



Formation continue de Médecine Interne Générale

21.02.2019

Facteurs d'échecs du traitement dans l'asthme et nouveautés thérapeutiques

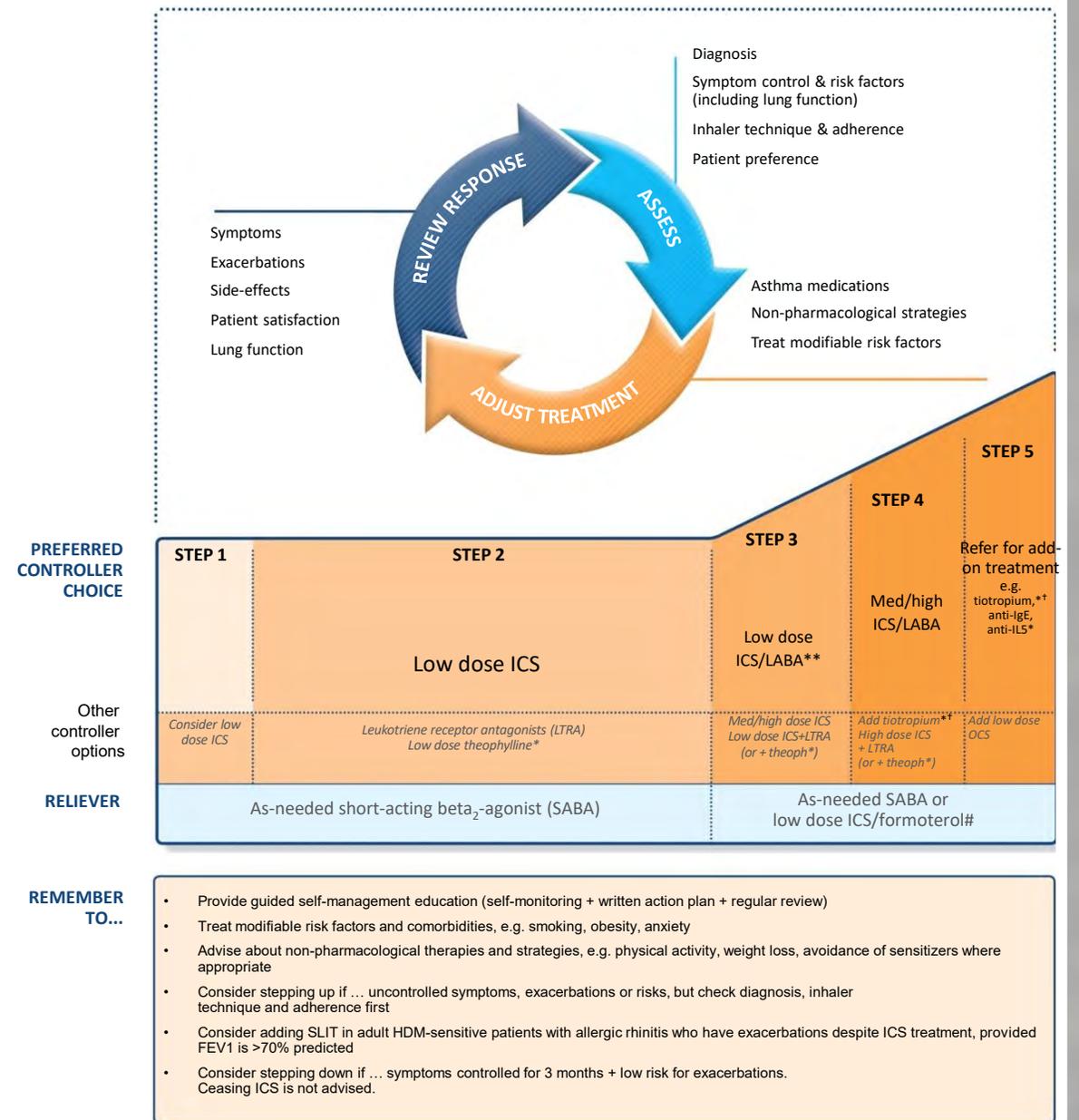
Alice Horisberger

Immunologie et Allergologie

CHUV Lausanne

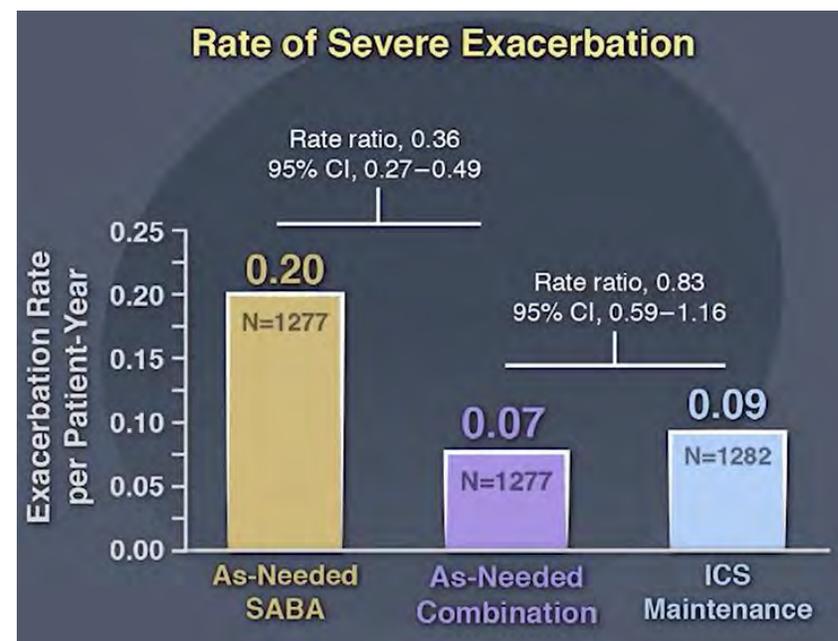
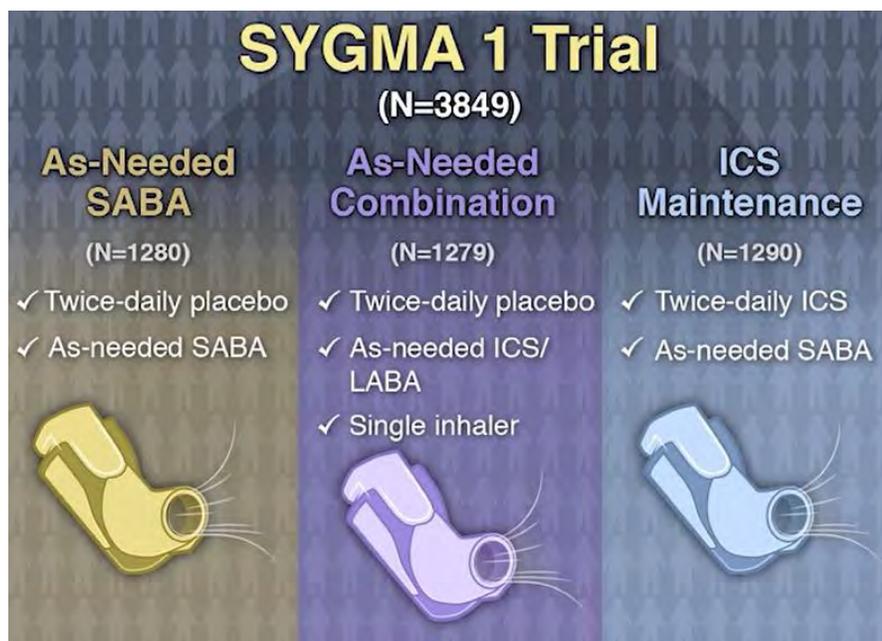
L'asthme chez l'adulte

- Affecte 10 % des adultes
- Cause de 354'000 décès à travers le monde
- Impact important sur la qualité de vie
- L'asthme peut être traité efficacement



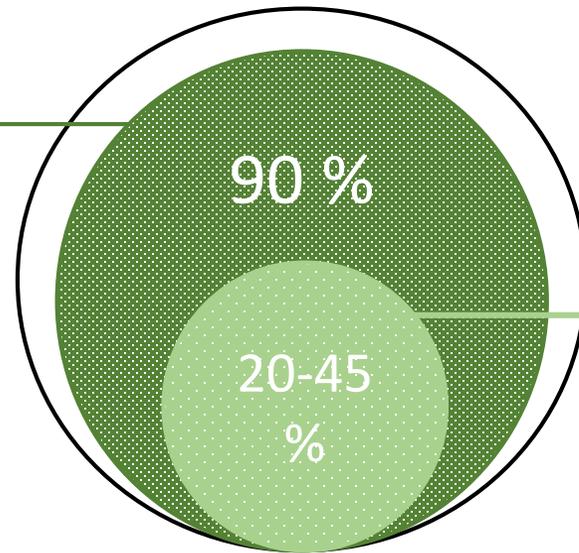
Nouveautés dans le traitement initial

- Asthme léger :



L'asthme dans la pratique

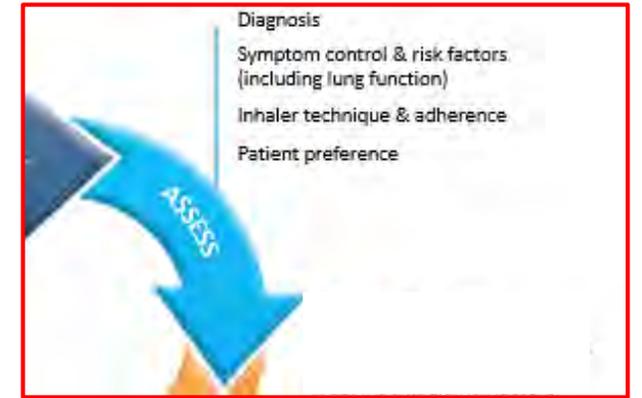
Patients qui
considèrent leur
asthme contrôlé



Patients avec un
asthme contrôlé selon
GINA

Lors d'échec thérapeutique

- Confirmer le diagnostic
- Rechercher des facteurs aggravants
 - Comorbidités : **obésité, rhinosinusite chronique**, reflux gastro-oesophagien...
 - Exposition : **tabagisme**, allergène
- S'assurer que le traitement contient des corticoïdes inhalés
- Revoir la compliance et la **technique d'inhalation**



Asthme et obésité

L'obésité comme facteur de risque d'asthme, d'exacerbation et de **mauvaise réponse thérapeutique**

- Biomarkers**
- Leptin ↑ [↓]
 - Adiponectin ↓ [↑]
 - Adipose tissue inflammation ↑ [↓]
 - Serum IL-6 ↑ [↓]
 - Oxidative stress ↑ [↓]
 - Exhaled nitric oxide ↓ [*]

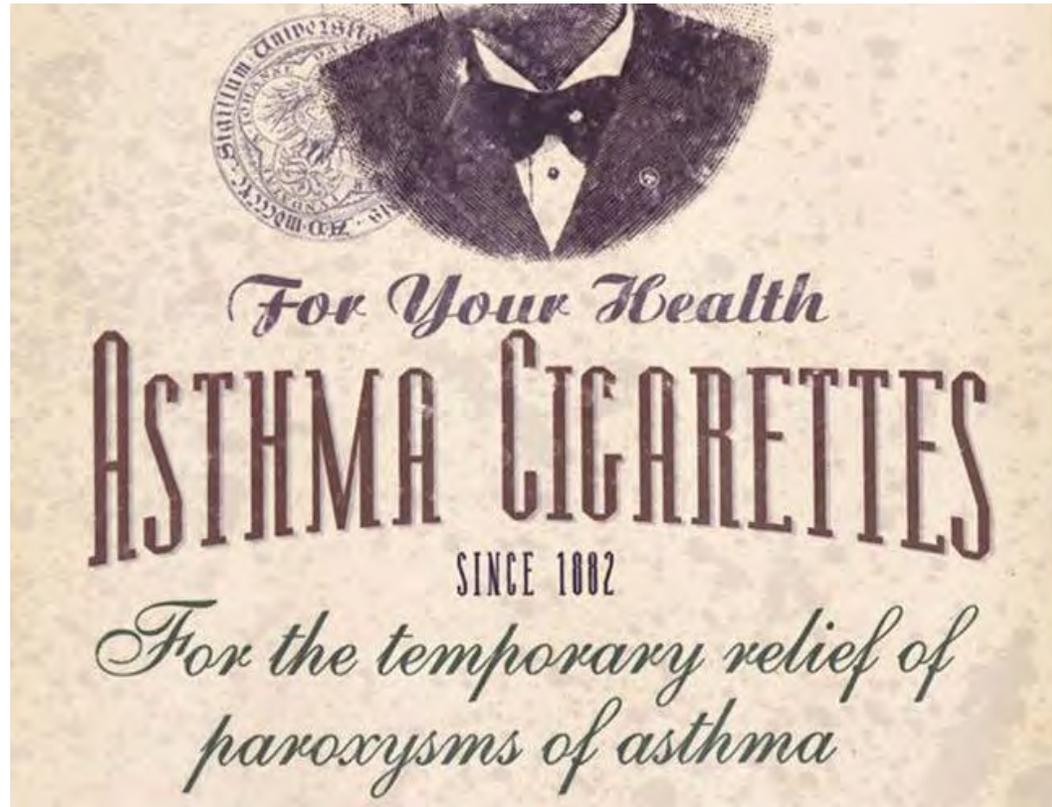
Syndrome inflammatoire chronique

Evaluation et suivi de l'asthme difficile

- Clinical Findings**
- Risk of incident asthma ↑ [↓]
 - Risk of asthma exacerbation ↑ [↓]
 - Asthma severity ↑ [↓]
 - Asthma control ↓ [↑]
 - Asthma quality of life ↓ [↑]
 - Treatment response ↓ [↑]
 - Susceptibility to air pollutants ↑ [↓]

- Lung Function and airway reactivity**
- FEV1 ↓ [↑]
 - Expiratory reserve volume ↓ [↑]
 - Functional residual capacity ↓ [↑]
 - Peak expired flow ↓ [↑]
 - Airway hyperresponsiveness ↑ [↓]
 - Bronchodilator responsiveness ↔ [*]

Asthme et tabagisme



- NON! Tabagisme comme facteur de risque connu d'exacerbation

MAIS...

- L'asthme est un facteur prédictif négatif d'arrêt du tabagisme
- La fumée (la nicotine) **réduit l'inflammation éosinophilique** et la fraction exhalée de NO
- Méthode de sevrage adaptée!

Asthme et rhinosinusite chronique

- Une seule maladie!
- Jusqu'à 85% des asthmatiques ont une atteinte ORL
- La rhinite allergique (RA) comme facteur de risque d'asthme
 - Bénéfice de la prévention de l'asthme par **désensibilisation aux pollens** lors de RA, chez les enfants/adolescent

Allergic Rhinitis and its Impact on Asthma (ARIA)



"One airway, one disease "

Bousquet J. et al. JACI 2001;108:S147-334.

Erreurs de technique d'inhalation

TABLE II. Frequency of inhaler errors, by type of inhaler device

Inhaler error/n (%), by inhaler device type (and decreasing order of frequency)					
	Turbohaler-Symbicort (n = 2074)	Diskus-Seretide (n = 826)		MDI-Seretide (n = 760)	
Twist errors (Device not held upright, base not twisted until it clicks or turn back to original position)	1012 (48.8)	Insufficient inhalation effort	317 (38.4)	Inspiratory effort not slow and deep	359 (47.2)
Did not have head tilted such that chin is slightly upward	712 (34.3)	Did not have head tilted such that chin is slightly upward	286 (34.6)	Did not have head tilted such that chin is slightly upward	259 (34.1)
Insufficient inspiratory effort	666 (32.1)	Did not breathe out to empty lungs before inhalation	268 (32.4)	Lack of device knowledge, or incorrect second dose preparation, timing, or inhalation	257 (34.7)
Did not breathe out to empty lungs before inhalation	544 (26.2)	No breath-hold following inhalation (or hold too short)	204 (24.7)	No breath-hold following inhalation (or holds too short)	254 (33.4)
Completely missed dose	459 (22.1)	Completely missed dose	98 (11.9)	Did not breathe out to empty lungs before inhalation	193 (25.4)
Incorrect timing of second dose, or use of second dose	327 (20.8)	Incorrect timing of second dose	44 (6.3)	Actuated inhaler before ready to inhale	189 (24.9)
Did not use inhaler correctly	71 (3.4)	Did not use inhaler correctly	39 (4.7)	Did not actuate or did not inhale through mouth	144 (19)
Patients expired inhaler	57 (2.75)	Expired inhaler	38 (4.6)	Exhaled uprigl	109 (14.3)
After inhalation did not replace cover	55 (2.65)	Did not replace cover	33 (4)	Actuated inhaler before ready to inhale	92 (12.1)
Did not put device in mouth and seal lips around mouthpiece	44 (2.1)	Dose not replaced because of shaking or tipping	29 (3.5)	Did not actuate or did not inhale through mouth	78 (10.3)
Exhaled into the inhaler before inhalation	36 (1.74)	After inhalation did not replace cover	17 (2.1)	Did not actuate or did not inhale through mouth	30 (3.9)
Patient has expired inhaler	24 (1.16)	Patient had an empty inhaler	16 (1.9)	Patient had an empty inhaler	23 (3)
Did not inhale through mouth	10 (0.5)	Did not inhale through mouth	7 (0.85)	Patient has expired inhaler	11 (1.5)
Did not remove cap	9 (0.43)	Patient has expired inhaler	4 (0.5)	After inhalation did not replace cap	9 (1.2)

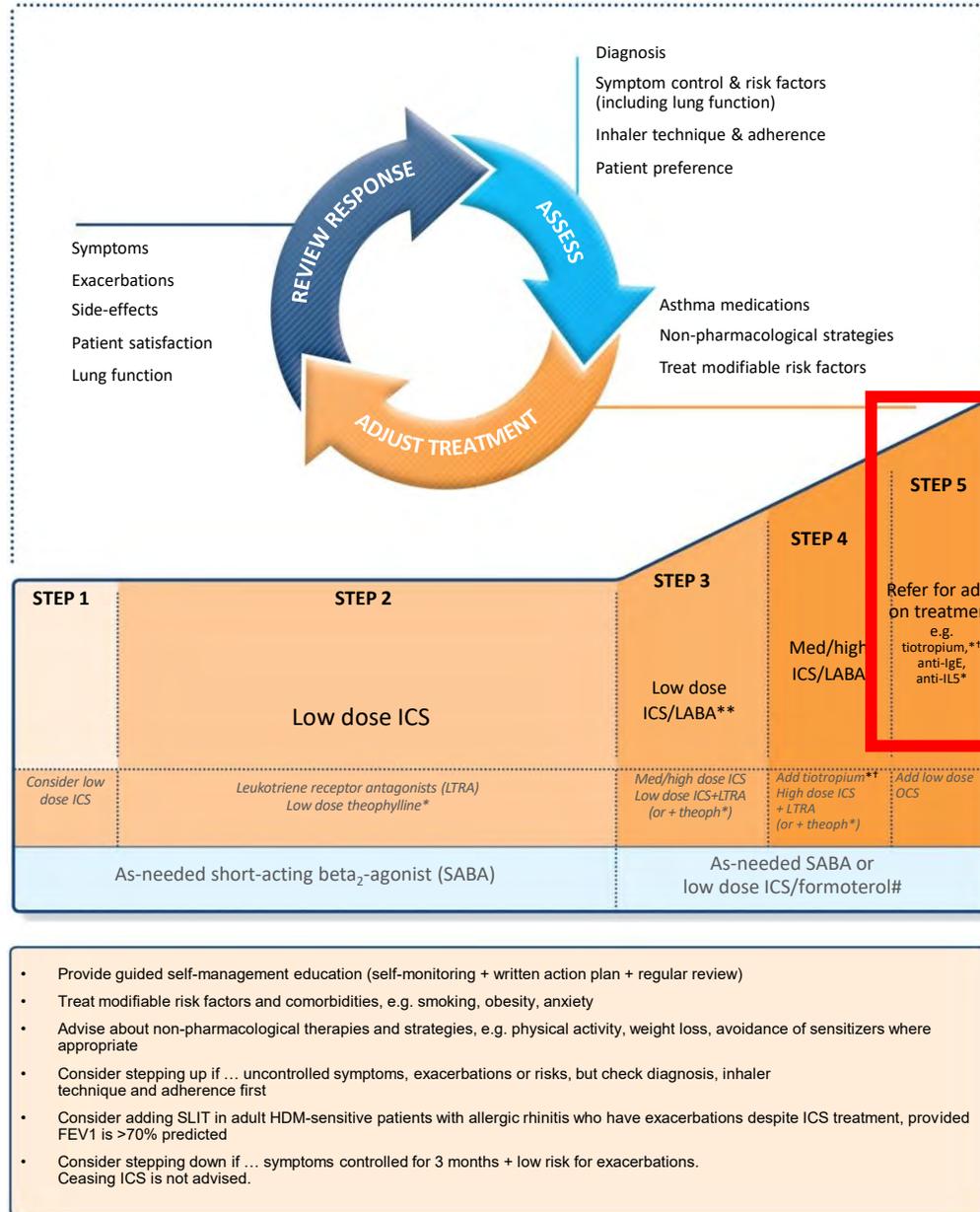


Impact de l'enseignement

Table 2

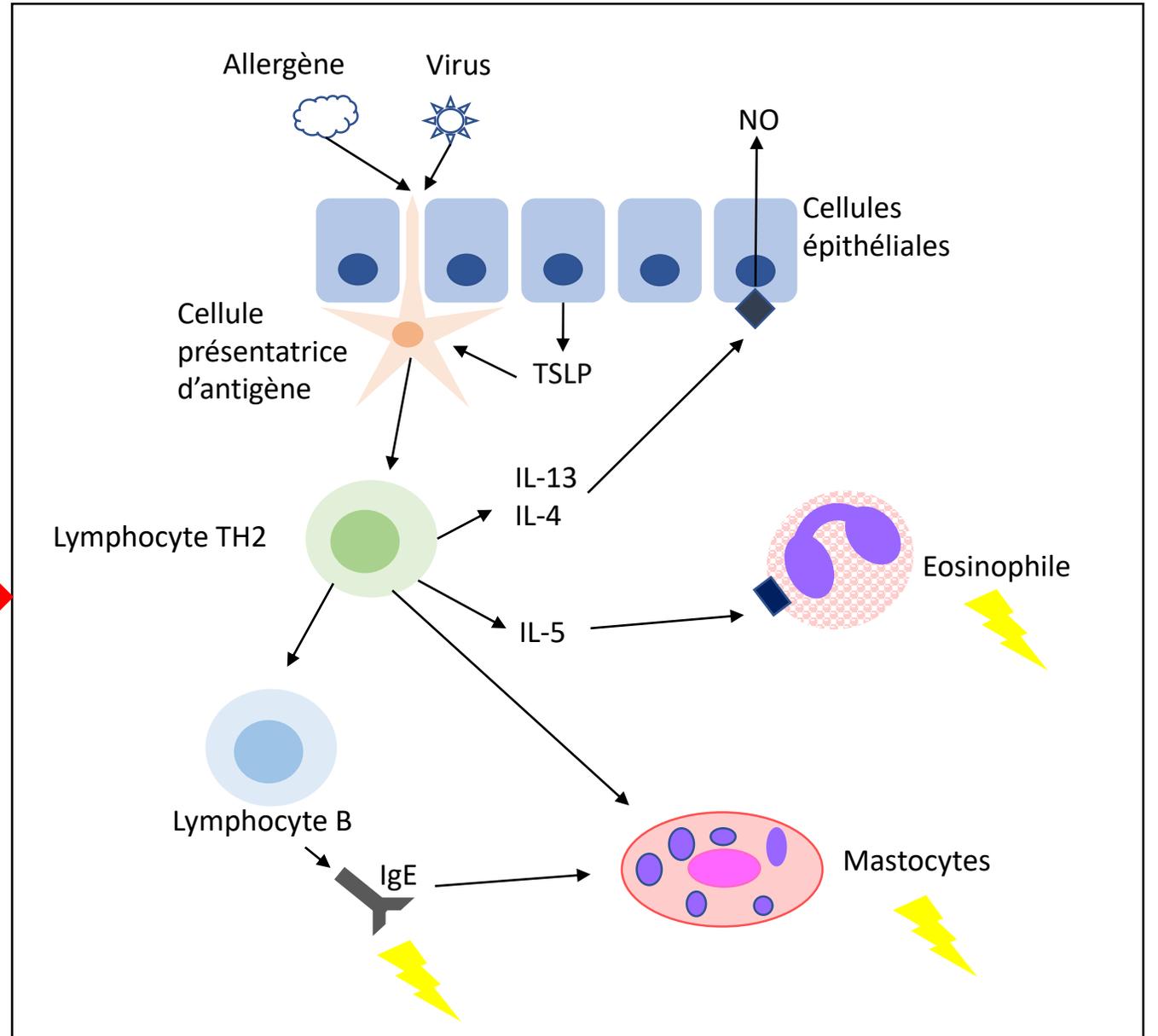
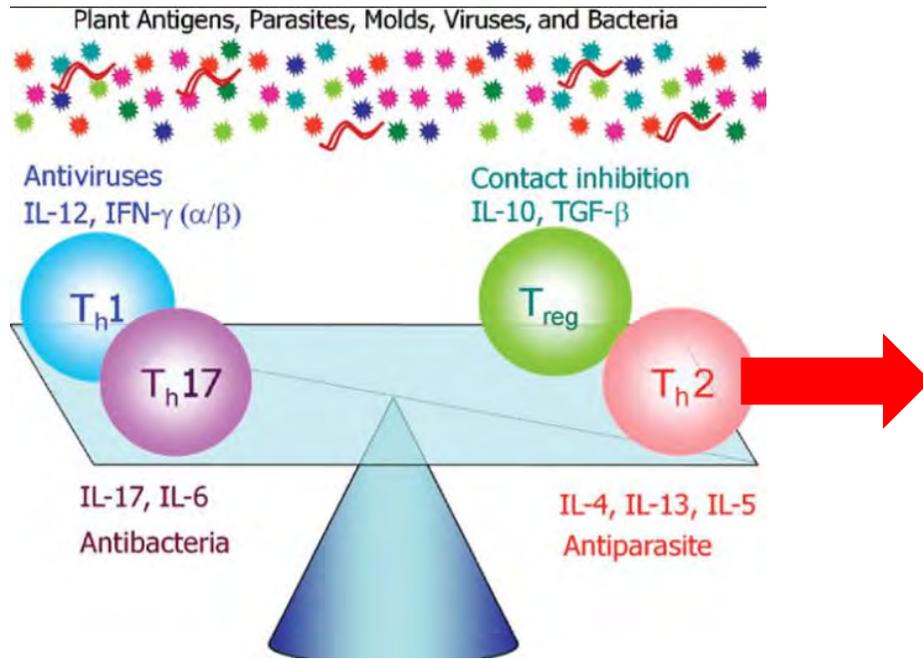
Asthma control	Intervention group		p	Control group		p
	Baseline visit	Three months visit		Baseline visit	Three months visit	
Controlled asthma, n %	32 (43%)	58 (77%)	< 0.001	43 (57%)	50 (67%)	> 0.1
ACT score, mean (± SD)	18.7 (± 4.4)	20.7 (± 3.8)	0.004	19.9(± 4.0)	20.4(± 3.9)	> 0.1
Knowledge of medication						
Number of correct answers mean (± SD)	3.17 (± 1.1)	4.62 (± 0.5)	< 0.001	3.11 (± 1.1)	3.36 (± 1.1)	> 0.1
Knowledge of device						
Patients presence of errors n (%)	23 (31%)	3 (3%)	< 0.001	24 (32%)	20 (27%)	> 0.1
Numbers of correct answers, mean (± SD)	2.64 (± 0.59)	2.96 (± 0.19)	< 0.001	2.53 (± 0.76)	2.59 (± 0.75)	> 0.1
Inhalation technique						
Absolute amount of errors n (%)						
0 errors	2 (3%)	29 (39%)		0 (0%)	0 (0%)	
1 errors	11 (15%)	35 (47%)		5 (7%)	5 (7%)	
2 errors	15 (20%)	7 (9%)		10 (13%)	13 (17%)	
3 errors	20 (27%)	2 (3%)		24 (32%)	14 (19%)	
4 errors	12 (16%)	1 (2%)		19 (25%)	16 (21%)	
5 errors	8 (11%)	0 (0%)		13 (17%)	19 (25%)	
6 errors	6 (8%)	0 (0%)		4 (5%)	8 (11%)	
Patients presence of errors n (%)	72 (97%)	45 (61%)	< 0.001	75 (100%)	75 (100%)	> 0.1
Numbers of errors, mean (± SD)	3.07 (± 1.61)	0.8 (± 0.8.3)	0.004	3.51 (± 1.3)	3.73 (± 1.9)	> 0.1

GINA guidelines : cas réfractaires

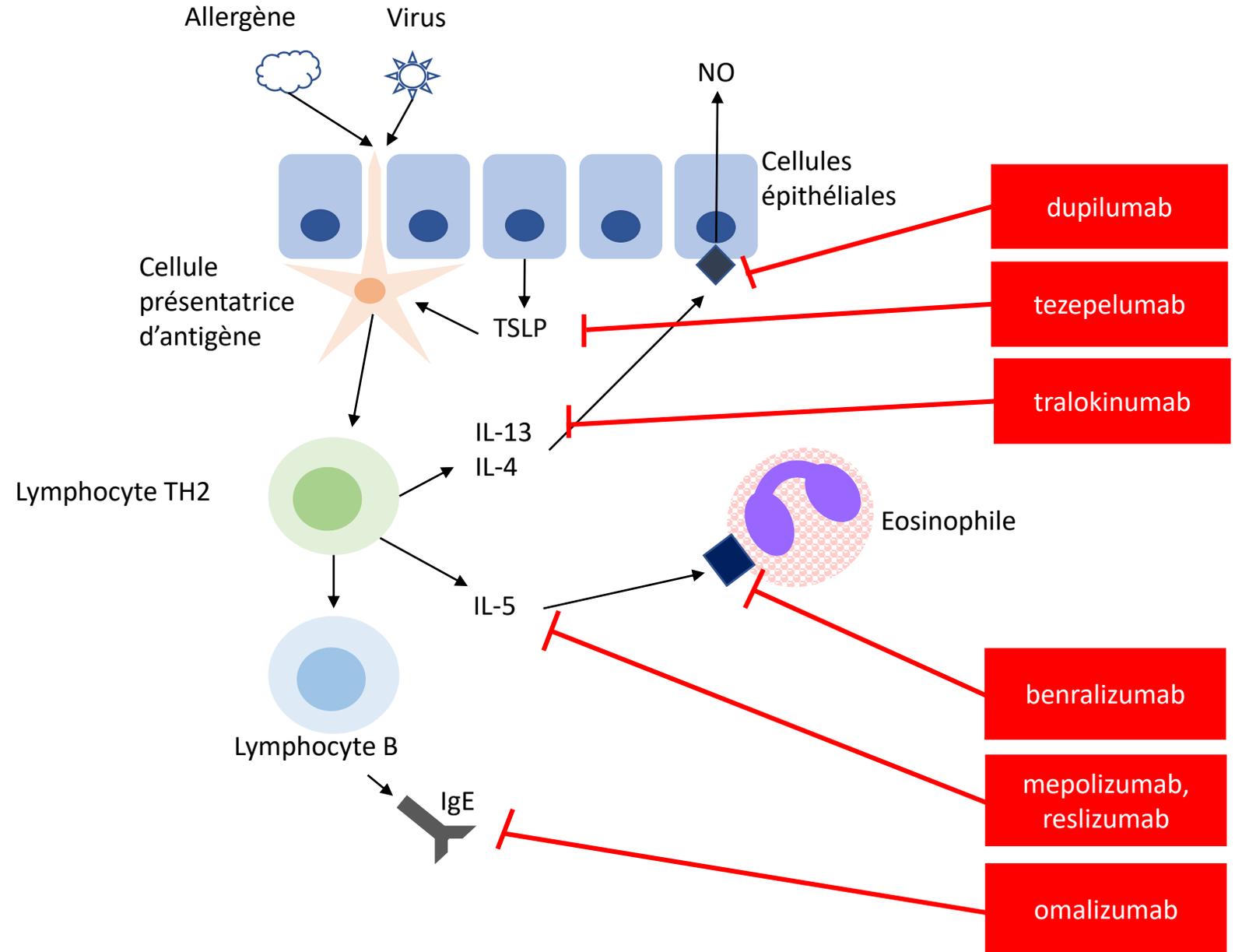


Asthme
éosinophilique
sévère

Physiopathologie



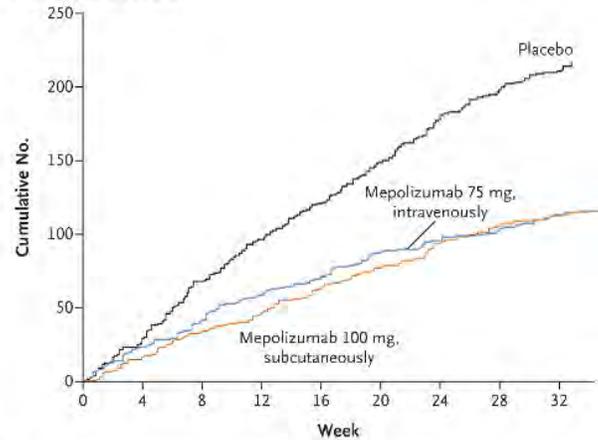
Traitements biologiques



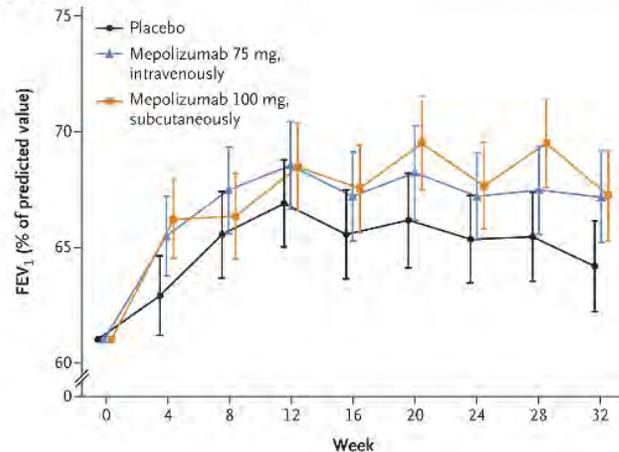
- Quel choix?
- Traitement personnalisé?

Mepolizumab - asthme et rhinosinusite chronique

A Asthma Exacerbations

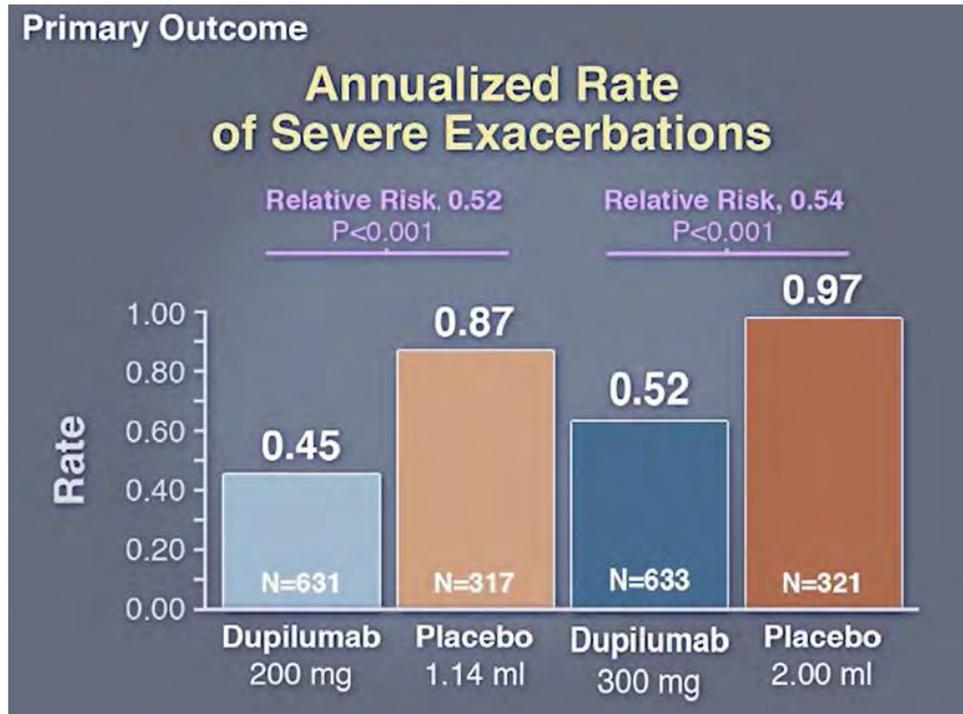


B FEV₁

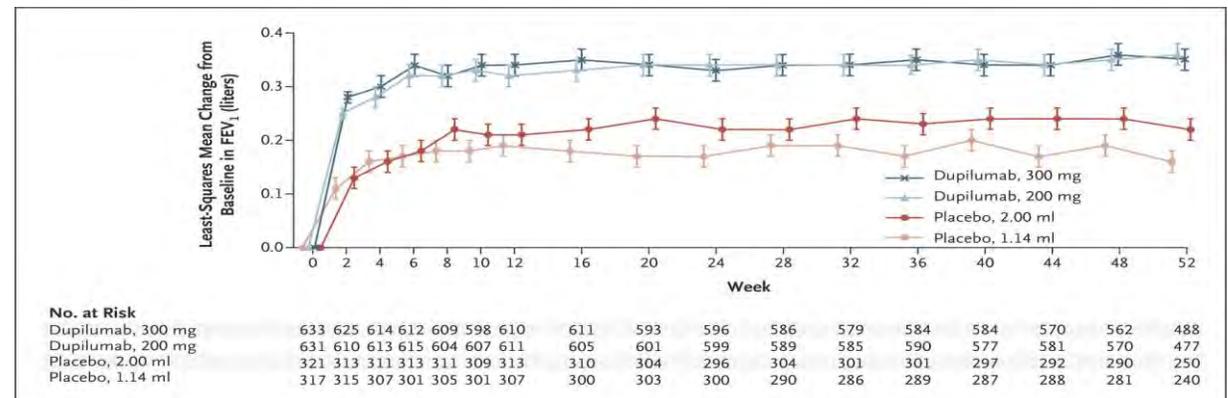


- RCT sur 576 patients avec exacerbations asthmatiques récurrentes (> 2 par an)
- Fréquence des exacerbations diminuée de 47% (iv) à 53% (sc)
- +
- Effet bénéfique également sur la rhinosinusite avec polypose

Dupilumab - asthme modéré à sévère non contrôlé



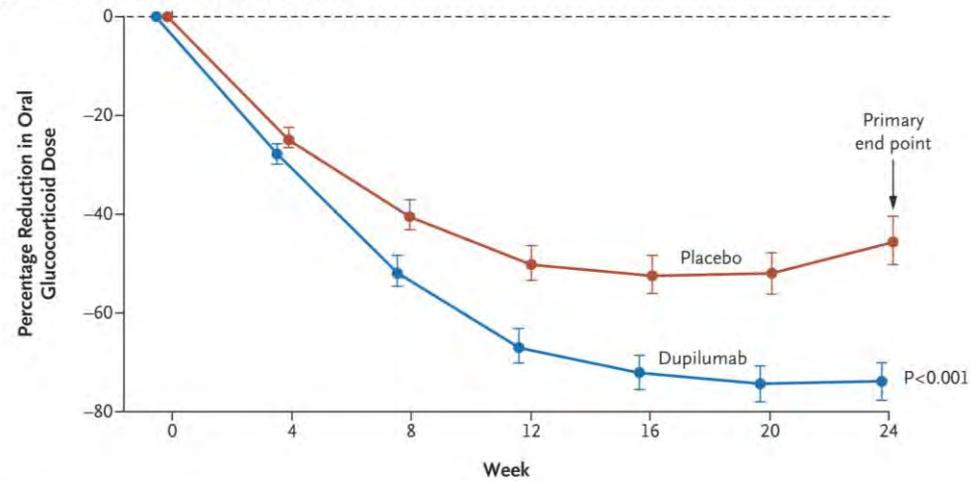
Change in the pre-bronchodilator FEV₁ from baseline over



Dupilumab - asthme cortico-dépendant

Reduction of oral corticosteroids

A Percentage Reduction in Oral Glucocorticoid Dose

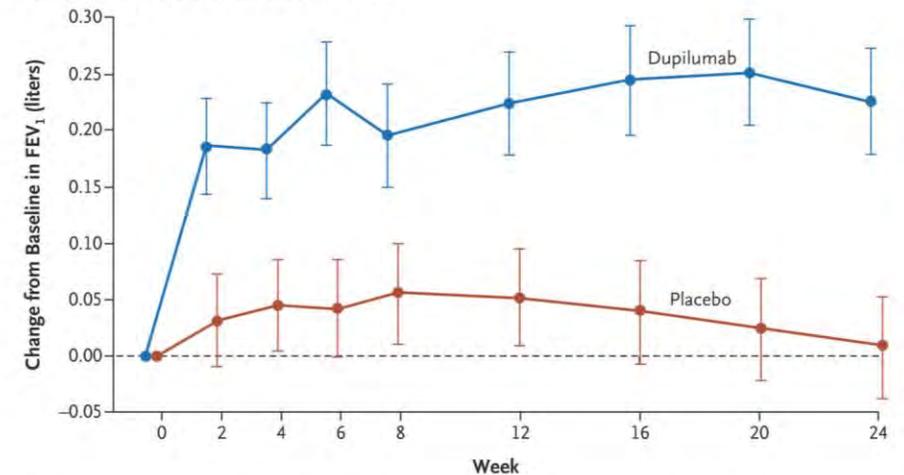


No. of Patients

Placebo	107	107	107	107	107	107	106
Dupilumab	103	103	102	101	101	101	101

Change in pre-bronchodilatory FEV1

B Change from Baseline in FEV₁ before Bronchodilator Use



No. of Patients

Dupilumab	103	101	98	101	100	99	98	100	97
Placebo	107	104	104	106	107	105	106	107	104

Traitements biologiques en Suisse

Principe actif	Préparation	Administration	Admission	Indications (Swissmedic)	Prix CHF
omalizumab	Xolair	SC 1x/mois	2006	Asthme allergique sévère Urticaire chronique spontané	1040
mepolizumab	Nucala	SC 1x/mois	2016	Asthme éosinophilique sévère	1400
reslizumab	Cinqaero	IV 1x/mois	2018	Asthme éosinophilique sévère	680 pour 10 ml
benralizumab	Fasenra	SC 1x/mois puis 1x/2mois	2018	Asthme éosinophilique sévère	2858
dupilumab	Dupixent		en cours	Dermatite atopique sévère	
tezepelumab					
tralokinumab					

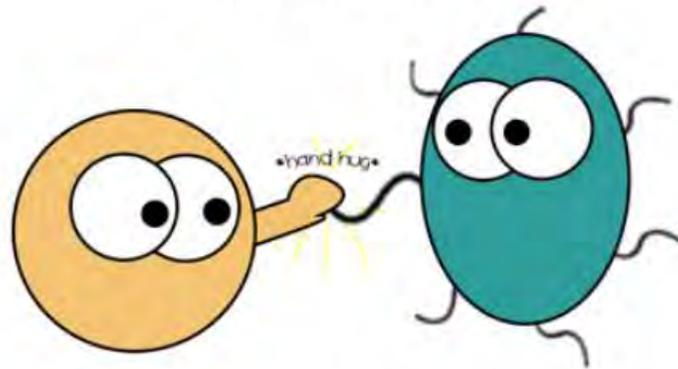
- *à condition que le traitement soit effectué par un spécialiste (pneumologue, allergologue).*

En conclusion

- L'asthme reste une **maladie chronique insuffisamment contrôlée**
- Recherche de **facteurs d'échec thérapeutique** comme première étape
- Fréquence importante de **mauvaise technique d'inhalation** dans la pratique
- La poursuite du **tabagisme** est peut-être associée à un effet anti-inflammatoire de la nicotine
- Considérer l'atteinte **ORL** et la traiter
- Référer les patients et considérer un **traitement biologique ciblé** chez ceux avec un asthme sévère éosinophilique malgré un traitement standard bien conduit
 - Personnaliser le traitement en fonction des comorbidités (?)

Des questions?

If our body cells & bacteria
can stay in harmony,
why can't we?



Make peace, not war

Combined Analysis of Asthma Safety Trials of LABA

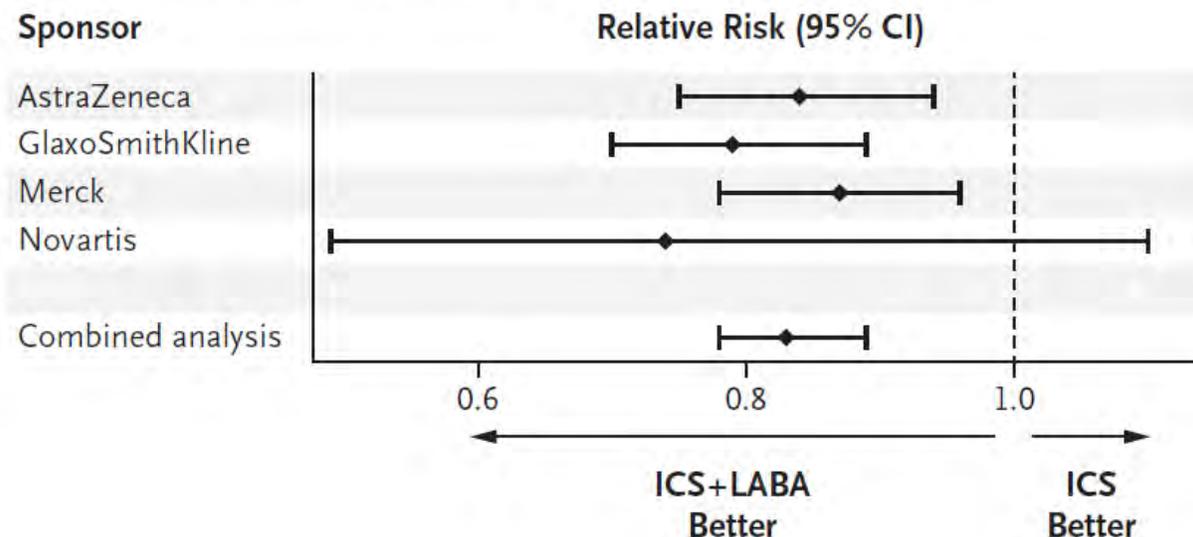
At least one asthma exacerbation:

ICS: 2100 patients (11.7%)

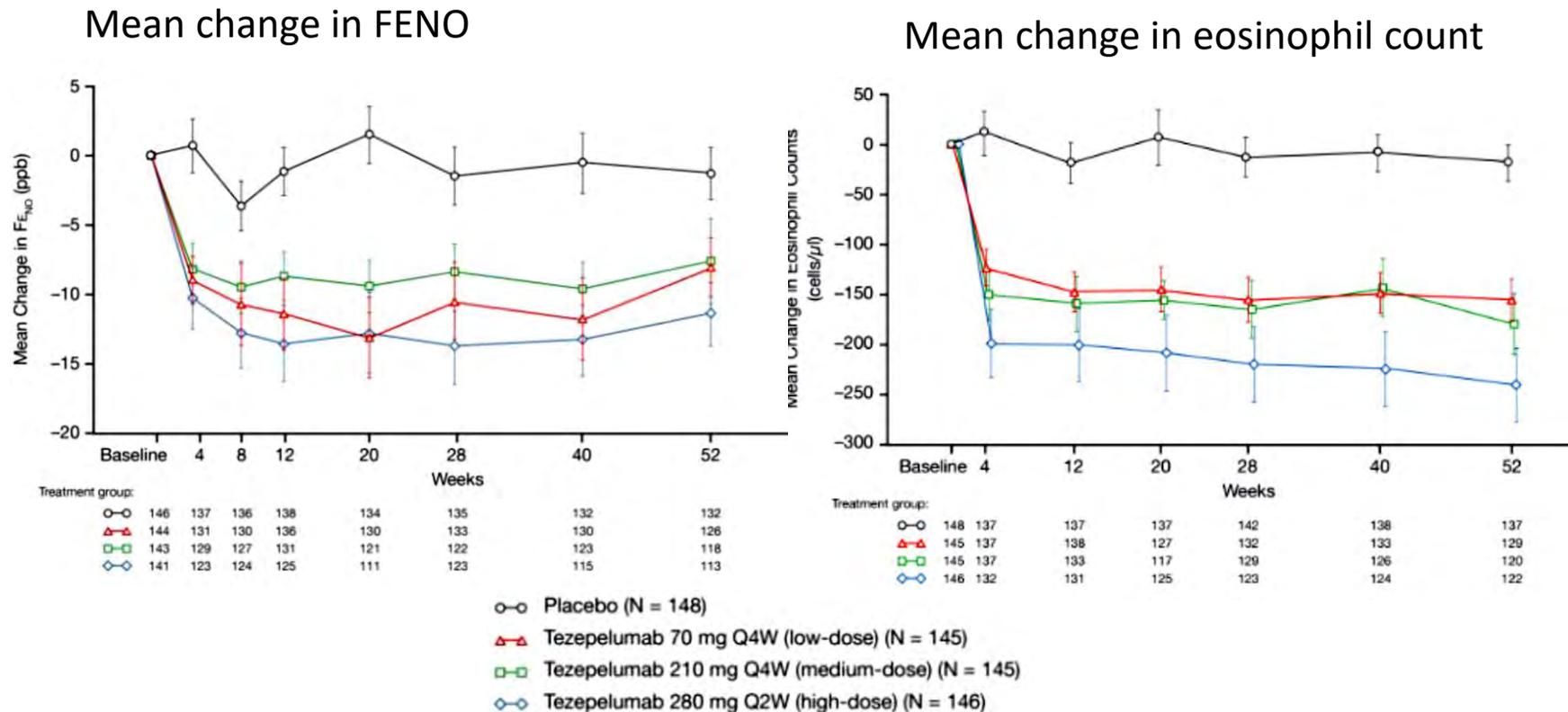
ICS + LABA: 1768 patients (9.8%), RR 0.83 [0.78-0.89; P<0.001]

Forest plot for relative risk of asthma exacerbation, according to trial

A Asthma Exacerbations, According to Sponsored Trial



Tezepelumab (anti-TSLP) in uncontrolled asthma

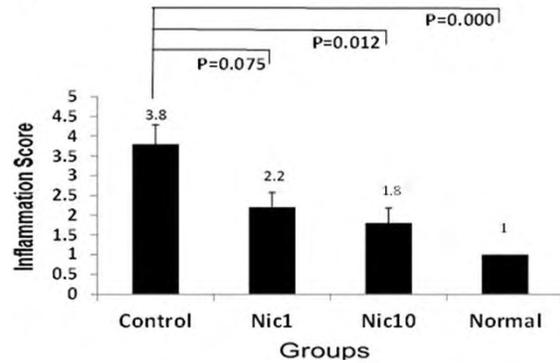


Anti-TSLP decreases exacerbation in both eosinophilic and non-eosinophilic asthma

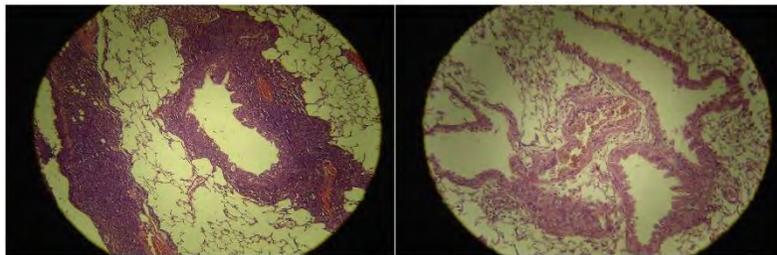
Also reduces both peripheral eosinophilia and FENO

Nicotine in a murine model of allergic asthma

A

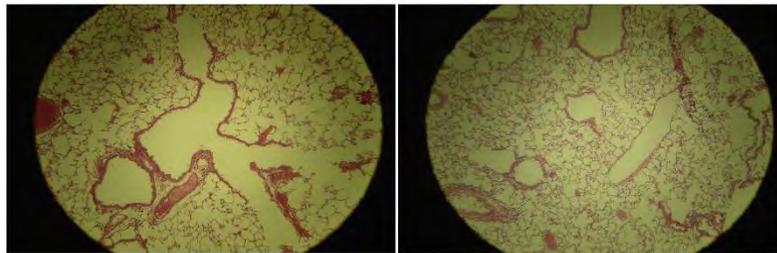


Inflammation



Control

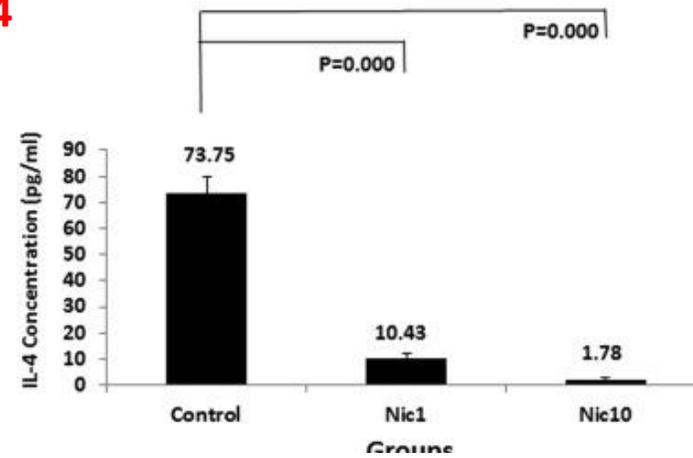
Nic1



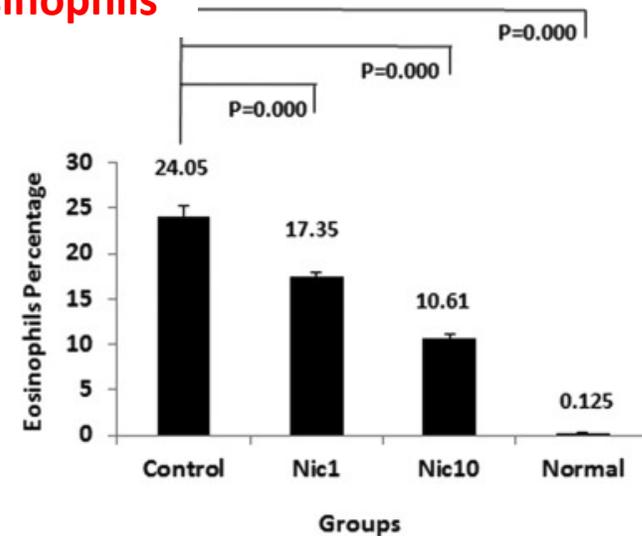
Nic10

Normal

IL-4



Eosinophils



Erreur d'inhalation selon le dispositif



TABLE E4. Number of errors made by patients, by device type

Inhaler device type	Number of errors made by patients				Total
	No errors	1 or 2 errors	3 or 4 errors	5+ errors	
Turbohaler-Symbicort	404 (19.5)	1054 (50.8)	448 (21.6)	168 (8.1)	2074
Diskus-Seretide	245 (29.7)	365 (44.2)	167 (20.2)	49 (5.9)	826
MDI-Seretide	102 (13.4)	336 (44.2)	191 (25.1)	131 (17.2)	760

Chi-square test found a significant association between the number of errors and device type ($P < .001$).