Cat PAD (ToleroMune Cat) for cat allergen-induced rhinoconjunctivitis – first line

SUMMARY

Cat-PAD (cat peptide antigen desensitisation, also known as ToleroMune Cat) is intended to be used as a first line therapy for the treatment of cat allergen-induced rhinoconjunctivitis. If licensed, Cat-PAD will offer an additional treatment option for people with moderate or severe cat allergen-induced rhinoconjunctivitis.

Allergic rhinitis has the highest prevalence of all allergic respiratory diseases, affecting over 20% of the UK population (equating to over 12 million people) and 400 million people worldwide. The prevalence of cat dander sensitisation in patients with allergic rhinitis in the developed world is around 72%. Over 56% of allergic rhinitis patients presenting for routine care in the UK have moderate or severe disease, and 52% have persistent disease, however this may be an underestimate. The number of people with moderate or severe allergic rhinitis caused by cat dander sensitisation in the UK would therefore equate to over 4.8 million. Allergic conjunctivitis is strongly associated with allergic rhinitis with around 90% of people with allergic rhinitis experiencing at least one day of ocular symptoms per week. Allergic rhinitis is closely linked to other inflammatory conditions, and epidemiological evidence has repeatedly shown the co-existence of rhinitis and asthma.

Allergen avoidance is recommended as first-line treatment for allergic rhinitis, followed by pharmacotherapy aimed at symptom control (mainly antihistamines and topical nasal corticosteroids). For patients with more severe disease, who do not respond to usual therapy, specific immunotherapy is recommended. Cat-PAD is currently in a phase III clinical trial comparing its effect on allergy symptoms and use of symptomatic medication against treatment with placebo.
TARGET GROUP

- Rhinoconjunctivitis: cat allergen-induced; moderate to severe – first line.

TECHNOLOGY

DESCRIPTION

Cat-PAD (cat peptide antigen desensitisation, also known as ToleroMune Cat) is the first in a new class of synthetic peptide immuno-regulatory epitopes (SPIREs) for the treatment of allergic disease. It is a mixture of seven small MHC II restricted peptides derived from the major cat allergen Fel d 1, a protein produced largely in cat saliva and sebaceous glands. It is has been developed to induce tolerance to cat allergens generated by cat dander (dry cat skin particles), which are a common cause of immunoglobulin E (IgE)-mediated allergic disease. Cat-PAD induces regulatory T cells to down-regulate T cell, B cell and mast cell responses to cat allergen. The short linear peptides in Cat-PAD have been designed to avoid cross-linking IgE on mast cells, which is responsible for both local injection site and systemic reactions. This enables immediate administration of therapeutic doses without the need for dose escalation, which is usually required in the administration of conventional immunotherapy.

Cat-PAD is administered by intradermal injection at approximately 70μg of peptides (in an injection volume of 60μl) for a total of four or eight doses given once every four weeks.

INNOVATION and/or ADVANTAGES

If licensed, Cat-PAD will offer an additional treatment option for people with moderate or severe cat allergen-induced rhinoconjunctivitis.

DEVELOPER

Circassia Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In a phase III clinical trial.

PATIENT GROUP

BACKGROUND

Rhinitis is characterised by nasal symptoms including anterior or posterior rhinorrhea, sneezing, nasal blockage and/or itching. Symptoms occur during two or more consecutive days for more than 1 hour on most days. Allergic rhinitis is the most common form of non-infectious rhinitis and is associated with an immunoglobulin E (IgE)-mediated immune response to specific allergens. It is often associated with ocular symptoms, with allergic conjunctivitis often accompanying allergic rhinitis.

Allergic rhinitis is classified by the severity (mild or moderate to severe) and persistence (intermittent or persistent) of symptoms. Symptoms are defined as ‘mild’ if all of the following
apply, normal sleep, no impairment of daily activities, no impairment of sport or leisure, no impairment of work or school, and symptoms present but are not troublesome; and ‘moderate to severe’ if one or more of the following apply, sleep disturbance, impairment of daily activities, impairment of sport or leisure, impairment of work or school, or troublesome symptoms. ‘Intermittent’ allergic rhinitis is defined as a symptom duration of <4 days per week or <4 consecutive weeks; and ‘persistent’ allergic rhinitis is defined as symptom duration of >4 days/week for >4 consecutive weeks.

NHS or GOVERNMENT PRIORITY AREA

None identified.

CLINICAL NEED and BURDEN OF DISEASE

Allergic rhinitis has the highest prevalence of all allergic respiratory diseases, affecting over 20% of the UK population (equating to over 12 million people) and 400 million people worldwide. The prevalence of cat dander sensitisation in patients with allergic rhinitis in the developed world is around 72%. Over 56% of allergic rhinitis patients presenting for routine care in the UK have moderate or severe disease, and 52% have persistent disease, however this may be an underestimate. The number of people with moderate or severe allergic rhinitis caused by cat dander sensitisation in the UK would therefore equate to over 4.8 million. Allergic conjunctivitis is strongly associated with allergic rhinitis with around 90% of people with allergic rhinitis experiencing at least one day of ocular symptoms per week. Allergic rhinitis onset is typically under the age of 30, with a peak incidence in childhood and adolescence. The symptoms of cat dander sensitisation range from rhinoconjunctivitis to potentially life-threatening asthmatic exacerbations. Studies have shown that sensitisation to cat is also a strong risk factor for asthma. About 20% of allergic rhinitis is not adequately controlled on currently available pharmacotherapy; however only a small percentage warrant desensitisation, principally those with occupational exposure.

Allergic rhinitis is closely linked to other inflammatory conditions, and epidemiological evidence has repeatedly shown the co-existence of rhinitis and asthma; around 80% of asthma patients and 80% of children with eczema also suffer from allergic rhinitis. Rhinitis represents a major cause of morbidity that includes interference with usual daily activities and impaired sleep quality, and it may adversely affect mood. Allergic rhinitis represents a significant healthcare burden; in 2004 treatment costs for allergic diseases and asthma accounted for 10% of all primary care prescribing costs, and direct UK National Health Service costs for managing allergic diseases were estimated at more than £1 billion per year. In 2012, there were 649 admissions for allergic perennial rhinitis (J30.3) in England, resulting in 54 bed-days and 650 finished consultant episodes.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- No relevant guidance identified.

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a Expert personal communication.
Other Guidance

- European Academy of Allergy and Clinical Immunology (EAACI). EAACI: A European Declaration on Immunotherapy. Designing the future of allergen specific immunotherapy. 2012¹².
- WHO Collaborating Center for Asthma and Rhinitis. Severe chronic allergic (and related) diseases: a uniform approach. A MeDALLᵇ, GA(2)LENᶜ and ARIAᵈ position paper. 2012¹³.
- GA(2)LEN–WHO Collaborating Center: Practical guide for skin prick tests in allergy to Aeroallergens. 2012¹⁴.
- British Society for Allergy & Clinical Immunology (BSACI). Immunotherapy for allergic rhinitis. 2011¹⁵.
- BSACI. BSACI guidelines for the management of allergic and non-allergic rhinitis. 2008¹⁵.
- ARIA. Allergic rhinitis management pocket reference. 2008⁴.
- EAACI. Requirements for medications commonly used in the treatment of allergic rhinitis. 2003¹⁶.

EXISTING COMPARATORS and TREATMENTS

The ARIA guidelines³,¹⁷ recommend allergen avoidance as first-line treatment for allergic rhinitis, followed by pharmacotherapy aimed at symptom control (mainly antihistamines and topical nasal corticosteroids). For patients with more severe disease, who cannot avoid exposure⁵, specific immunotherapy is recommended. The only potentially curative treatment in IgE-dependent allergic disease is specific immunotherapy⁷. Pharmacological treatment options for allergic rhinitis include³,¹⁰,¹⁴,¹⁵,¹⁸,¹⁹:
- Saline nasal douching.
- Oral and nasal H1-antihistamines – first-line therapy for intermittent and persistent symptoms – non-sedating (bilastine, desloratadine, rupatadine) or sedating (ketotifen).
- Oral decongestants – adjuvant, intermittent use – ephedrine, phenylephrine, phenylpropanolamine and pseudoephedrine.
- Intranasal decongestants – adjuvant, intermittent use – oxymethazoline, xylometazoline and ipratropium.
- Leukotriene antagonists (unlicensed for this indication) – first-line therapy for intermittent and persistent symptoms – montelukast, pranlukast and zafirlukast.
- Topical cromones – first-line therapy for moderate to severe intermittent, and mild persistent symptoms – e.g. cromoglicate.
- Nasal corticosteroids – first-line therapy for moderate to severe intermittent and persistent symptoms – mometasone, fluticasone, betamethasone, dexamethasone and budesonide.
- Oral corticosteroids – second line therapy for moderate to severe persistent symptoms.
- Specific allergen immunotherapy (unlicensed for this indication) – third-line therapy for moderate to severe persistent symptoms⁶.
Sublingual cat dander extract—e.g. via Oralvac compact pump.

SC cat dander extract – e.g. Alutard SQ.

Treatments for conjunctivitis in association with allergic rhinitis include:

- saline drops (mild cases).
- oral H1-antihistamines.
- intraocular H1-antihistamines – e.g. antazoline, azelastine.
- intraocular cromones – e.g. nedocromil.

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01620762, CP007; aged 12-65 years; Cat-PAD vs placebo; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Circassia Limited.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry[^20^][^21^], manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (not UK), USA and Canada.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n= 1,182 (planned); aged 12-65 years; rhinoconjunctivitis on exposure to cats for ≥2 years; moderate to severe; positive skin prick test to cat hair; cat dander specific IgE ≥0.35kU/L[^6^]; excludes patients with partly controlled and uncontrolled asthma; excludes FEV1 &lt;80% of predicted[^7^].</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to Cat-PAD 6nmol intradermal injection or placebo once every 4 weeks for 28 weeks (4 active doses followed by 4 placebo doses to maintain blinding); Cat-PAD 6nmol intradermal injection once every 4 weeks for 28 weeks (2 courses of 4 active doses amounting to 8 doses); or placebo intradermal injection once every 4 weeks for 28 weeks.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment 28 weeks; follow-up symptom measurements at one year after start of treatment.</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>Measurement of subject allergy symptoms and use of allergy medication.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Symptom scores, rescue medication use, quality of life and incidence and frequency of adverse events (AEs).</td>
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<tr>
<td>Expected reporting date</td>
<td>Not reported.</td>
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</tbody>
</table>

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[^6^]: 1 kU/L = 1 international unit (IU)/ml (1 IU/ml = 3.4ng/ml of human serum IgE).
[^7^]: FEV1: Forced Vital Capacity 1 is the amount of air a person can exhale during the first second of a forced breath.
| Participants | n= 202; aged 18-65 years; rhinoconjunctivitis on exposure to cats for ≥1 year; positive skin prick test to cat allergen; minimum qualifying rhinoconjunctivitis symptom score; excludes patients with partly controlled and uncontrolled asthma, history of anaphylaxis to cat allergen and FEV1 <70% predicted. | n= 89; completed NCT01033344. | n= 50; completed NCT01033344 and NCT01272323. |
| Schedule | Randomised to Cat-PAD 6nmol intradermal injection or placebo intradermal injection once every 2 weeks for 14 weeks (alternating active and placebo for 4 active doses); Cat-PAD 3nmol intradermal injection once every 2 weeks for 14 weeks (8 active doses); or placebo intradermal injection once every 2 weeks for 14 weeks. Subjects then exposed to allergens (Fel d 1 50.19±3.70ng/m³) for 3 hours in an environmental exposure chamber for 4 consecutive days 18-22 weeks after the start of treatment. | Subjects exposed to allergens (Fel d 1 50.19±3.70ng/m³) for 3 hours in an environmental exposure chamber for 4 consecutive days 50-54 weeks after the start of treatment in clinical trial NCT01033344. | Subjects exposed to allergens (Fel d 1 50.19±3.70ng/m³) for 3 hours in an environmental exposure chamber for 4 consecutive days 100-104 weeks after the start of treatment in clinical trial NCT01033344. |
| Follow-up | Active treatment for 14 weeks, then exposure to allergen and follow-up 18-22 weeks after first administration. | Exposure to allergen and follow-up 50-54 weeks after the start of treatment in clinical trial NCT01033344. | Exposure to allergen and follow-up 100-104 weeks after the start of treatment in clinical trial NCT01033344. |
| Primary outcome | Total rhinoconjunctivitis symptom score (TRSS). | TRSS. | TRSS. |
| Secondary outcomes | Total ocular symptom score (TOSS), total nasal symptom score (TNSS), acoustic rhinometry, cat specific IgE and treatment-emergent AEs (TEAEs). | TNSS and TOSS. | TNSS and TOSS. |
| Key results | Cat-PAD 6nmol x 4 doses, Cat-PAD 3nmol x 8 doses vs placebo, respectively at 18-22 weeks: Nonasthmatic population: mean reduction in TRSS, 5.406, 5.136 vs 2.786; mean reduction in TNSS, 2.838, 2.452 vs 1.515; mean reduction in TOSS, 2.568, 2.684 vs 1.271. | Cat-PAD 6nmol x 4 doses, Cat-PAD 3nmol x 8 doses vs placebo, respectively (p value vs Cat-PAD 6nmol) at 50-54 weeks: Nonasthmatic population: mean reduction in TRSS, 6.778, 3.893 (p=0.034) vs 2.908 (p=0.010); mean reduction in TNSS, 3.435, 2.177 (p=0.0702) vs 1.625 | Cat-PAD 6nmol x 4 doses, Cat-PAD 3nmol x 8 doses vs placebo, respectively (p value vs Cat-PAD 6nmol) at 100-104 weeks: mean reduction in TRSS, 5.87, not reported (NR) vs 2.02; mean TNSS at 2 hr exposure, 4.818, NR vs 7.762 (p=0.0090); at 2.5 hr exposure, 5.091, NR vs
Pooled asthmatic and nonasthmatic population: mean reduction in TRSS, 4.992, 4.610 vs 3.096. (p=0.0200); mean reduction in TOSS, 3.343, 1.716 (p=0.0292) vs 1.283 (p=0.0121).

Pooled asthmatic and nonasthmatic population: mean reduction in TRSS, 6.353, 3.636 (p=0.311) vs 2.488 (p=0.006).

AEs

Cat-PAD 6nmol x 4 doses, Cat-PAD 3nmol x 8 doses vs placebo:
TEAEs ≥10%; nervous system disorders, 22.7%, 22.4% vs 33.3%; respiratory, thoracic and mediastinal disorders, 19.7%, 26.9% vs 29%; infections and infestations, 18.2%, 23.9% vs 13%; skin and subcutaneous tissue disorders, 3.0%, 10.4% vs 5.8%.

TEAEs considered related to study drug, 21.2%, 26.9% vs 18.8%.

Not applicable.

Not applicable.

ESTIMATED COST and IMPACT

COST

The cost of Cat-PAD is not yet known. The 2010 costs of other selected immunotherapies (unlicensed in the UK) obtained from a BSACI survey of immunotherapy clinics in the UK are as follows:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Annual cost</th>
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<tbody>
<tr>
<td>Cat subcutaneous injection vaccine: Alutard SQ (ALK Abelló).</td>
<td>200µg Fel d 1 per year (25 injections in first year)</td>
<td>£1,359 (1st year)</td>
</tr>
<tr>
<td>Cat sublingual injection vaccine: Oralvac Compact (Allergy Therapeutics)</td>
<td>144µg total dose per year (0.59µg major allergen per day, 3 puffs per day for 8 months)</td>
<td>£629</td>
</tr>
</tbody>
</table>

IMPACT - SPECULATIVE

Impact on Patients and Carers

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other:
- No impact identified
Impact on Services

- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- None identified
- Other:

Impact on Costs

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
- Other reduction in costs:
- Other:
  - uncertain unit cost compared to existing treatments.
- None identified

Other Issues

- Clinical uncertainty or other research question identified:
  - expert opinion states that hospital on-costs for injectable immunotherapies also needs to be considered.
- None identified

REFERENCES

2. Grönlund H, Saarne T, Gafvelin G et al. The major cat allergen, Fel d 1, in diagnosis and therapy. International Archives of Allergy and Immunology 2010;151(4):265-274.
8. Scadding GK and Williams A. The burden of allergic rhinitis as reported by UK patients compared with their doctors. Rhinology 2008;46(2):99-106.


