Immunothérapie allergénique et marche atopique

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PLAN

- La marche allergique revisitée
- Les bio-marqueurs de la marche allergique
- Comment marche immunothérapie allergénique
- Efficacité de immunothérapie allergénique dans la prévention de la marche allergique
  - Quels phénotypes de rhinite allergique
  - Prévention de l'asthme
  - Quels phénotypes d'asthme (prévention tertiaire)

Atopic march revisited

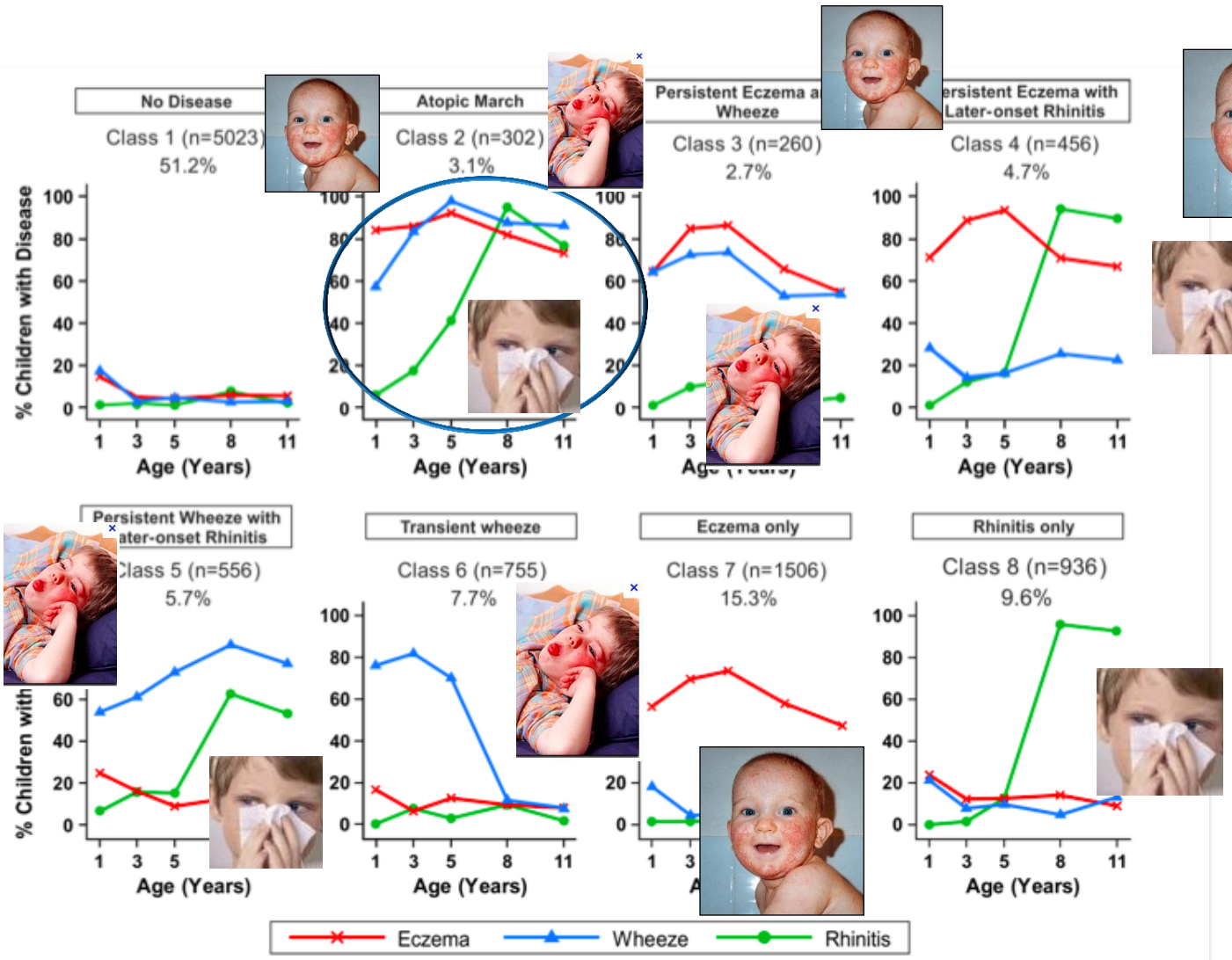


Figure 5. Distinct disease profile classes. Using Bayesian machine learning joint modelling of eczema, wheeze, and rhinitis across two population-based birth cohorts, we identified eight distinct disease profile classes. The number of children and the proportion of the study population are indicated for each class. Plots indicate longitudinal trajectories of wheeze, eczema, and rhinitis within each class.
doi:10.1371/journal.pmed.1001748.g005

Data from two population-based birth cohorts : MAAS & ALSPAC

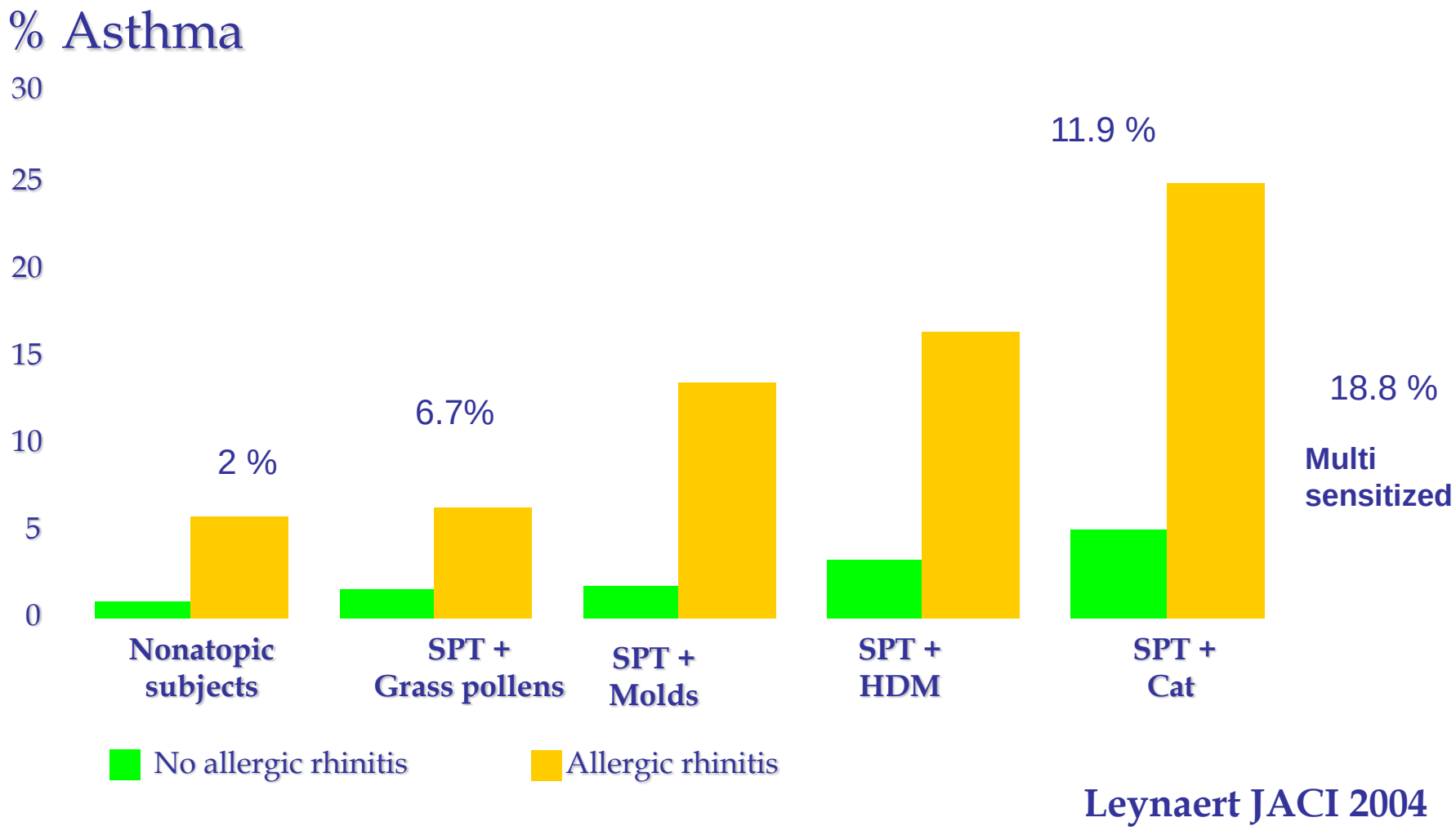
Atopic march revisited

Table 3. Sensitisation distribution in different classes (data on sensitisation from both MAAS and ALSPAC cohorts at age 8 y).

Class Number	Class	Not Sensitised, *N* (Percent)	Sensitised, *N* (Percent)	OR (95% CI)	*p*-Value
1	No disease	3,036 (93.0)	228 (7.0)	Baseline	Baseline
2	Atopic march	62 (29.0)	152 (71.0)	32.6 (23.6–45.2)	<0.001
3	Persistent eczema and wheeze	136 (70.1)	58 (29.9)	5.7 (4.1–7.9)	<0.001
4	Persistent eczema with later-onset rhinitis	159 (47.5)	176 (52.5)	14.7 (11.4–19.0)	<0.001
5	Persistent wheeze with later-onset rhinitis	203 (53.8)	174 (46.2)	11.4 (9.0–14.6)	<0.001
6	Transient wheeze	439 (90.1)	48 (9.9)	1.5 (1.0–2.0)	0.024
7	Eczema only	869 (86.3)	138 (13.7)	2.1 (1.7–2.6)	<0.001
8	Rhinitis only	458 (68.2)	184 (31.8)	5.3 (4.3–6.7)	<0.001
	Total	**5,265 (81.9)**	**1,162 (18.1)**		

Belgrave DC et al. PLoS Med. 2014 Oct; 11(10): e1001748.

Atopic march revisited



Leynaert JACI 2004

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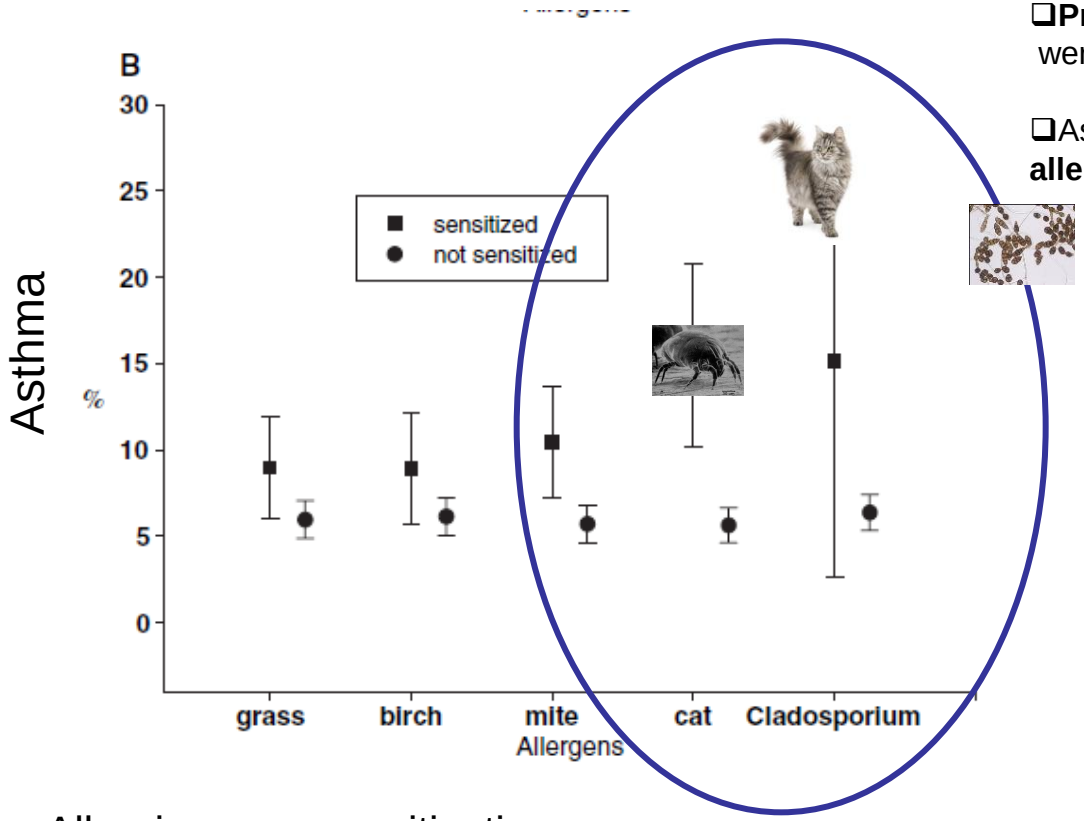
Biomarkers associated with allergic rhinitis phenotypes at asthma progression



- **Prospective** study in which 2656 participants were revaluated at **ten years interval**
- Associations between **perannual and seasonal allergic sensitization** and **incident allergic diseases**

Allergic sensitization **outdoor allergens** (grass and birch pollen) was an important predictor for incident hay fever and at least degree for asthma

Specific IgE antibodies **to indoor allergens** (mite, cat dander, mold) were mainly related to **asthma risk**

Schoefer Y et al . Allergy 2008.63:81-86

RA saisonnière sévère

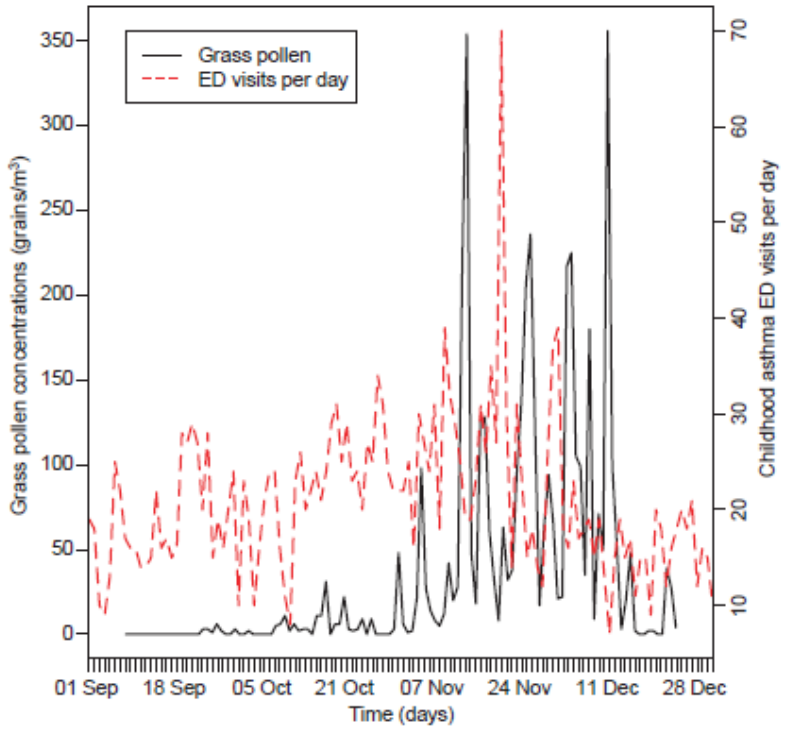


Fig. 1. Daily levels of grass pollen and asthma emergency department presentations among children less than 15 years of age in Victoria between January and December 2003. Dotted line represents emergency department presentations and solid line represents grass pollen during the 2003 grass pollen season.

- Grains pollens augmentent de 20 grammes par m^2
- le risque de venue aux urgences pour crise d'asthme augmentent $p<0,001$

Erbas CEA 2012

Biomarkers associated with allergic rhinitis onset: multiple molecular allergic sensitizations

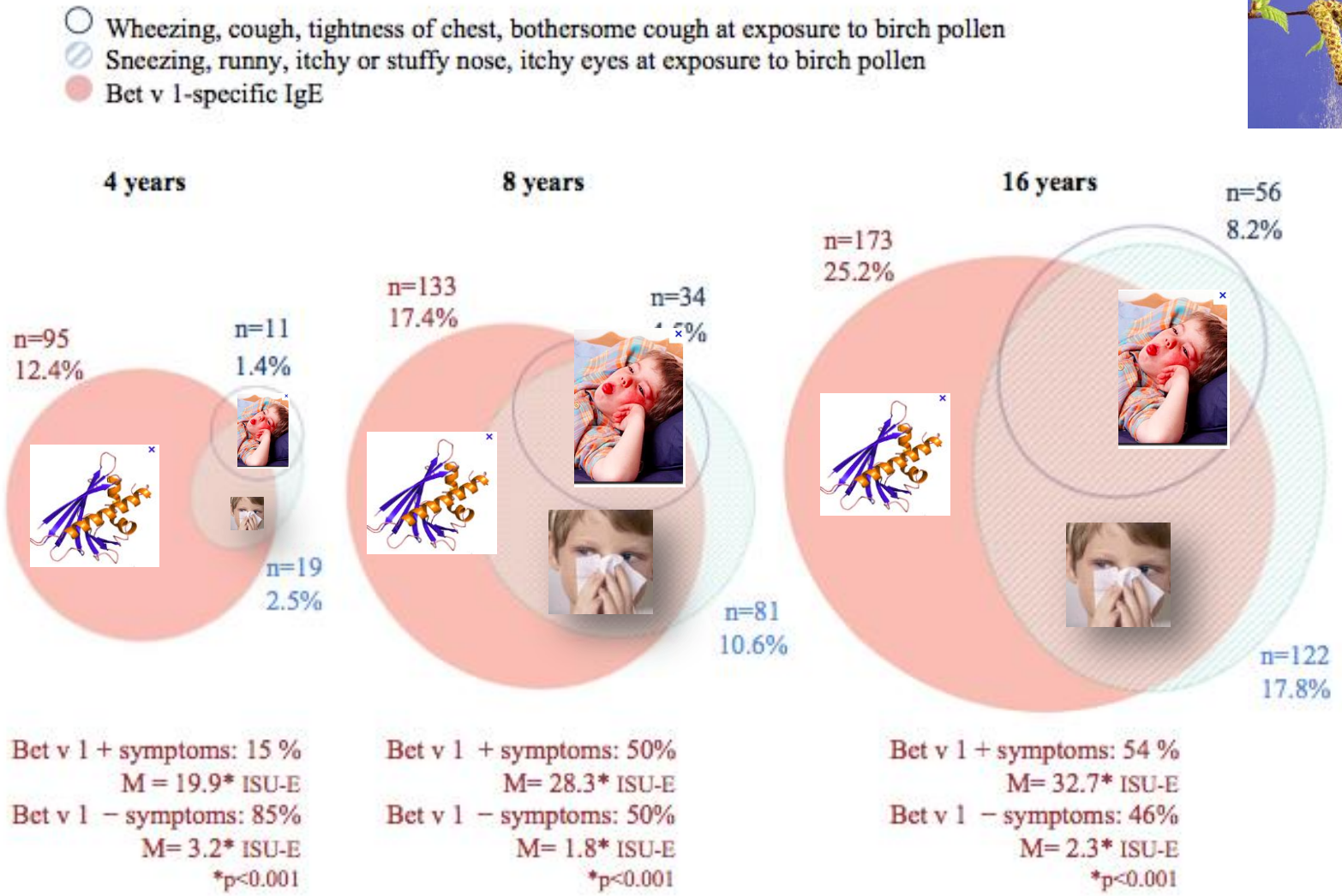


FIG 3. Proportional Venn diagram of numbers of children who reported symptoms after exposure to birch pollen from the *upper* and *lower* airways, respectively, and IgE reactivity to Bet v 1 at 4 (n = 764), 8 (n = 763), and 16 (n = 686) years of age.

Westman M et al. J Allergy Clin Immunol. 2015;135:1199-206

Biomarkers associated with allergic rhinitis onset: multiple molecular allergic sensitizations

LCA identify trajectory of cross sectional sensitization over time

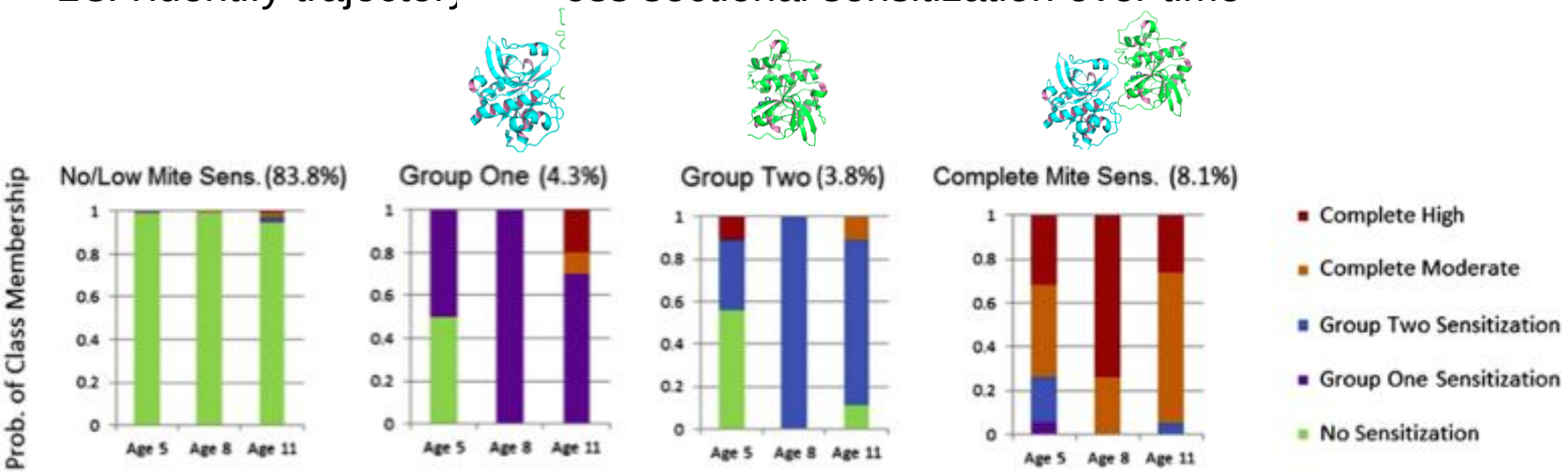
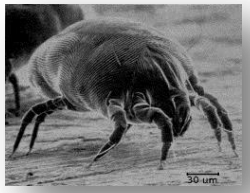
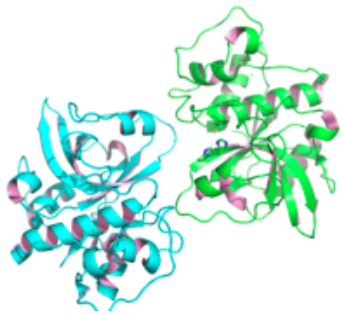


FIG 3. Latent classes inferred for house dust mite allergens to identify trajectories of cross-sectional sensitization classes over time.

Sensitization profiles to components of HDM were stable at 5, 8 and 11 years





Custovic A et al. JACI 2015 May 8. doi: 10.1016/j.jaci.2015.03.041.

Biomarkers associated with allergic rhinitis onset: multiple molecular allergic sensitizations

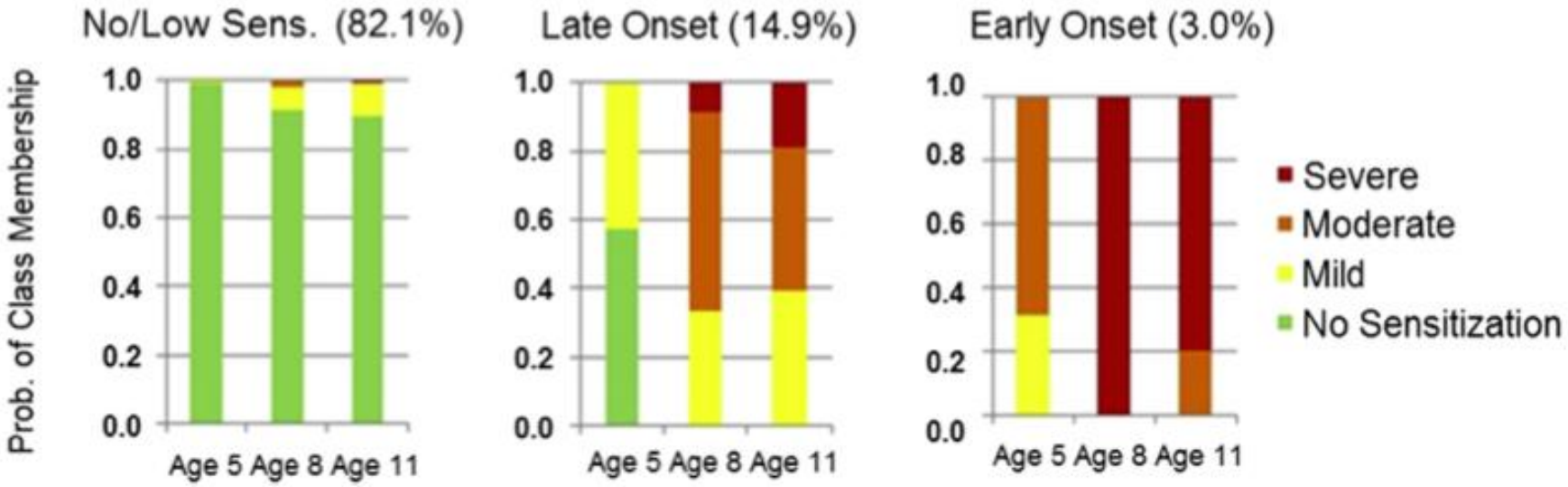


FIG 2. Latent classes inferred for timothy grass allergens to identify trajectories of cross-sectional sensitization classes over time.

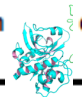
8 molecular components for timothy available at three age time points : 5,8,and 11 years

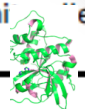
4 cross-sectional sensitization profiles were defined for timothy molecules, as no sensitization, mild, moderate, and severe sensitization.

Early onset trajectory belonged to more severe sensitization profiles over the time compared to late onset

Custovic A et al. JACI 2015 May 8. doi: 10.1016/j.jaci.2015.03.041.

Biomarkers associated with allergic rhinitis onset: multiple molecular allergic sensitizations





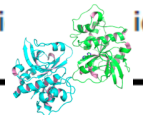


TABLE II. Relationship between longitudinal trajectories for timothy grass and h dust mi ergens in relati ical outcomes of asthma, rhinitis, and eczema

	Timothy grass longitudinal sensitization trajectories		Dust mite longitudinal sensitization trajectories		
	Late onset (n = 97), OR (95% CI), *P* value	Early onset (n = 23), OR (95% CI), *P* value	Group 1 allergens (n = 23), OR (95% CI), *P* value	Group 2 allergens (n = 22), OR (95% CI), *P* value	Complete mite sensitization (n = 54), OR (95% CI), *P* value
Positive methacholine challenge	1.68 (0.97-2.91), .062	2.86 (0.99-8.28), .052	6.90 (2.17-21.97), .001	2.30 (0.84-6.32), .106	6.44 (3.00-13.82), <.001
Current wheeze	1.31 (0.73-2.35), .364	3.63 (1.49-8.86), .005	4.24 (1.69-10.63), .002	4.24 (1.69-10.63), .002	7.13 (3.81-13.34), <.001
Current asthma	1.53 (0.85-2.76), .158	6.20 (2.56-15.01), <.00	4.60 (1.83-11.56), .001	3.02 (1.12-8.10), .029	7.15 (3.80-13.44), <.001
Current rhinitis	5.84 (3.59-9.50), <.00	11.84 (4.25-33.01), <.00	6.11 (2.42-15.38), <.001	2.37 (0.99-5.66), .051	4.07 (2.23-7.42), <.001
Current eczema	1.15 (0.64-2.08), .637	3.71 (1.50-9.18), .004	3.21 (1.28-8.06), .013	0.82 (0.24-2.87), .761	2.17 (1.12-4.20), .021
Current asthma, rhinitis, and eczema	2.20 (0.65-7.46), .207	17.91 (5.55-57.74), <.00	4.43 (0.90-21.88), .068	2.11 (0.26-17.45), .488	5.91 (2.01-17.37), .001
Severe asthma exacerbation ever among wheezy children	1.96 (1.03-3.74), .041	3.91 (1.39-11.02), .010	1.82 (0.68-4.89), .233	1.30 (0.44-3.88), .63	3.29 (1.62-6.67), .001

ORs, 95% CIs, and *P* values are from univariate logistic regression. The reference category is the no/low grass sensitization trajectory.

Custovic A et al. JACI 2015 May 8. doi: 10.1016/j.jaci.2015.03.041.

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Epigenetic modifications and improved regulatory T-cell function in subjects undergoing dual sublingual immunotherapy

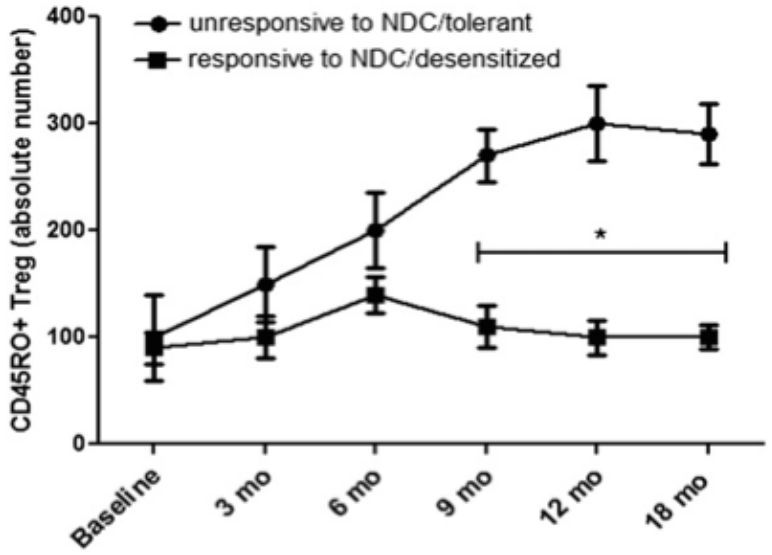

FIG 6. Increased memory Treg cells in tolerized subjects. Longitudinal analysis of memory $CD4^{+}CD25^{high}CD127^{lo}CD45RO^{+}CD62L^{-}Foxp3^{+}$ Treg cells from tolerant (*circles*, n = 7) and desensitized (*squares*, n = 9) subjects after dual SLIT is shown. $*P < .05$. *mo*, Months after baseline.

- The study assessed 20 allergic subjects receiving dual SLIT versus 10 allergic subjects receiving placebo.
- All 30 subjects had documented clinical reactions, positive skin test results, and allergen-specific IgE levels to DM and TG.

Ravi S. Swamy. J Allergy Clin Immunol 2012;130:215-24

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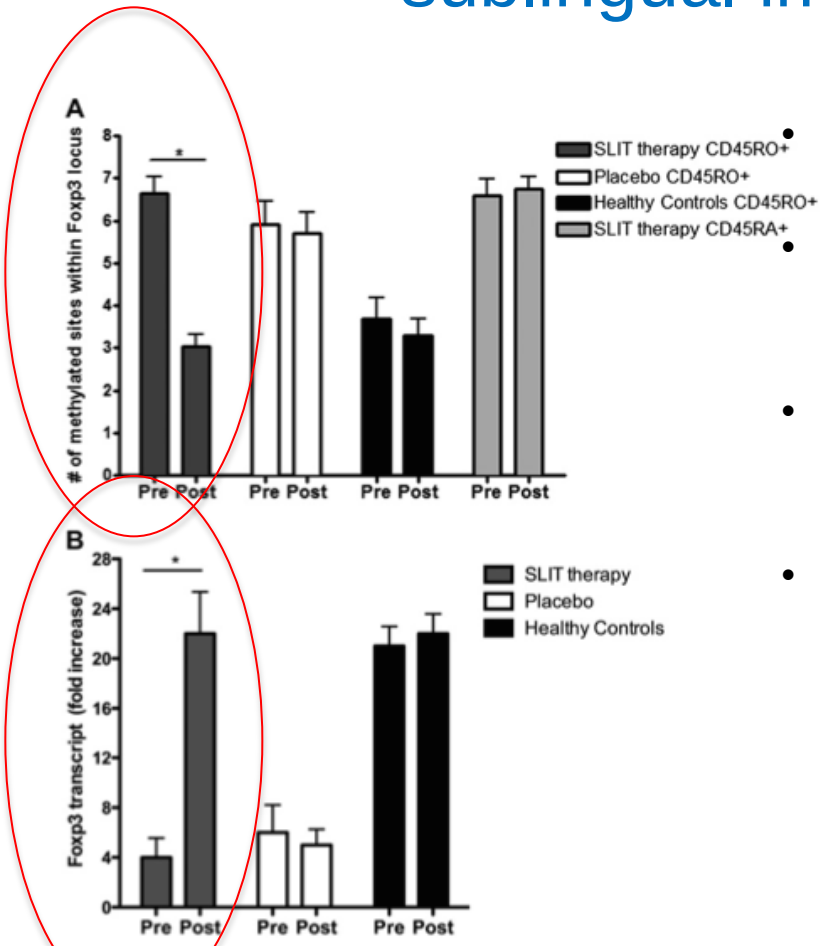

FIG 5. Epigenetic regulation of Foxp3 in Treg cells from subjects treated with dual SLIT. **A,** CpG methylation of purified memory or naive Treg cells from subjects before *(Pre)* and 12 months after *(Post)* therapy. **B,** Analysis of Foxp3 transcript from memory Treg cells. Foxp3 transcription levels are shown as relative fold increase over expression of the housekeeping gene β-glucuronidase. *$P < .05$.

- **cDNA** was synthesized with 500 ng of total RNA transcribed
- Gene expression was measured in real time with primers and reagents . All **PCR assays were performed in triplicates**.
- Data were presented as relative **fold expression of Foxp3 to the expression of the housekeeping gene b2-microglobulin.**
- For quantification of CpG methylation islands,
  - **genomic DNA (Qiagen) purified from memory Treg cells** before and after SLIT was bisulfite treated and sequenced for CpG methylation sites
  - in the promoter (n 5 8 sites) and intronic (n 5 13 sites) regions of the Foxp3 locus.

Ravi S. Swamy. J Allergy Clin Immunol 2012;130:215-24

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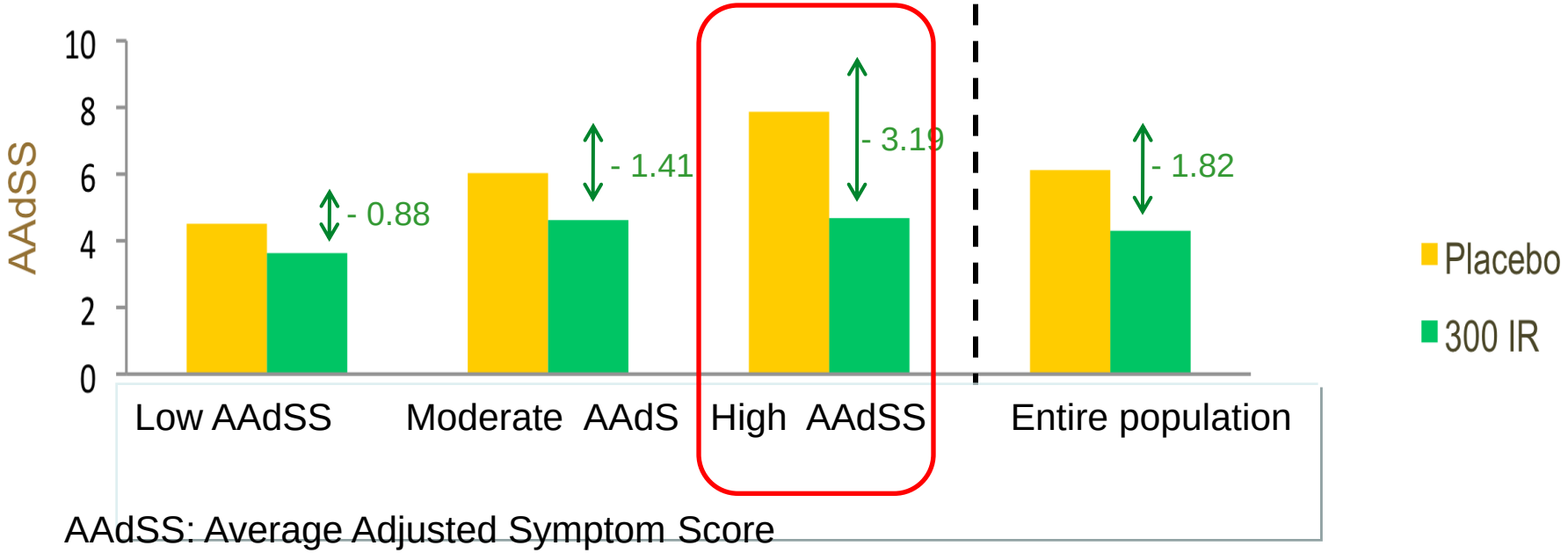
Allergic rhinitis phenotype: Moderate to severe allergic rhinitis

278 Children and adolescents with grass pollen-AR, efficacy of 300IR five-grass pollen tablet administrated on pre and co-seasonal protocol compared to placebo



AAdSS: Average Adjusted Symptom Score

The most improvement is in the group with more severe disease, which may define a good responder phenotype

Wahn Journal of Allergy and Clinical Immunology 2009

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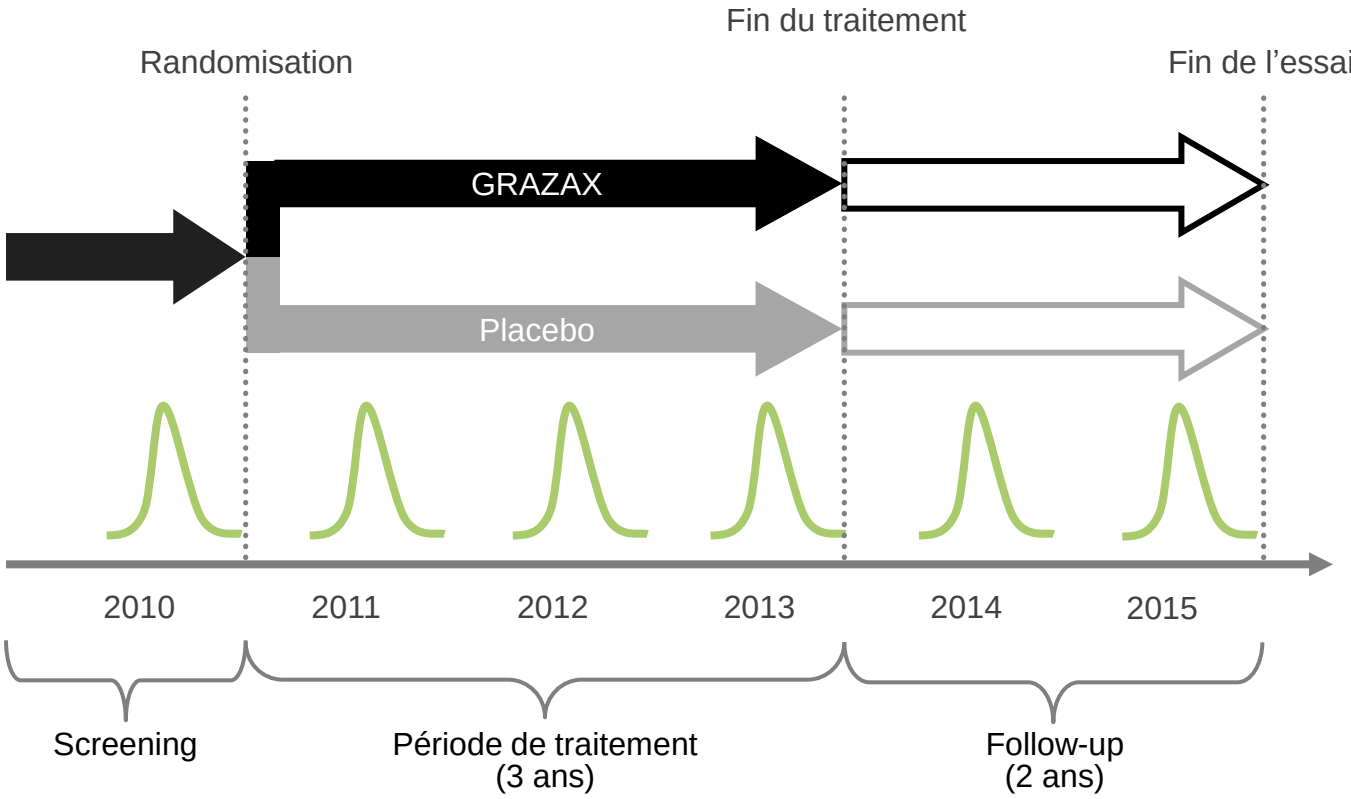
GAP : schéma de l'essai



Valovirta E et al. Clin Therapeutics 2011; 33(10):1537-46

GAP : Diagnostic de l'Asthme

1. **période écoulée durant la dernière visite**
    1. Au moins 1 épisode de **sifflement/toux/souffle court ou oppression thoracique**

        ET

        une modification du **VEMS ≥ 12% après administration de β2 agoniste**

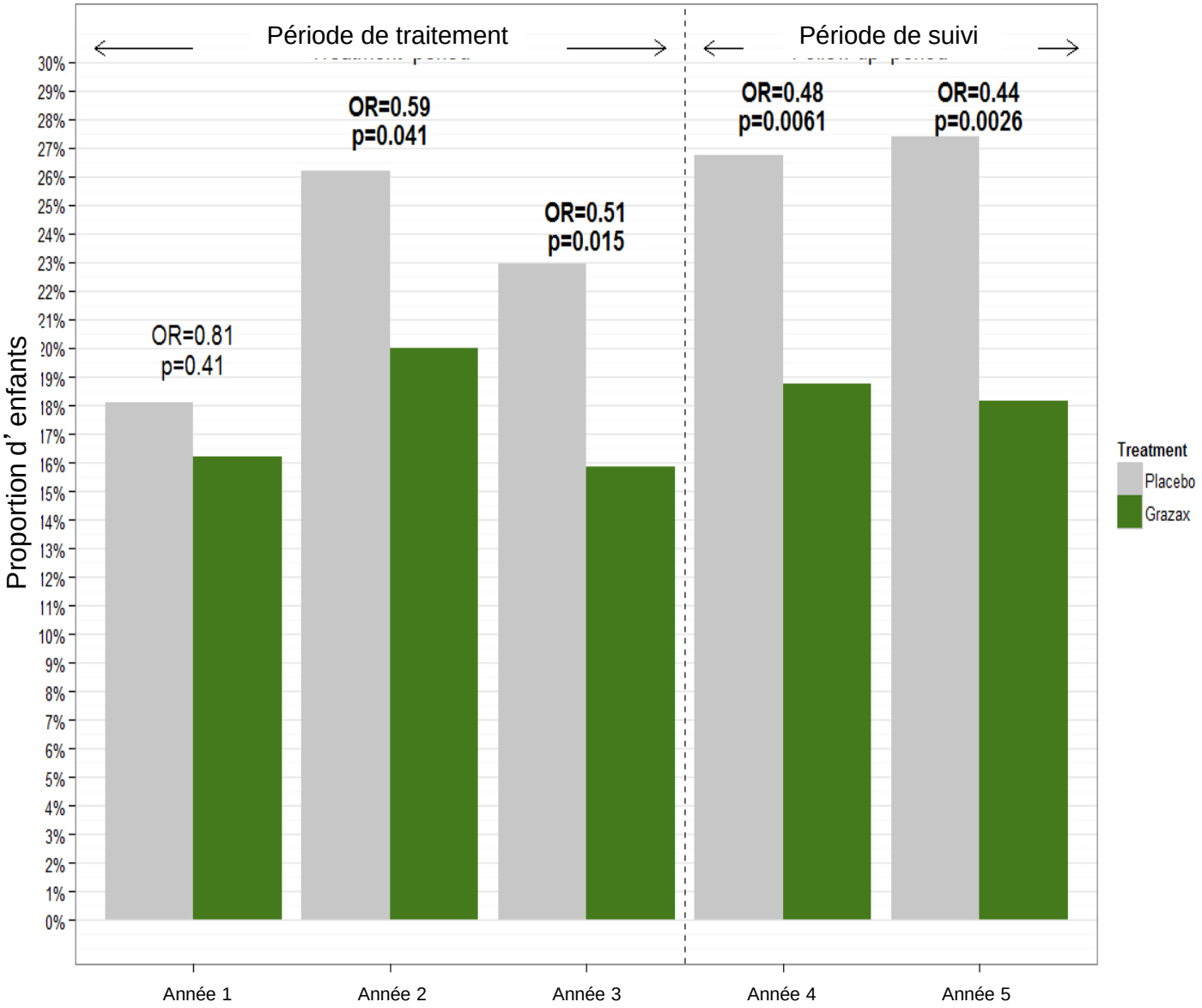
2. **durant l'examen physique**
    1. **Sifflement** avec ou sans bradypnée expiratoire et **amélioration clinique**

        ET

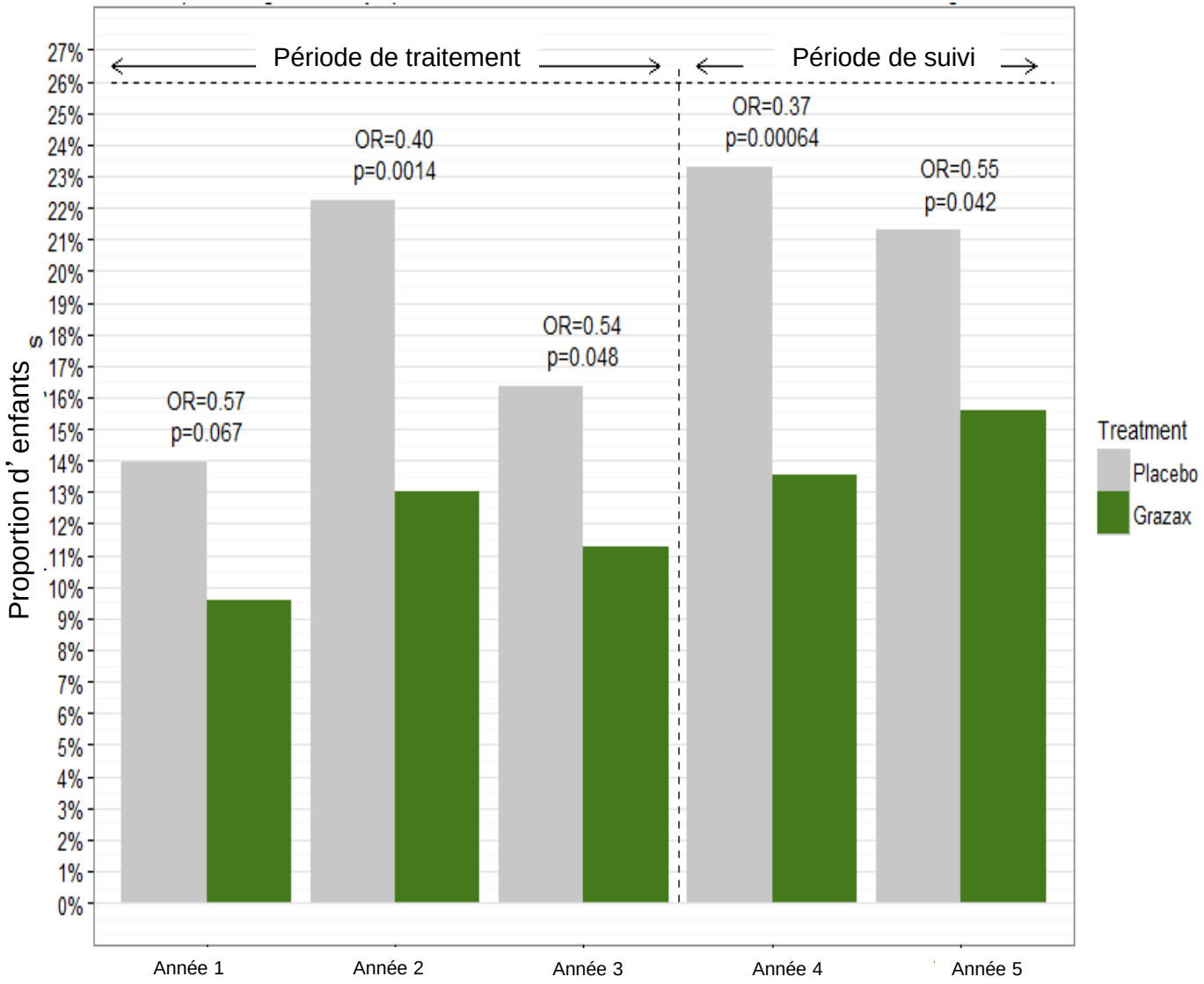
        1.a après prise de médicaments pour l'asthme constaté par l'investigateur

        1.b ou amélioration du **VEMS ≥ 12%** après administration de β2 agoniste

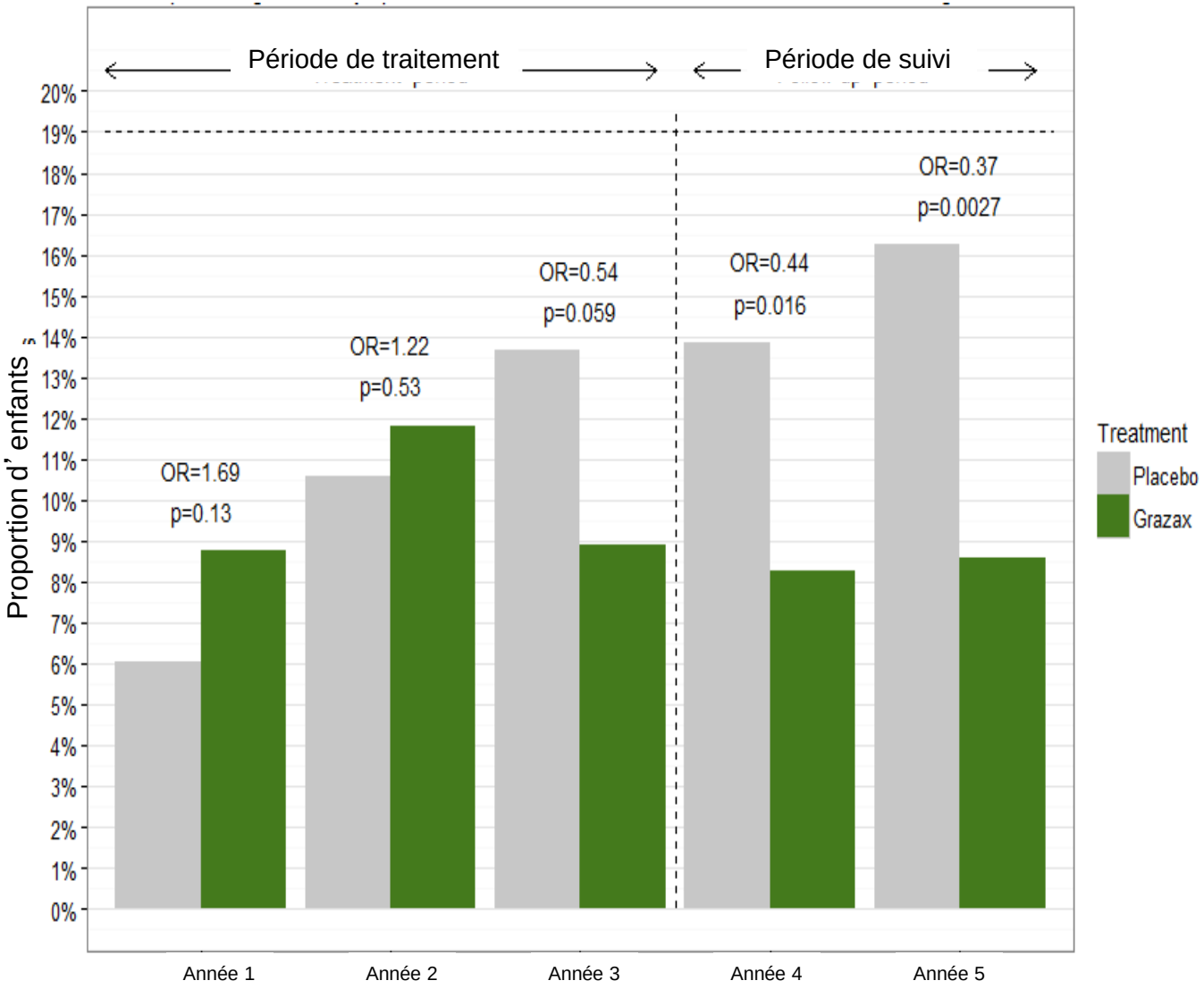
Symptômes d’asthme ou médicaments pour l’asthme



Symptômes d'asthme ou médicaments pour l'asthme – Visites en saison pollinique



Symptômes d'asthme ou médicaments pour l'asthme - Visites en hiver



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Asthme allergique de l'enfant devient multiple

Table I. Characteristics of children according to cluster analysis in the entire population (n = 125)

	Total cohort (n = 125)	Cluster 1 "Multiple Allergies and Severe Asthma" (n = 20)	Cluster 2 "Pollen Sensitization with Severe Exacerbations" (n = 12)	Cluster 3 "Multiple Allergic Sensitizations and Mild Asthma" (n = 36)	Cluster 4 "HDM Sensitization and Mild Asthma" (n = 57)	P value*
Male sex n (%)	85 (68)	15 (75)	**11 (92)**	28 (78)	31 (54)	**.018**
Age (y)	8.9 ± 2.6	9.3 ± 2.2	8.9 ± 2.8	**10** ± 2.6	8.3 ± 2.4	**.016**
Asthma duration (y)	5.5 ± 3.2	6.8 ± 2.9	5.0 ± 3.1	5.6 ± 3.1	5.1 ± 3.3	.136
Eczema n (%)	58 (46)	**18 (90)**	6 (50)	14 (39)	20 (35)	**<.001**
Food allergy n (%)	13 (10)	1 (5)	**4 (33)**	6 (17)	2 (4)	**.013**
Asthma severity† n (%)						
Moderate to severe asthma	46 (37)	**19 (95)**	11 (92)	1 (3)	15 (26)	**<.001**
≥1 hospitalization for asthma exacerbation	26 (21)	7 (35)	**11 (92)**	0 (0)	8 (14)	**<.001**
Controlled without high-dose of ICS	10 (8)	0 (0)	**0 (0)**	5 (14)	5 (9)	
Uncontrolled with high-dose of ICS	7 (6)	2 (10)	**1 (8)**	1 (3)	3 (5)	.173
Serum total IgE (kU/L)	688 ± 962	**1123** ± 1344	601 ± 410	581 ± 545	622 ± 1066	**.006**
Specific IgE n (%) against						
multiple allergens	61 (49)	**20 (100)**	5 (42)	35 (97)	1 (2)	**<.001**
HDM	96 (77)	**19 (95)**	3 (25)	32 (89)	**42 (74)**	**<.001**
Pollens	47 (38)	12 (60)	**11 (92)**	20 (56)	**4** (7)	**<.001**
Cat or dog dander	45 (36)	**14 (70)**	2 (17)	25 (69)	**4** (7)	**<.001**
Mould	15 (12)	4 (20)	0 (0)	**11 (31)**	0 (0)	**<.001**
Functional parameters						
FVC (% pred)	97.8 ± 11.8	97.9 ± 13.6	94 ± 10.3	99.8 ± 10.7	97.3 ± 12.2	.701
FEV_1 (% pred)	97.6 ± 12.4	91.6 ± 17.2	98.4 ± 10.1	101.6 ± 10.8	97 ± 11.1	.182
$FEF_{25\%-75\%}$ (% pred)	84.3 ± 25.9	**71** ± 34	95.1 ± 21.6	90.2 ± 18.6	82.7 ± 26.2	**.009**
FeNO (ppb)	53.4 ± 27	**67.3** ± 30	56.5 ± 27.5	55.5 ± 24.7)	46.6 ± 25.7	**.031**

The variables age, asthma duration, serum total IgE, and functional parameters are expressed as (mean ± SD); other variables are expressed in absolute number (%). Boldface values indicate statistical significance.

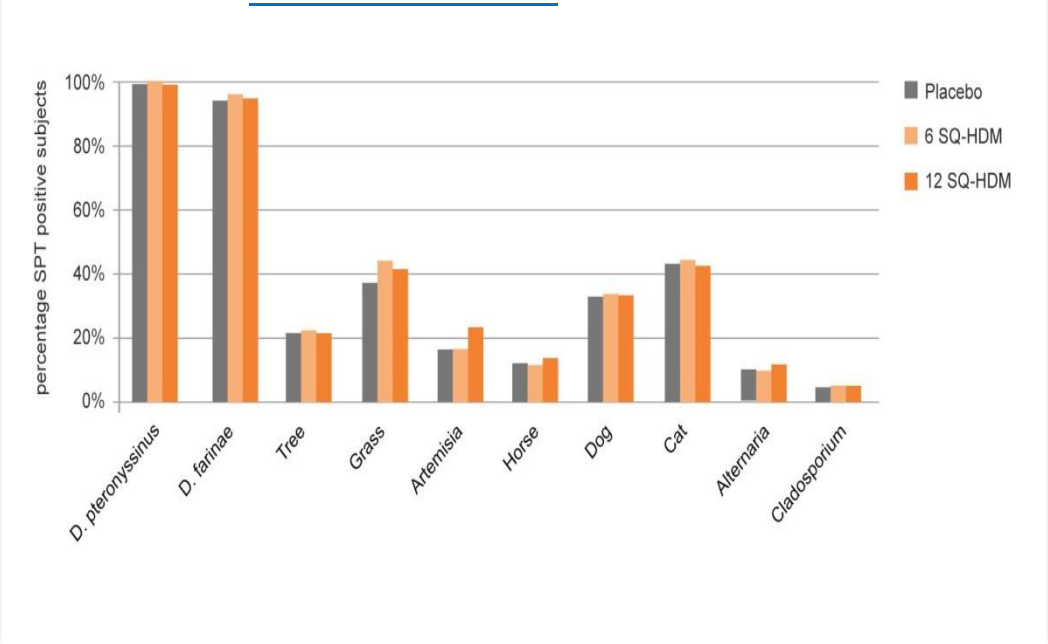
*ANOVA or χ^2 test when conditions were respected, Kruskal–Wallis or Fisher exact test otherwise.

†According to the Global Initiative for Asthma. Uncontrolled: no control or partially controlled. High-doses of ICS were defined as ≥500 μg fluticasone equivalents per day.

Just J, J pediatrics 2014

Asthme allergie aux acariens : Prévention des exacerbations: Caractéristique de la population

Age moyen 33 ans, 48% de femmes
Durée moyenne de l'asthme : 13 ans
66% multi-sensibilisé
72% des patients avaient un asthme *partiellement contrôlé* et
28% un asthme *non contrôlé* selon GINA à la randomisation



J. Christian Virchow, JAMA 2016;315(16):1715-1725.

Asthme allergie aux acariens : Prévention des exacerbations

- Double-blind, randomized, placebo-controlled trial
- 109 European trial sites.
- 834 adults with HDM allergy–related asthma not well controlled by ICS or combination products and with HDM allergy–related rhinitis.
- Key exclusion criteria were FEV1 less than 70% of predicted value or hospitalization due to asthma within 3 months before randomization.
- Efficacy was assessed during the last 6 months of the trial when ICS was reduced by 50% for 3 months and then completely withdrawn for 3 months.

J. Christian Virchow, JAMA 2016;315(16):1715-1725.

Asthme allergie aux acariens : Prévention des exacerbations: définition de l'exacerbation sévère

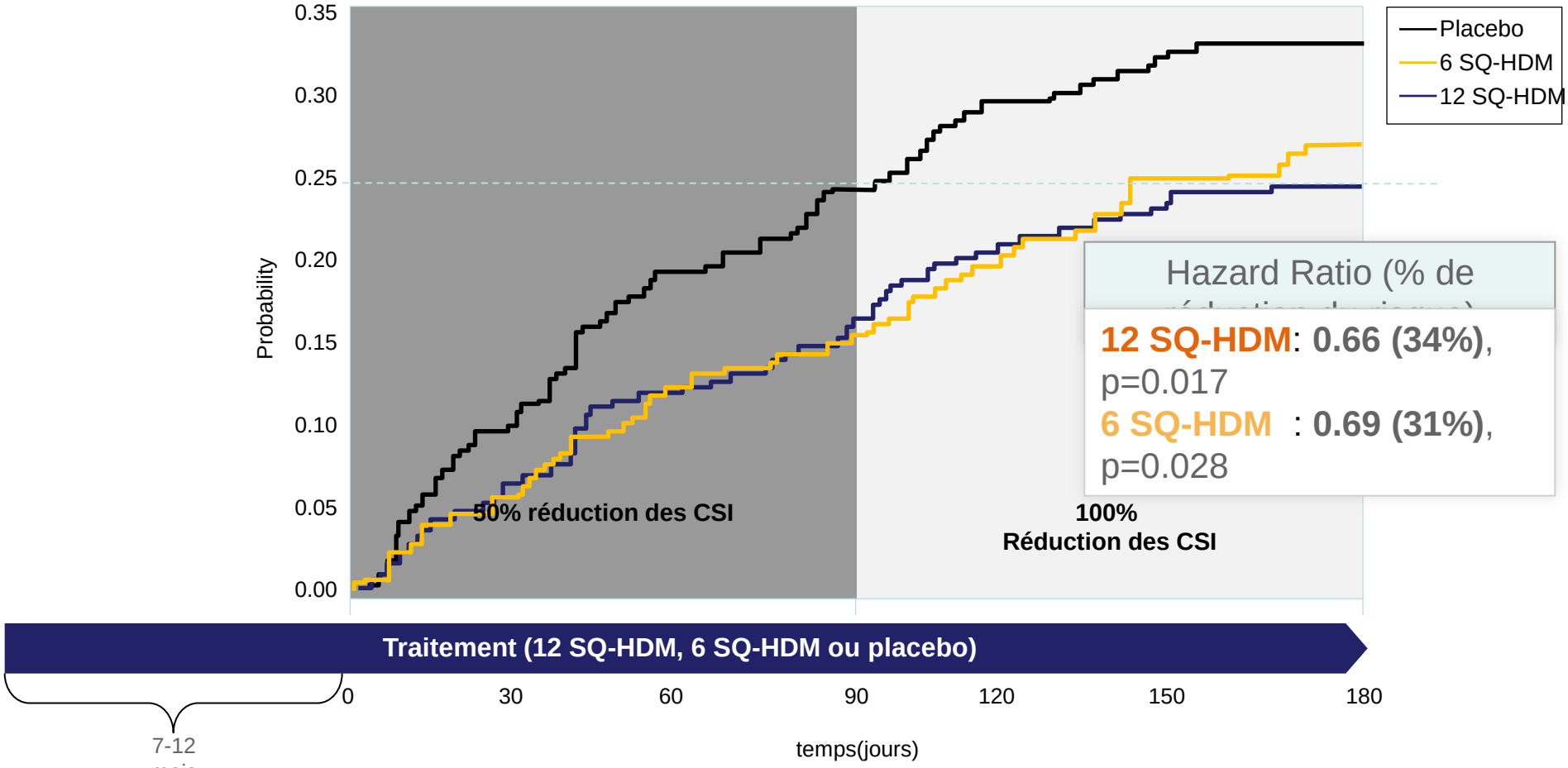
e) Besoin de corticoïdes par voie générale pour traitement de l'asthme pour au moins 3 jours

f) Passage aux urgences pour asthme nécessitant des corticoïdes par voie générale ou une hospitalisation pour plus de 12h

J. Christian Virchow, JAMA 2016;315(16):1715-1725.

Asthme allergie aux acariens : délai d'apparition de l'exacerbation

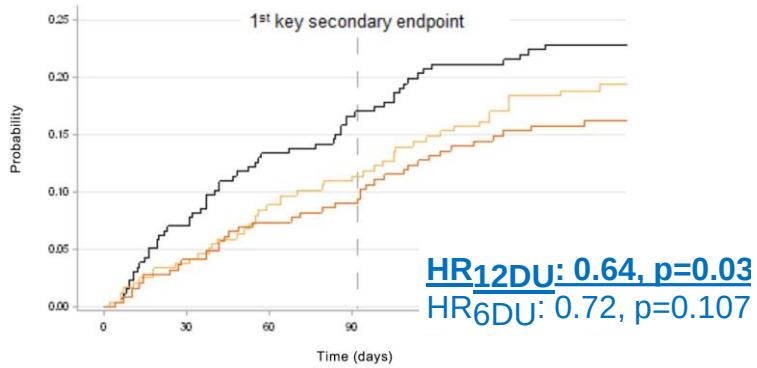
Délai d'apparition d'une exacerbation modérée ou sévère



J. Christian Virchow, JAMA 2016;315(16):1715-1725.

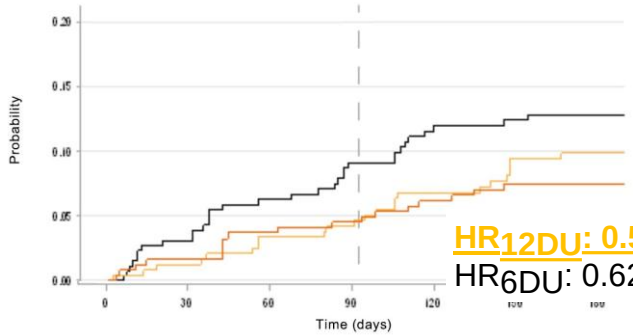
Asthme allergie aux acariens : Prévention des exacerbations: critères secondaires d'efficacité

Sympômes



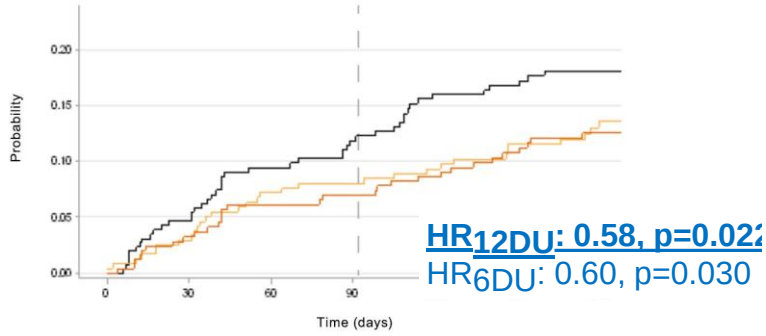
HR_{12DU}: 0.64, p=0.03
HR_{6DU}: 0.72, p=0.107

SABA



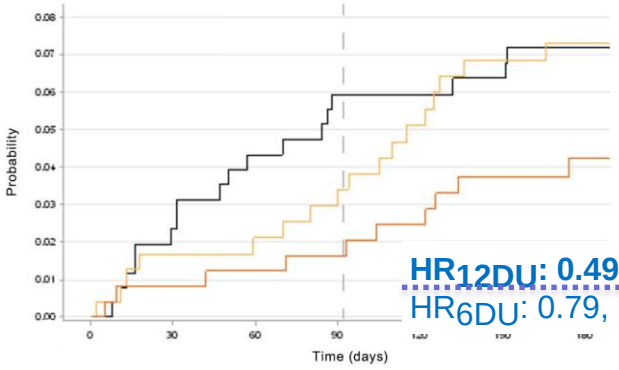
HR_{12DU}: 0.52, p=0.029
HR_{6DU}: 0.62, p=0.086

Fonction Pulmonaire



HR_{12DU}: 0.58, p=0.022
HR_{6DU}: 0.60, p=0.030

Exacerbation Sévères

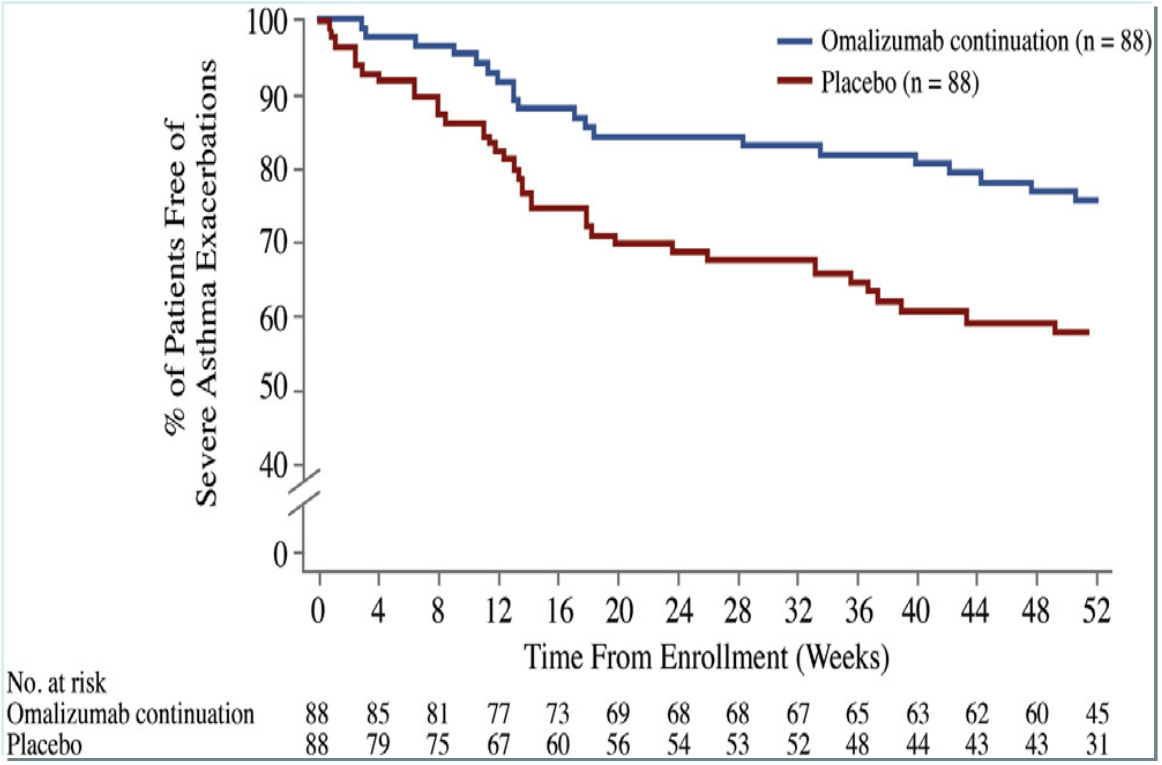


HR_{12DU}: 0.49, p=0.076
HR_{6DU}: 0.79, p=0.489

Placebo
6 SQ-HDI
12 SQ-HDI

J. Christian Virchow, JAMA 2016;315(16):1715-1725.

Effet rémanent de l'omalizumab après l'arrêt sur les exacerbations



- 1 an de l'arrêt de Omalizumab versus placebo 67% versus 47,7% n'ont pas eu d'exacerbation
- Soit une différence absolue de 19,3% (IC à 95%, 5,0%, 33,6%)

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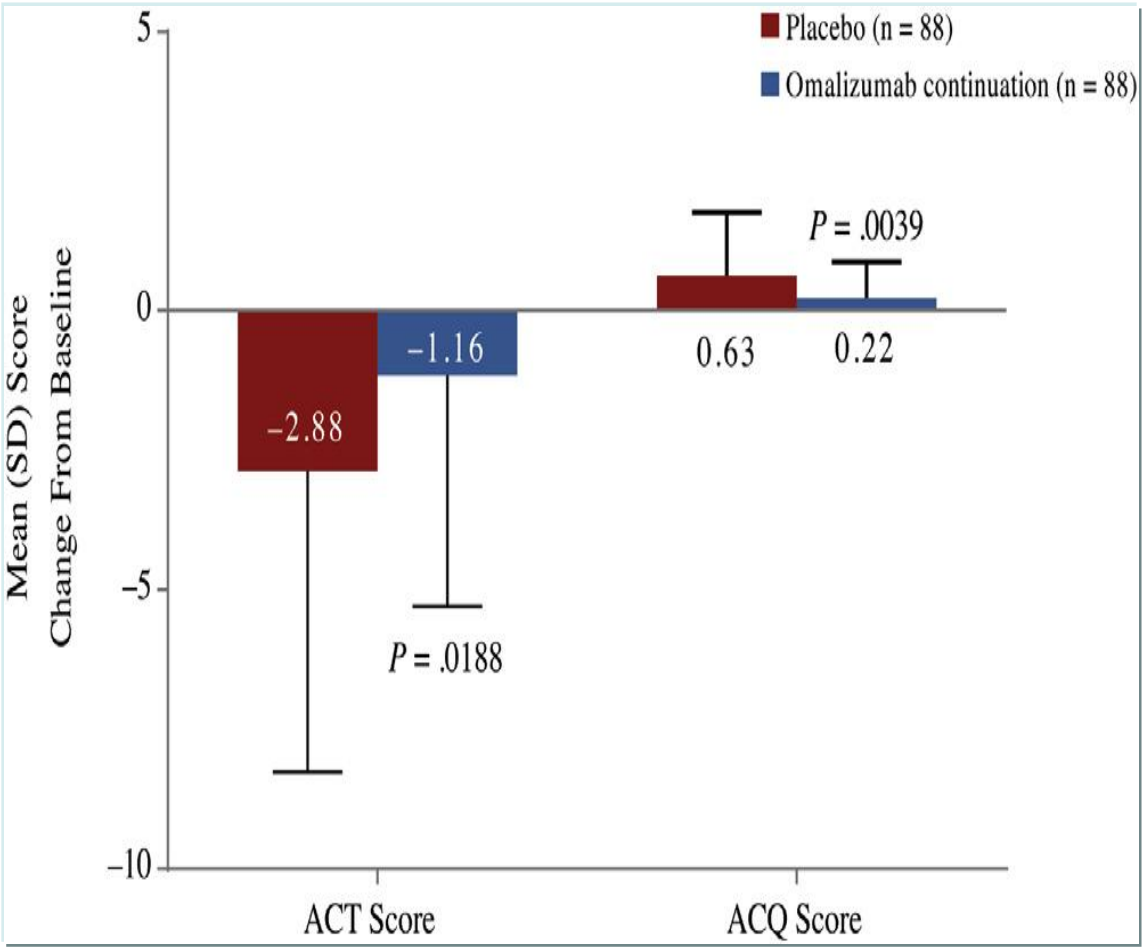
Effet rémanent du Xolair après l'arrêt sur le contrôle de l'asthme



- Asthme Control Test score pour l'omalizumab était de 21,16 [4,14] vs 22,88 [5,38] pour le placebo,p 0,0188
- ACQ était de 0,22 [0,66] vs 0,63 [1,13] pour le groupe placebo, p 0,0039).

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Conclusions

- Prévention de l'asthme allergique existe
- Pour l'instant les arguments s'accumulent pour ITA en prévention secondaire et tertiaire
- Un prévention tertiaire serait possible avec anti IgE dans l'asthme sévère

SPA soin primaire en allergologie 25 Avril 2017

- Mardi APM la veuille de la CFA
- Programme sur le site du CFA
- ½ journée : 60 euros donnant la gratuité a la première journée de la CFA