]. Dogs also share the same environmental conditions, and concomitant occurrence of allergies has been shown in humans and their pets [38]. Interestingly, despite the fact that environmental sensitizations are extremely common in dogs with AD, this species does not experience the “atopic march” in the sense that no development of asthma occurs, even in the individuals with the most severe dermatitis [39]. It is common, however, for the disease to have a chronic progressive course with deterioration of dermatitis and complication by secondary skin infections. Disease starts in young adults and has a familial predilection. A subset of atopic dogs also has food allergies as triggering factor that aggravates the AD flare-ups. Dogs also have a skin barrier impairment, which leads to increased risk for allergic sensitization which progresses with age and pollen exposure. Areas typically affected are the flexural surfaces, and abnormal skin barrier function exists in those areas in young dogs even in absence of clinically appreciable disease. It is currently unknown whether the skin barrier defect is primary or secondary or both. Most dogs with AD have the extrinsic form of the disease with detectable allergen specific IgE to environmental allergens.

Allergen-specific immunotherapy has been successfully used for decades in veterinary medicine and has been recommended whenever feasible for the long-term management of canine AD [40–43]. Traditionally, ASIT in dogs was done by subcutaneous route and it is overall well tolerated [39]. Many protocols and regimen schedules are currently used for SCIT by different dermatologists and no robust studies have been done to compare different protocols. One study evaluated the efficacy between a low dose protocol and a standard protocol and found no significant differences in efficacy [44]. Some clinicians may consider rush protocols for special cases. Although this regimen has been proven to be

reasonably safe and effective [45,46], it is not commonly adopted by most veterinary dermatologists in practice, as it is more labor intensive. Controversy also exists on the maximum number of allergens to be included in SCIT although a general assumption is that using too many allergens may not be ideal as it could possibly dilute the amount of each allergen used and therefore interfere with efficacy. Similarly it is typically not recommended to use mixes and it is preferred to use individual allergens. This recommendation is derived by studies done in human medicine [47,48]. Controlled studies should be done in veterinary medicine to specifically investigate this variable in veterinary medicine. No real standardization has been done in veterinary medicine regarding the extracts, and most of them are crude preparations whose strength is reported in weight/volume and protein content. In terms of mechanisms of action of ASIT in veterinary medicine, one of the investigated mechanisms in dogs is the shift from Th2 to a Th1 response [49] and stimulation of T regulatory response.

Despite the overall good efficacy and safety of subcutaneous ASIT, some owners are reluctant to give injections to their pets emphasizing the need in veterinary medicine for alternative routes of allergen delivery. SLIT is fairly new to veterinary medicine but is so far showing good promise. Great debate exists on how to best utilize SLIT, whether it should be given once daily or twice daily, the best concentration and how its efficacy may compare to SCIT. Due to these uncertainties SLIT is still considered by many dermatologists not the standard of care but a second line of therapy.

In one uncontrolled multi-centric study, 217 privately owned dogs with naturally occurring AD were enrolled to evaluate the efficacy of SLIT while allowing other treatments such as glucocorticoids and cyclosporine [50]. SLIT was administered twice daily in a non-aqueous vehicle using an escalating dosing regimen. Selection of allergens was based on allergy testing and was tailored to each individual patient. The response was recorded after a minimum of 6 months of therapy. Investigators reported a 55% good-to-excellent response to SLIT, meaning that some medication was still required to control symptoms but that the dose or frequency of rescue medications was decreased. Interestingly some dogs that had failed traditional SCIT were able to tolerate and have a favorable response to SLIT. Thus SLIT was effective in decreasing the need for rescue medications and was worth trying in patients that had not responded to SCIT. The reasons for why a patient may respond to SLIT and not SCIT are unknown at this time and need to be investigated. Compliance could be one of them as some owners are reluctant to give injections and are more likely to skip doses than with SLIT. Another interesting observation of this study was that the response to SLIT seemed to be faster than with traditional SCIT with some patients showing a positive response within a few months of therapy. Traditionally with SCIT minimal improvement is expected for the first 6–9 months of therapy. This study was uncontrolled, and it is likely that some placebo effect may have occurred. Placebo effect is well documented in medicine [51] and can be seen in owners' perception of improvement as well as investigator's assessment. Additionally in this open study no evaluation of the effect of immunologic parameters was done.

A vehicle controlled study using a validated experimental model for canine AD also showed a beneficial effect of SLIT [52]. For this study, which lasted one year, eighteen atopic beagles were experimentally sensitized to HDM, timothy grass, and ragweed. Although this study used a small number of patients, it had the strength of being vehicle-controlled, blinded, and controlled for confounding factors such as diet and type of allergy and allergen exposure. Six dogs were allocated to vehicle (glycerin) and twelve to active ingredient (allergens). Response was evaluated both clinically using a validated scoring system and immunologically, measuring allergen-specific IgE, IL-10, and

TGF-beta production by peripheral blood mononuclear cells at various time points. Allergens were administered once daily on an increasing dose over several months' period. Although both groups showed some clinical improvement at the end of the study, the improvement was twice as high in the active ingredient group as in the control group. The authors speculated that the improvement seen in the control group was possibly due to the fact that no allergen exposure was done for many months during the course of the study. Thus the lack of allergen exposure for a year may have led in itself to some improvement of clinical disease. The lack of statistical significance was possibly due to the small number of cases used for this study and the variability among subjects. From the clinical stand point the improvement in some dogs of the active group was considered clinically striking by the investigators as these dogs had been in the colony for a long time and had had a chronic history of severe disease. Larger controlled studies are needed to further investigate whether the lack of significance between vehicle and active ingredient group is real or simply due to small size. SLIT was found to be well tolerated, and no adverse effects were reported during the course of the study. Significant increases in the IL-10 and TGF-beta were found for several allergens in the active group when compared to vehicle supporting the hypothesis of increased T regulatory function. No significant changes in allergen-specific IgE response were noted in that study. A 2-month follow-up after the discontinuation of SLIT demonstrated that some of the immunologic changes induced during SLIT were partially reversed once SLIT was stopped suggesting the need for prolonged treatment.

Interestingly a previous study using oral IT using the same experimental model did not show any benefit [53]. Possible reasons for this reported lack of efficacy may include the short duration of the study (7 months rather than a full year) and the fact that swallowing the allergen immediately rather than placing it sublingually leads to decreased stimulation of the immune system in the oral cavity.

4. Conclusions and Directions for the Future

In conclusion, SLIT represents a safe and effective strategy to help with management of allergic diseases in both people and animals. Much work still needs to be done to standardize protocols and optimize success. The ease of administration and the safety and are all very favorable aspects. Although the ideal dose and protocol have not been established, overall the cumulative dose of allergen used is higher than what is used with SCIT. This could lead to increased cost for the patient.

In veterinary medicine SLIT is particularly new and has still a lot of unknowns. There is no study that has investigated the efficacy of SLIT for food allergies or respiratory disease representing an area where much work still needs to be done. No study has been done either to directly compare the efficacy of SCIT and SLIT, and uncertainty exists on the most effective protocol for SLIT. Practitioners and veterinary dermatologists are currently prescribing SLIT as alternative to SCIT for cases in which owners are reluctant to give injections and/or in case where adverse effects are noted with the SCIT. SLIT typically will require larger amounts of allergens and may not be the appropriate choice for owners with busy schedules due to the fact that it requires daily administration. Some practitioners prescribe SLIT twice daily while others prescribe it once daily. No direct comparison between these two protocols has been done thus the most effective treatment regimen to recommend is unknown. Finally no study has been done in veterinary medicine regarding rush protocols using SLIT. Thus there are a lot of unknowns in veterinary medicine about the best protocol in terms of doses,

number of allergens, and frequency of administration of SLIT. Although SLIT is frequently recommended on the veterinary side, it is important to highlight that there are very few studies and a lot of variables that have not been investigated and that will need to be addressed in order to obtain strong evidence for or against the efficacy of this therapy. A list of some of the unmet needs for canine AD and SLIT is provided in Table 1. Thus, although SLIT has been shown to be effective in human medicine, it may be wise, in veterinary medicine, to recommend SLIT in specific cases rather than for all cases as a first line of treatment. Suitable cases may be cases in which the animal does not tolerate SCIT, did not respond to SCIT or when owners will not do ASIT altogether due to needle phobia.

Table 1. Unmet needs in canine atopic dermatitis (AD).

Evaluation of clinical efficacy of sublingual immunotherapy (SLIT) compared to subcutaneous immunotherapy (SCIT) in large controlled double blinded studies using dogs with naturally occurring disease and evaluation of differences in speed of action between the two routes
Evaluation of clinical efficacy of twice daily *versus* once daily protocol for SLIT
Evaluation of clinical efficacy of SLIT for mites *versus* grasses and single ingredient *versus* mixes
Evaluation of clinical efficacy of high doses *versus* low doses of SLIT
Evaluation of SLIT to decrease new sensitization over time compared to conventional pharmaceutical therapy

As we increase our knowledge in comparative medicine it is becoming more and more evident that the separation between veterinary and human medicine is not as marked as previously accepted and that we can benefit from knowledge that is developed on one species as it may have potential applications to another one. Although clearly more studies are needed in veterinary medicine to establish the most appropriate protocol and strength of allergens to use for SLIT, so far, this route of administration of allergens has been proven to be well tolerated and able to provide relief to canine patients as it does to humans. Of all therapies available for allergies, ASIT is the only one that can halt the progression of the disease, and even if this has not been demonstrated in dogs yet, it could be beneficial to encourage starting IT at young age in dogs to possibly minimize progression of severity.

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Author Contributions

Ibrahim Ozmen, a human dermatologist, wrote the part of the manuscript on the human experience with SLIT. Rosanna Marsella, a veterinary dermatologist, wrote the veterinary aspect of the paper and took care of all the revisions and final editing.

Conflicts of Interest

The authors declare no conflict of interest.

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