Asthme non contrôlé
Difficile à traiter ? Sévère ?
Phénotype-Endotype
Traitement de fond: Les options

DESC, DES, Capacité
Lyon le 08/03/2019

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Conflicts of interest

Consultancy: Novartis Pharma, Astra-Zeneca, GSK, Boehringer Ingelheim, Mundi Pharma, Vivisol, Sanofi, Chiesi, ALK, Teva, Menarini

Participation to medical meeting: GSK, Astra-Zeneca, Novartis Pharma, Chiesi, MSD, Takeda, AGIR à dom, Orkyn, Mundi Pharma, ALK, Stallergène, Boehringer Ingelheim, Teva

Clinical trial (investigator): GSK, ALK, Novartis Pharma, Boehringer-Ingelheim, Vitalair, AB Science, Amgen, Lilly, Astra-Zeneca, Sanofi, Roche, Teva

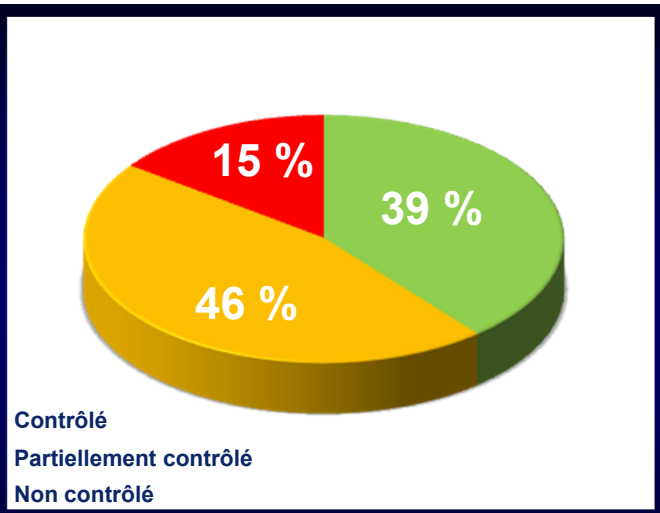
Research grants: GSK, Novartis Pharma, MSD, Chiesi, AGIR à dom.

Asthme non ou mal contrôlé

	Contrôlé (Tous les critères présents)	Partiellement contrôlé (Au moins un critère présent lors d'une même semaine)	Non contrôlé
Symptômes	Aucun (≤ 2/sem)	> 2/sem	Présence d'au moins 3 des critères présent dans l'asthme partiellement contrôlé sur une semaine
Limitation des activités	Aucune	Au moins 1	
Symptômes ou réveils nocturnes	Aucuns	Au moins 1	
Recours à un traitement des symptômes	Aucun (≤ 2/sem)	> 2/sem	
Fonction pulmonaire (DEP ou VEMS)	Normale	< 80 % de la valeur prédite ou mesurée	
Exacerbation	Aucune	≥ 1/an	1/ semaine

GINA 2006 NIH/NHBLI. Global INitiative for Asthma updated 2006 from NHBLI/WO World Report Global Strategy for asthma management and prevention. Issued Nov 2006.

Niveaux de contrôle (GINA 2006)



6 patients sur 10 sont insuffisamment contrôlés

IRDES Enquête Santé Protection Sociale 2006

GINA - World Report Global Strategy for asthma management and prevention. Issued Nov 2007.

Asthme « sévère »
« Consensus mondial 2010 »

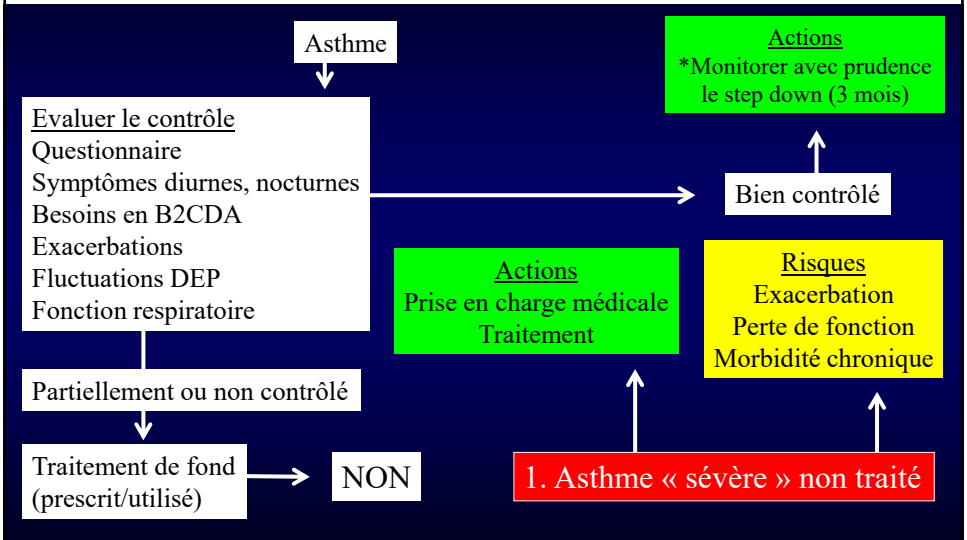
→ 3 situations cliniques, +/- associées

1. Asthme « sévère » non traité (≠ consensus ATS !!!)

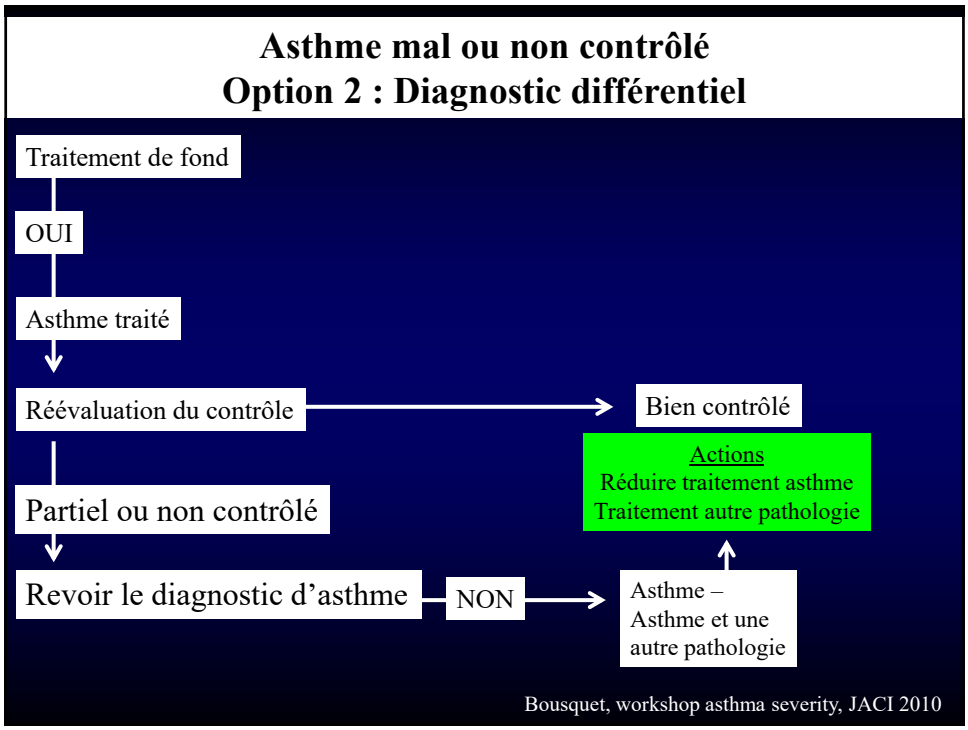
2. Asthme « sévère » difficile à traiter

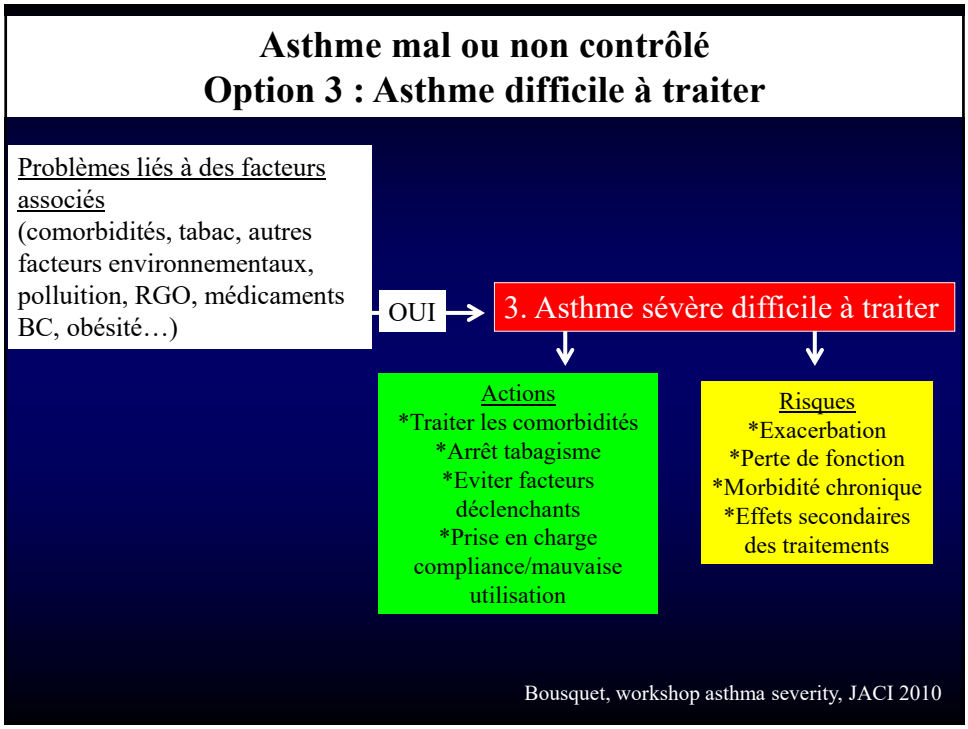
3. Asthme sévère résistant au traitement
→ 3a. Manque de contrôle malgré le plus haut niveau thérapeutique recommandé: asthme sévère réfractaire
→ 3b. Contrôle obtenu avec la plus forte pression thérapeutique

Asthme mal ou non contrôlé
Option 1 : Pas ou peu ou mal traité



Bousquet, workshop asthma severity, JACI 2010


Asthme mal ou non contrôlé
Option 2 : Diagnostic différentiel
Traitement de fond
OUI
Asthme traité
Réévaluation du contrôle
Bien contrôlé
Actions
Réduire traitement asthme
Traitement autre pathologie
Partiel ou non contrôlé
Revoir le diagnostic d'asthme
NON
Asthme –
Asthme et une
autre pathologie
Bousquet, workshop asthma severity, JACI 2010


Asthme mal ou non contrôlé
Option 3 : Asthme difficile à traiter
Problèmes liés à des facteurs associés
(comorbidités, tabac, autres facteurs environnementaux, polluition, RGO, médicaments BC, obésité…)
OUI
3. Asthme sévère difficile à traiter
Actions
*Traiter les comorbidités
*Arrêt tabagisme
*Eviter facteurs déclenchants
*Prise en charge compliance/mauvaise utilisation
Risques
*Exacerbation
*Perte de fonction
*Morbidité chronique
*Effets secondaires des traitements
Bousquet, workshop asthma severity, JACI 2010

Asthme mal ou non contrôlé
Option 4 : Asthme sévère

NON
Majoration traitement

NON

Réévaluation du contrôle

OUI
(contrôle avec traitement maximal)

4b. Asthme sévère résistant au traitement:
Asthme réfractaire

Risques
*Exacerbation
*Perte de fonction
*Morbidité chronique
*Effets secondaires des traitements

Actions
*Nouvelles thérapies
*Nouvelles stratégies
(recherche clinique)

Actions
*Monitorer avec prudence le step down
*Recherche clinique

4a. Asthme sévère « non » résistant au traitement:
Besoin d'un haut niveau thérapeutique au long cours

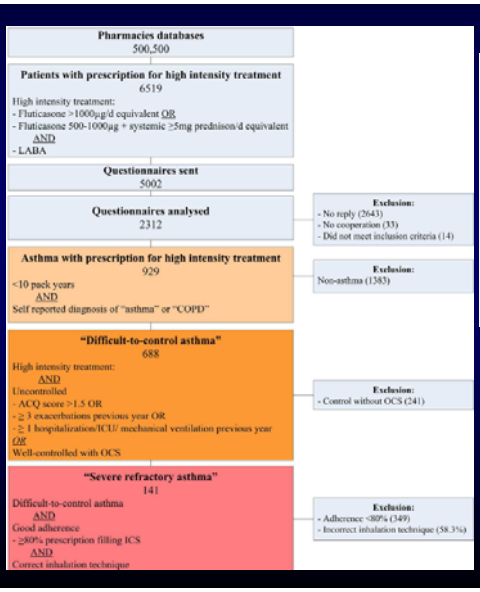
M12

Bousquet, workshop asthma severity, JACI 2010

The prevalence of severe refractory asthma

J Allergy Clin Immunol
2015;

Pieter-Paul W. Hekking, MD,[a] Reinier R. Wener, MD,[a] Marijke Amelink, MD,[a] Aelko H. Zwinderman, PhD,[b]
Marcel L. Bouvy, MD, PhD,[c] and Elisabeth H. Bel, MD, PhD[a] *Amsterdam and Leiden, The Netherlands*



Methods: Adult patients with a prescription for high-intensity treatment (high-dose inhaled corticosteroids and long-acting β_2-agonists or medium- to high-dose inhaled corticosteroids combined with oral corticosteroids and long-acting β_2-agonists) were extracted from 65 Dutch pharmacy databases, representing 3% of the population (500,500 inhabitants). Questionnaires were sent to 5,002 patients, of which 2,312 were analyzed. The diagnosis of asthma and degree of asthma control were derived from questionnaires to identify patients with difficult-to-control asthma. Inhalation technique was assessed in a random sample of 60 adherent patients (prescription filling, ≥80%). Patients with difficult-to-control asthma, adherence to treatment, and a correct inhalation technique were qualified as having severe refractory asthma. Results were mirrored to the Dutch population.

Study design: differentiating steps to get to a diagnosis of severe refractory asthma.

Results database	Dutch population
Asthma	Asthma
Difficult-to-control asthma	Difficult-to-control asthma
Severe refractory asthma	Severe refractory asthma

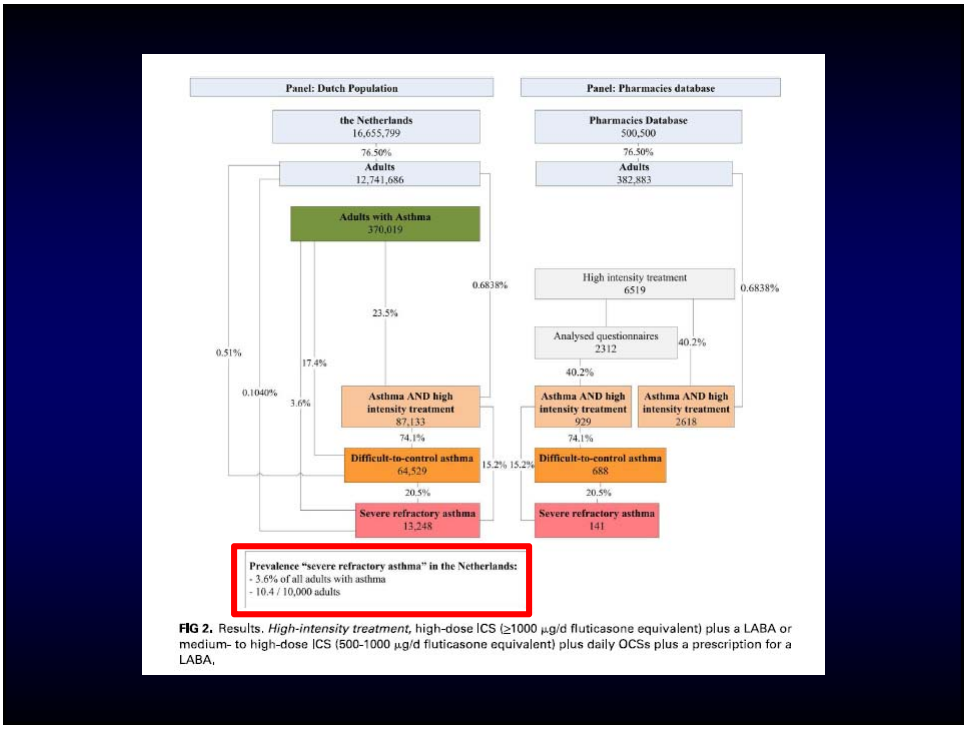


FIG 2. Results. *High-intensity treatment,* high-dose ICS (≥1000 μg/d fluticasone equivalent) plus a LABA or medium- to high-dose ICS (500-1000 μg/d fluticasone equivalent) plus daily OCSs plus a prescription for a LABA,

Asthme et sévérité: GINA 2014

- *Mild asthma* is asthma that is well controlled with Step 1 or Step 2 treatment (Box 3-5, p31), i.e. with as-needed reliever medication alone, or with low-intensity controller treatment such as low dose ICS, leukotriene receptor antagonists or chromones.
- *Moderate asthma* is asthma that is well controlled with Step 3 treatment e.g. low dose ICS/LABA.
- *Severe asthma* is asthma that requires Step 4 or 5 treatment (Box 3-5, p31), e.g. high-dose ICS/LABA, to prevent it from becoming 'uncontrolled', or asthma that remains 'uncontrolled' despite this treatment. While many patients with uncontrolled asthma may be difficult to treat due to inadequate or inappropriate treatment, or persistent problems with adherence or comorbidities such as chronic rhinosinusitis or obesity, the European Respiratory Society/American Thoracic Society Task Force on Severe Asthma considered that the definition of severe asthma should be reserved for patients with refractory asthma and those in whom response to treatment of comorbidities is incomplete.[110]

European Respiratory Journal
erj.ersjournals.com
Published online before print December 12, 2013, doi: 10.1183/09031936.00202013
ERJ February 1, 2014 vol. 43 no. 2 343–373

International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

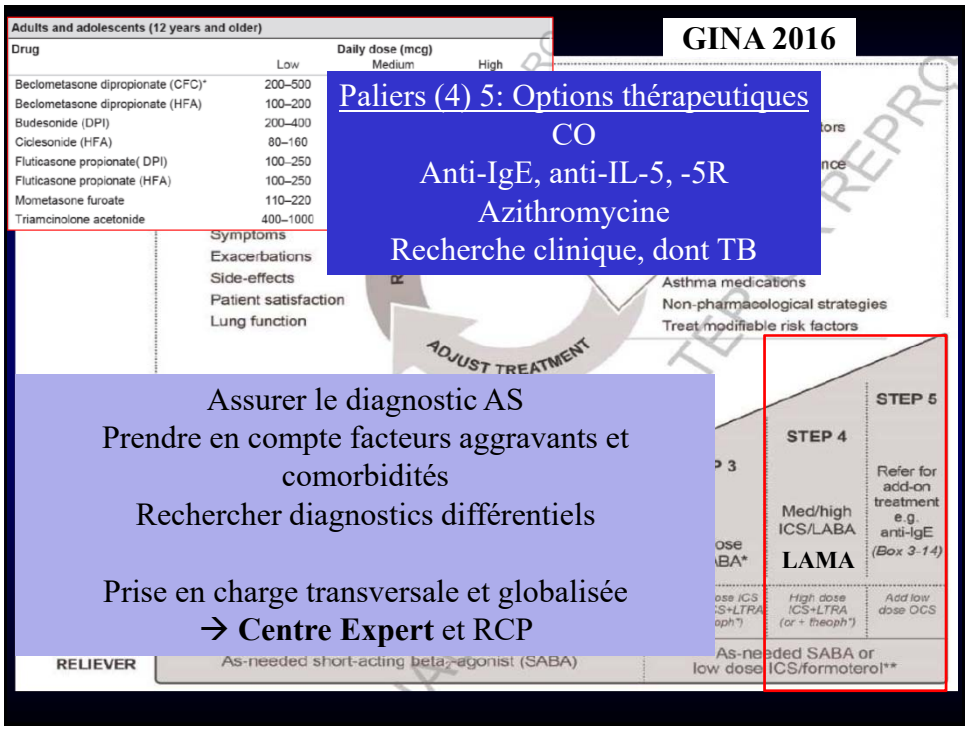
TABLE 3 Definition of severe asthma for patients aged ⩾6 years

Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose ICS# and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for ⩾50% of the previous year to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy

Uncontrolled asthma defined as at least one of the following:

1) Poor symptom control: ACQ consistently >1.5, ACT <20 (or "not well controlled" by NAEPP/GINA guidelines)
2) Frequent severe exacerbations: two or more bursts of systemic CS (>3 days each) in the previous year
3) Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year
4) Airflow limitation: after appropriate bronchodilator withhold FEV1 <80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)

Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)



Prise en charge de l'asthme sévère
Concept de « Centre Expert »

Quand adresser un asthmatique sévère ?

Tout asthmatique prenant un traitement de palier 4 devrait être suivi par le médecin traitant en lien avec un pneumologue.

Un avis auprès d'un Centre d'asthme sévère devrait être sollicité pour un asthme restant non contrôlé, en particulier:

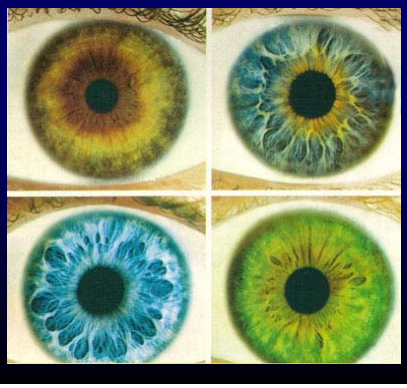
- -si VEMS < 60%
- -Prédominante de toux ou d'expectorations chroniques
- -Suspicion d'autre diagnostic
- -Corticodépendance (orale)
- -Avant de débuter ou de changer de traitement de palier 5
- -Avant d'envisager un traitement d'exception (bioT ou TB)

Centre d'Asthme Sévère ?

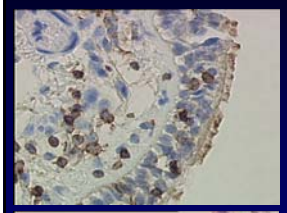
-File active ≥ 150 patients et ≥ 50 nouveaux patients par an
-Coordonner un programme d'ETP dédié et validé par l'ARS
-Accès aux essais cliniques (au moins 1 par an)
-Participer à la recherche clinique AS
-Coordonner une RCP AS
-Structure d'urgences respiratoires (soins intensifs ou réanimation dans le même service ou au moins dans l'établissement avec un médecin H24 sur place)
-Expertise en allergologie respiratoire et alimentaire
-Plateau technique EFR et EFX
-Accès à l'endoscopie bronchique ou à l'expectoration induite
-Réseau de correspondants ORL, psychologues, médecin du travail, CMEI, kinésithérapeutes, nutritionnistes … ayant l'habitude de la prise en charge de l'AS.

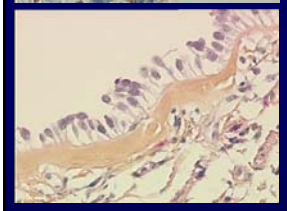
Qu'est ce qu'un phenotype ?

Caractéristiques observables d'un individu
Elles résultent de l'intéraction de son génotype avec l'environnement



Asthme: de la définition(s) aux premiers concepts de phénotype





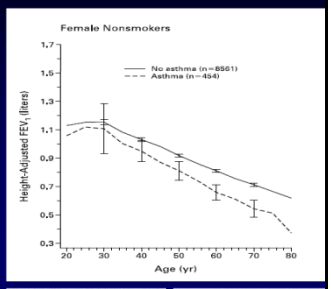
Reddel, Lancet 1999

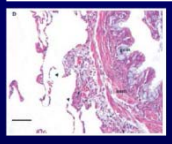
Asthme

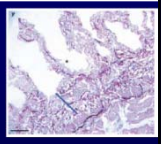
Symptômes paroxystiques
Obstruction bronchique
Inflammation bronchique
HRB
Réversibilité…

Asthmatiques
avec des profils cliniques,
réponses thérapeutiques,
évolutions, pronostics…
variables

Phénotypes initiaux





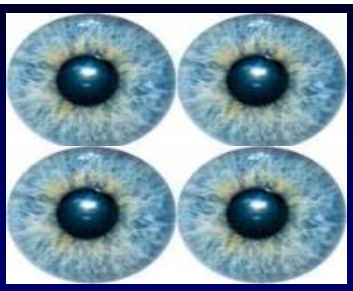


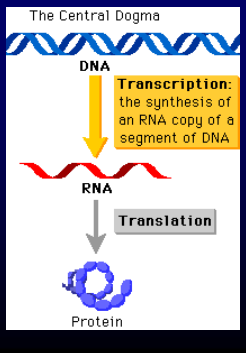
Mauad, AJRCCM 2004
Lange, NEJM 1998

Exacerbation
(inflammation)

Obstruction bronchique fixée
(perte de fonction)

Phénotypes “cachés”

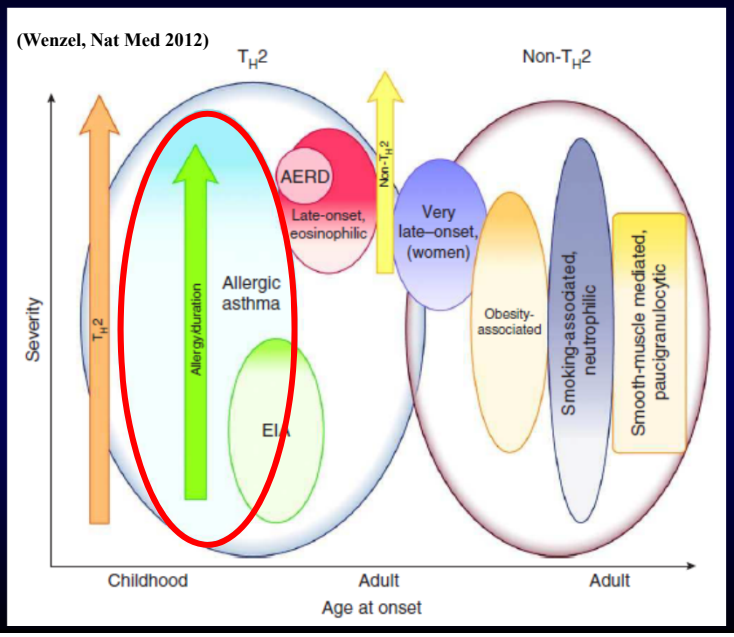




Phénotype = Gène X Environment

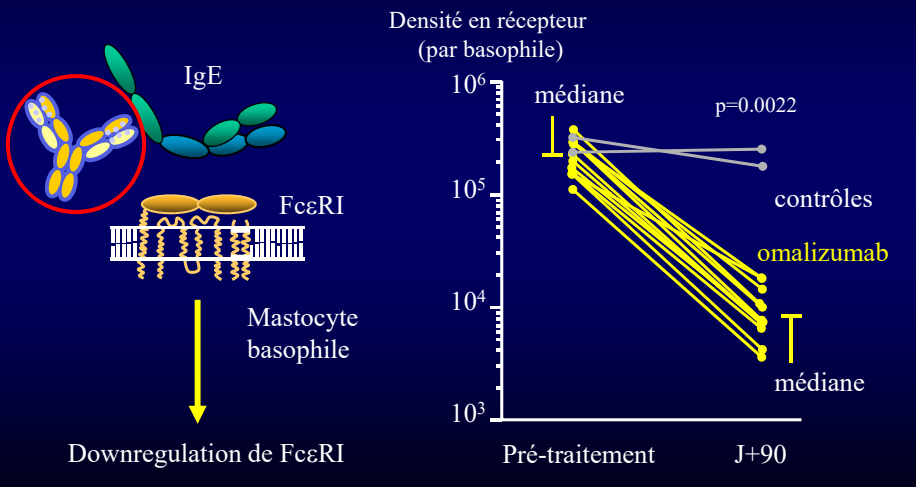
Identification d’un biomarqueur
IgE
Eosinophile
FeNO
Périostine ? … autre(s) ?

Propositions de phénotypes « théoriques » Th2/nonTH2 et de l'âge de survenue



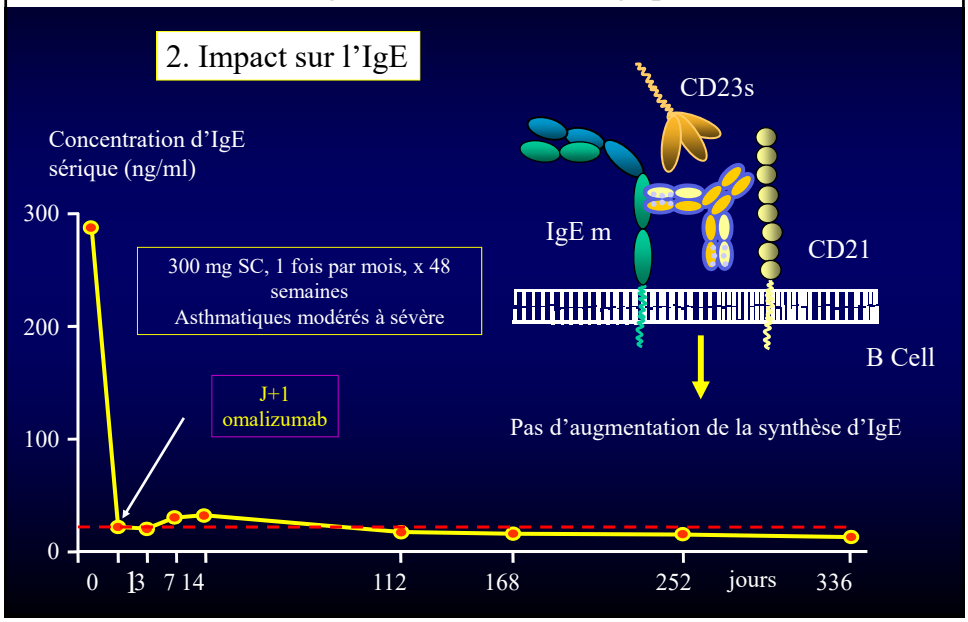
Caractéristiques de l'Ac anti-IgE et arguments immunologiques

1. Impact sur l'expression de FcεRI

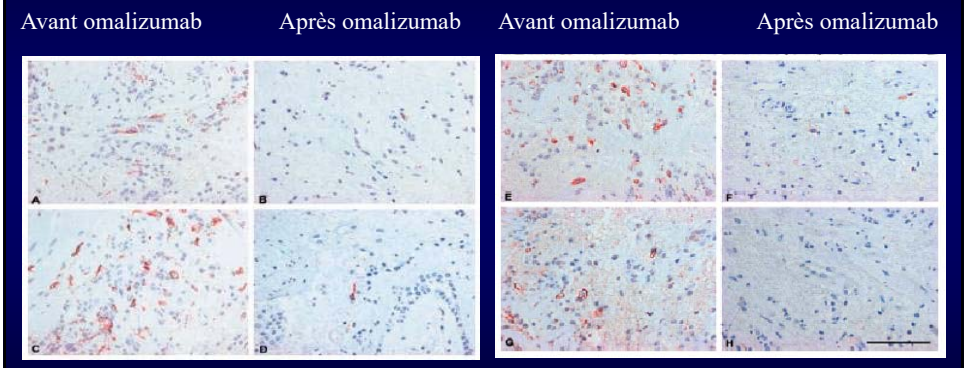


(MacGlashan, J Immunol 1997)

Caractéristiques de l'Ac anti-IgE et arguments immunologiques



Inflammation et omalizumab Analyse IHC de biopsies bronchiques



AB : Eosinophiles

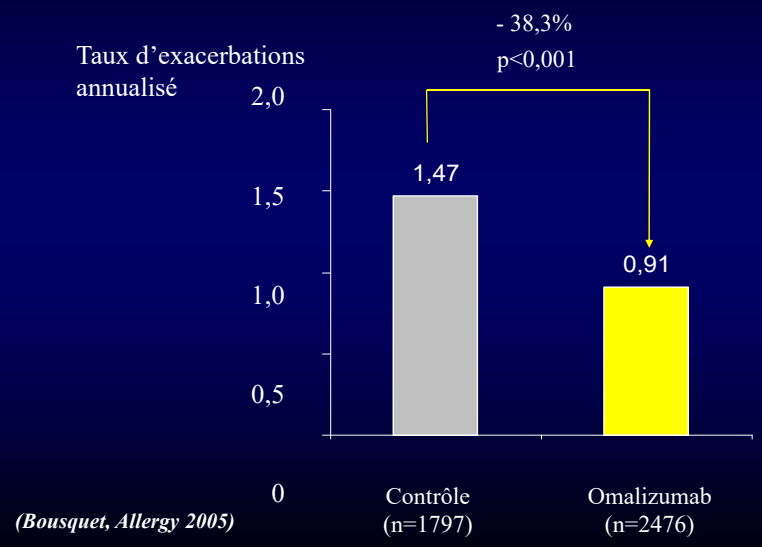
CD : IgE de surface

EF : Récepteurs FcεRI

GH : IL-4

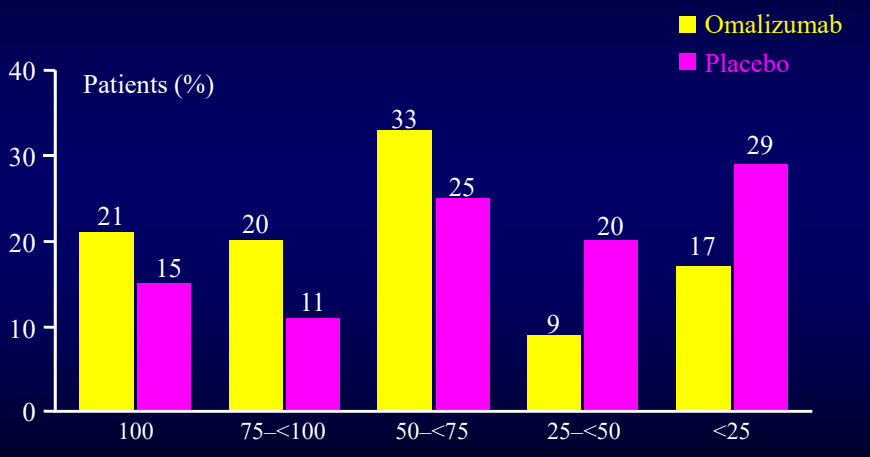
(Djukanović, AJRCCM 2004)

Omalizumab réduit le taux d'exacerbations (Analyse groupée)



(Bousquet, Allergy 2005)

Réduction des besoins en corticoïdes



Holgate et al. AJRCCM 2001 (abstract)

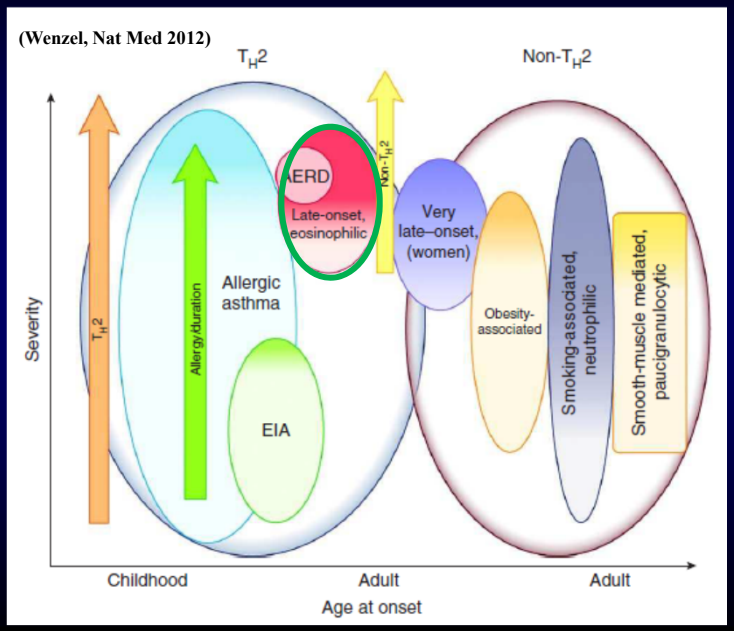
Asthme sévère allergique

→ Omalizumab

Traitement de première ligne
Evaluation 4-6 mois

Taux d'IgE (UI/mL)	Poids corporel (kg)								
	20–30	>30–40	>40–50	>50–60	>60–70	>70–80	>80–90	>90–125	>125–150
>30–100	150	150	150	150	150	150	150	300	300
>100–200	150	150	300	300	300	300	300	450	600
>200–300	150	300	300	300	450	450	450	600	750
>300–400	300	300	450	450	450	600	600		
>400–500	300	450	450	600	600	750	750		
>500–600	300	450	600	600	750				
>600–700	450	450	600	750					

Propositions de phénotypes « théoriques » Th2/nonTH2 et de l'âge de survenue

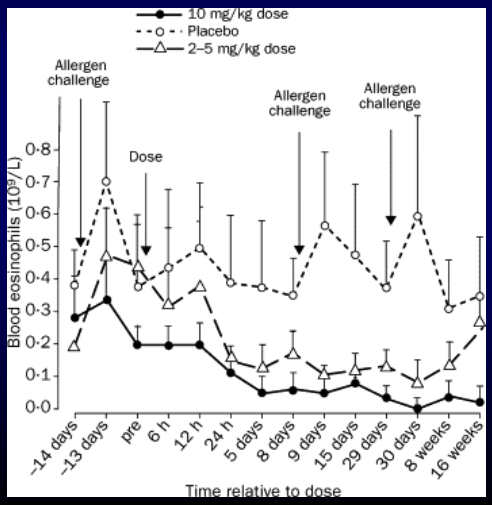


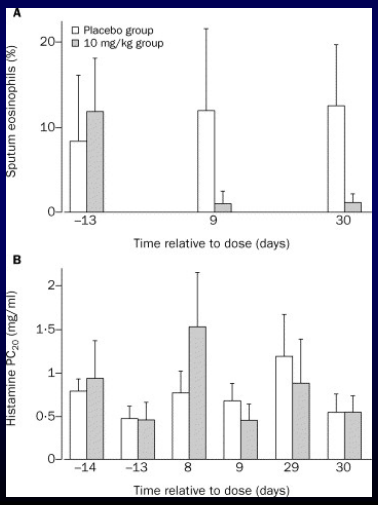
mAc anti-IL-5 (Mépolizumab)
Réponse biologique prolongée !!!

Mépolizumab (SB-240563)

Asthme persistant léger allergique
Placebo *vs* mAb 2.5 ou 10 mg/Kg

(Leckie, Lancet 2000)



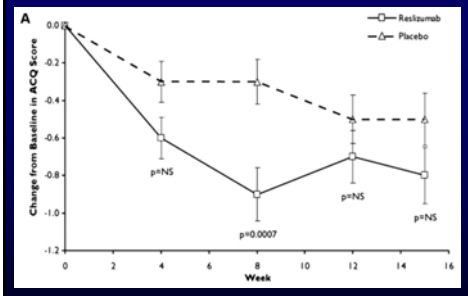


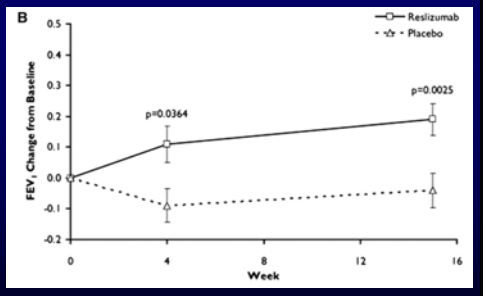
mAb anti-IL-5 (Reslizumab)

Reslizumab for Poorly Controlled, Eosinophilic Asthma
A Randomized, Placebo-controlled Study

Mario Castro[1], Sameer Mathur[2], Frederick Hargreave[3†], Louis-Philippe Boulet[4], Fang Xie[5], James Young[6], H. Jeffrey Wilkins[5], Timothy Henkel[5], and Parameswaran Nair[3]; for the Res-5-0010 Study Group

[1]Washington University School of Medicine, St. Louis, Missouri; [2]University of Wisconsin, Madison, Madison, Wisconsin; [3]McMaster University, Hamilton, Ontario, Canada; [4]Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec, Canada; [5]Cephalon, Inc., Frazer, Pennsylvania; and [6]United BioSource Corporation, Ann Arbor, Michigan





Castro AJRCCM 2011

Response to anti-IL5 and "true eosinophil phenotype"

Study	Intervention	Sputum eos at entry	Success
Flood-Page (AJRCCM, 2007)	mepolizumab	5% patients had >3% eos	X
Kips (AJRCCM, 2003)	reslizumab	~30% patients had >3% eos	X
Haldar (NEJM, 2009)	mepolizumab	all had >3% on one occasion in 2 yrs	√
Castro, Nair (AJRCCM, 2011)	reslizumab	all had >3% at randomization	√√
Nair (NEJM, 2009)	mepolizumab	All had >3% on ≥3 occasions	√√√

Hargreave FE, Nair P. Chest 2011; 139: 1270-3.

ORIGINAL ARTICLE

Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

Hector G. Ortega, M.D., Sc.D., Mark C. Liu, M.D., Ian D. Pavord, D.M., Guy G. Brusselle, M.D., J. Mark FitzGerald, M.D., Alfredo Chetta, M.D., Marc Humbert, M.D., Ph.D., Lynn E. Katz, Pharm.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., and Pascal Chanez M.D., Ph.D., for the MENSA Investigators*

N Engl J Med 2014;371:1198-207.

MENSA

576 asthmatiques éosinophiliques exacerbateurs

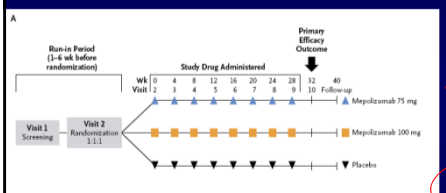
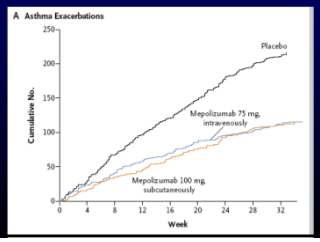
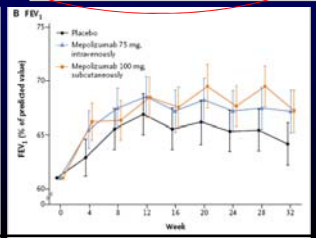


Table 1. Characteristics of the Patients at Baseline in the Intention-to-Treat Population.*

Characteristic	Placebo (N=191)	Mepolizumab	
		Intravenous (N=191)	Subcutaneous (N=194)
Mean age (range) — yr	49 (12–76)	50 (13–82)	51 (12–81)
Female sex — no. (%)	107 (56)	106 (55)	116 (60)
Body-mass index†	28.0±5.6	27.7±5.7	27.6±6.2
Former smoker — no. (%)	57 (30)	52 (27)	50 (26)
Duration of asthma — yr	19.5±14.6	19.8±14.0	20.5±12.9
Use of oral glucocorticoids			
Maintenance use — no. (%)	44 (23)	48 (25)	52 (27)
Mean daily dose (range) — mg‡	15.1 (5–80)	12.0 (1–40)	12.6 (2–50)
Allergic rhinitis — no. (%)	95 (50)	91 (48)	95 (49)
FEV_1			
Before bronchodilation — liters§	1.86±0.63	1.86±0.70	1.73±0.66
Percent of predicted value before bronchodilation¶	62.4±18.1	61.4±18.3	59.3±17.5
Reversibility — %	27.4±20.8	25.4±19.6	27.9±24.0
FEV_1:FVC ratio — %‖	64±13	64±13	63±13
Morning peak expiratory flow — liters/min	277±106	269±112	255±108
Score on Asthma Control Questionnaire**	2.28±1.19	2.12±1.13	2.26±1.27
Score on St. George's Respiratory Questionnaire††	46.9±19.8	44.4±19.4	47.9±19.4
Geometric mean IgE on $\log_e$ scale — U/ml	150±1.5	180±1.5	150±1.5
Geometric mean blood eosinophil count on $\log_e$ scale — cells/μl‡‡	320±938	280±987	290±1050
Asthma exacerbations			
Severe episodes in previous year — no./patient	3.6±2.8	3.5±2.2	3.8±2.7
Necessitating hospitalization in previous year — no. (%)	35 (18)	41 (21)	33 (17)
History of asthma-related intubation — no. (%)	3 (2)	10 (5)	8 (4)





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Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

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135 asthmatiques éosinophiliques sévères

SIRIUS

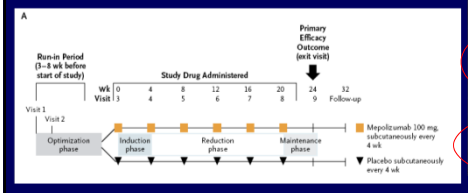
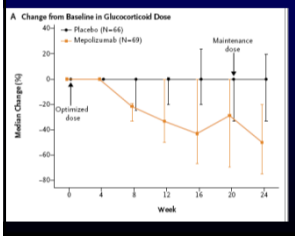
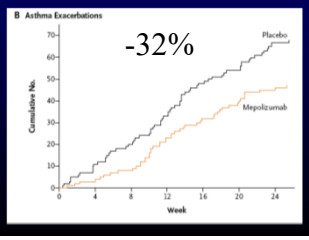
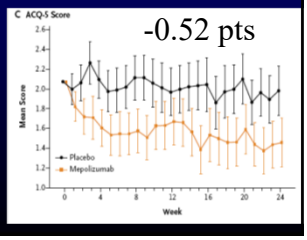


Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Placebo (N = 66)	Mepolizumab (N = 69)
Mean age (range) — yr	50 (28–70)	50 (16–74)
Female sex — no. (%)	30 (45)	44 (64)
Body-mass index†	29.5±6.0	27.8±5.9
Former smoker — no. (%)	25 (38)	28 (41)
Duration of asthma — yr	20.1±14.4	17.4±11.8
Median daily oral glucocorticoid dose — mg‡		
At screening	15.0	12.5
During optimization phase	12.5	10.0
Duration of oral glucocorticoid use ≥5 yr — no. (%)	31 (47)	34 (49)
FEV_1 before bronchodilation		
Mean — liters	2.00±0.82	1.90±0.66
Percent of predicted value	57.8±18.5	59.6±17.0
FEV_1/FVC ratio before bronchodilation — %§	61±11.7	63±12.4
Percent reversibility of FEV_1	24.8±18.1	27.3±17.4
ACQ-5 score¶	2.0±1.2	2.2±1.3
SGRQ score‖	45±18	50±18
Geometric mean IgE on $\log_e$ scale — U/ml	114±1	117±1
Geometric mean blood eosinophil count on $\log_e$ scale — cells/μl**	230±1001	250±1245
Severe exacerbations in previous year — no./patient	2.9±2.8	3.3±3.4
Exacerbations in the previous year requiring hospitalization — no. (%)	9 (14)	14 (20)
History of asthma-related intubation — no. (%)	3 (5)	2 (3)





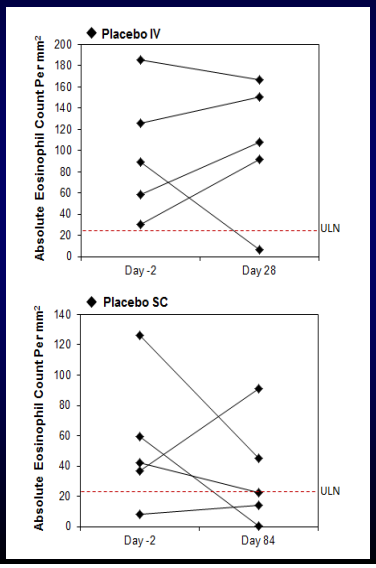


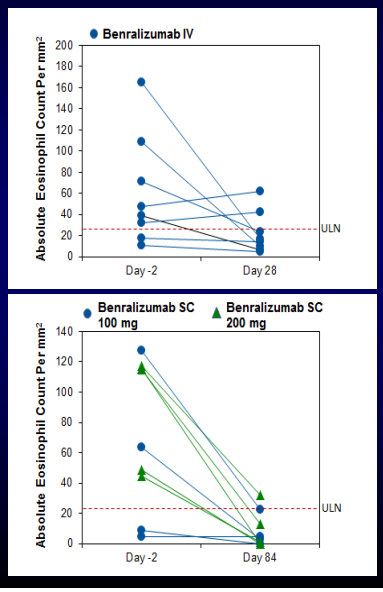
mAc anti-IL-5Rα (Benralizumab)

17 asthmatiques traités (IV ou SC vs 10 placebo)

Gossage et al. ATS meeting 2012

Éosinophiles (expectoration) ≥ 2.5%





SIROCCO

Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial

Lancet 2016

	All patients (n=1204)			High-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per µL (n=809)			High-dosage ICS plus LABA with baseline blood eosinophils <300 cells per µL (n=395)		
	Placebo (n=407)	Benralizumab 30 mg Q4W (n=399)	Benralizumab 30 mg Q8W (n=398)	Placebo (n=267)	Benralizumab 30 mg Q4W (n=275)	Benralizumab 30 mg Q8W (n=267)	Placebo (n=140)	Benralizumab 30 mg Q4W (n=124)	Benralizumab 30 mg Q8W (n=131)
Age (years)	48·7 (14·9)	50·1 (13·4)	47·6 (14·5)	48·6 (14·7)	49·2 (13·1)	47·6 (14·6)	49·0 (15·3)	52·0 (13·9)	47·8 (14·3)
Age group (years)									
≥12 to <18	23 (6%)	11 (3%)	19 (5%)	12 (4%)	8 (3%)	10 (4%)	11 (8%)	3 (2%)	9 (7%)
≥18 to 75	384 (94%)	388 (97%)	379 (95%)	255 (96%)	267 (97%)	257 (96%)	129 (92%)	121 (98%)	122 (93%)
Sex									
Male	138 (34%)	124 (31%)	146 (37%)	87 (33%)	102 (37%)	93 (35%)	51 (36%)	22 (18%)	53 (40%)
Female	269 (66%)	275 (69%)	252 (63%)	180 (67%)	173 (63%)	174 (65%)	89 (64%)	102 (82%)	78 (60%)
Race									
White	302 (74%)	285 (71%)	287 (72%)	191 (72%)	191 (69%)	192 (72%)	111 (79%)	94 (76%)	95 (73%)
Black or African American	16 (4%)	15 (4%)	15 (4%)	10 (4%)	11 (4%)	10 (4%)	6 (4%)	4 (3%)	5 (4%)
Asian	50 (12%)	54 (14%)	50 (13%)	36 (13%)	39 (14%)	35 (13%)	14 (10%)	15 (12%)	15 (11%)
Other*	39 (10%)	45 (11%)	46 (12%)	30 (11%)	34 (12%)	30 (11%)	9 (6%)	11 (9%)	16 (12%)
Ethnic group									
Hispanic or Latino	77 (19%)	73 (18%)	80 (20%)	57 (21%)	52 (19%)	52 (19%)	20 (14%)	21 (17%)	28 (21%)
Not Hispanic or Latino	330 (81%)	326 (82%)	318 (80%)	210 (79%)	223 (81%)	215 (81%)	120 (86%)	103 (83%)	103 (79%)
Body-mass index (kg/m²)	28·9 (7·1)	29·2 (7·1)	28·2 (6·2)	28·7 (7·0)	28·9 (6·9)	27·7 (6·1)	29·3 (7·1)	29·9 (7·3)	29·3 (6·2)
Missing data	0	2	0	0	2	0	0	0	0
Eosinophil count (cells per µL)	370 (0-2690)	390 (0-3440)	360 (0-3100)	500 (300-2690)	500 (300-3440)	500 (300-3100)	130 (0-290)	160 (0-297)	180 (0-290)
Missing data	4	4	6	3	1	4	1	3	2
Central eosinophil count (cells per µL)	350 (0-3580)	360 (0-3170)	325 (0-3110)	480 (70-2220)	470 (40-3170)	460 (10-3110)	130 (0-3580)	160 (0-760)	150 (0-460)
Missing data	12	12	16	9	6	10	3	6	6
Prebronchodilator FEV_1 (L)	1·660 (0·584)	1·655 (0·553)	1·680 (0·582)	1·654 (0·580)	1·673 (0·577)	1·660 (0·574)	1·672 (0·594)	1·615 (0·493)	1·721 (0·597)
Predicted normal (%)	56·6% (15·0)	57·4% (14·1)	56·1% (14·6)	56·4% (14·6)	56·5% (14·4)	55·5% (14·6)	57·0% (15·7)	59·4% (13·2)	57·3% (14·7)
Missing data	7	6	1	5	2	1	2	4	0
Prebronchodilator FEV_1/FVC	61 (13)	62 (12)	61 (13)	61 (13)	62 (12)	60 (13)	62 (13)	63 (12)	62 (14)
Missing data	7	6	1	5	2	1	2	4	0
Reversibility (%)	20% (-26 to 154)	18% (-7 to 136)	22% (-12 to 157)	20% (-26 to 154)	18% (-7 to 136)	21% (-10 to 157)	20% (-7 to 138)	17% (-2 to 96)	22% (-12 to 134)
Missing data	26	24	23	16	13	14	10	11	9
ACQ-6 score†	2·87 (0·94)	2·77 (0·96)	2·80 (0·88)	2·90 (0·95)	2·77 (0·95)	2·81 (0·89)	2·82 (0·93)	2·78 (1·00)	2·78 (0·85)

(Table 1 coninues on next page)

	All patients (n=1204)			High-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per µL (n=809)			High-dosage ICS plus LABA with baseline blood eosinophils <300 cells per µL (n=395)		
	Placebo (n=407)	Benralizumab 30 mg Q4W (n=399)	Benralizumab 30 mg Q8W (n=398)	Placebo (n=267)	Benralizumab 30 mg Q4W (n=275)	Benralizumab 30 mg Q8W (n=267)	Placebo (n=140)	Benralizumab 30 mg Q4W (n=124)	Benralizumab 30 mg Q8W (n=131)
(Continued from previous page)									
Time since asthma diagnosis (years)	14·2 (1·1-72·4)	15·3 (1·1-70·4)	14·4 (1·1-66·9)	13·4 (1·1-65·2)	14·9 (1·1-62·6)	14·6 (1·1-66·9)	16·8 (1·1-72·4)	17·4 (1·2-70·4)	14·0 (1·2-58·8)
Number of exacerbations in the past 12 months	3·0 (1·8)	2·9 (1·8)	2·8 (1·5)	3·1 (2·0)	3·0 (2·0)	2·8 (1·5)	2·7 (1·5)	2·7 (1·2)	2·6 (1·3)
Number resulting in ED visit	0·3 (0·8)	0·3 (1·0)	0·2 (0·8)	0·3 (0·8)	0·4 (1·0)	0·3 (0·9)	0·2 (0·8)	0·2 (0·9)	0·2 (0·6)
Patients with ≥1 exacerbations resulting in ED visit	67 (16%)	64 (16%)	53 (13%)	48 (18%)	51 (19%)	40 (15%)	19 (14%)	13 (10%)	13 (10%)
Number resulting in hospital admission	0·4 (0·8)	0·4 (0·7)	0·4 (0·8)	0·4 (0·8)	0·3 (0·7)	0·4 (0·9)	0·4 (0·8)	0·4 (0·9)	0·3 (0·8)
Patients with ≥1 exacerbations resulting in hospital admission	107 (26%)	98 (25%)	100 (25%)	67 (25%)	66 (24%)	71 (27%)	40 (29%)	32 (26%)	29 (22%)
Total asthma symptom score	2·68 (1·07)	2·72 (1·02)	2·70 (1·11)	2·74 (1·08)	2·67 (1·01)	2·68 (1·09)	2·57 (1·07)	2·84 (1·02)	2·73 (1·14)
Missing data	0	1	3	0	1	2	0	0	1
Diagnosis of allergic rhinitis	220 (54%)	207 (52%)	219 (55%)	156 (58%)	148 (54%)	150 (56%)	64 (46%)	59 (48%)	69 (53%)
Nasal polyps	79 (19%)	84 (21%)	74 (19%)	62 (23%)	66 (24%)	62 (23%)	17 (12%)	18 (15%)	12 (9%)
Atopic (based on Phadiatop test)	230 (57%)	231 (58%)	244 (61%)	152 (57%)	156 (57%)	169 (63%)	78 (56%)	75 (60%)	75 (57%)
History of omalizumab treatment	31 (8%)	29 (7%)	28 (7%)	22 (8%)	16 (6%)	18 (7%)	9 (6%)	13 (10%)	10 (8%)
Missing data	3	1	1	2	1	1	1	0	0
AQLQ(S)+12 score‡	3·90 (1·02)	3·93 (0·98)	3·94 (1·00)	3·87 (0·99)	3·93 (1·00)	3·93 (0·97)	3·97 (1·07)	3·92 (0·95)	3·97 (1·04)
Missing data	15	17	17	12	12	12	3	5	5
Smoker	5 (1%)	0	1 (<1%)	1 (<1%)	0	1 (<1%)	4 (3%)	0	0
Nicotine pack-years	5·0 (0-9)	5·0 (0-9)	5·0 (0-9)	5·0 (0-9)	6·0 (0-9)	5·0 (0-9)	5·0 (0-9)	5·0 (1-9)	5·0 (0-9)

Data are mean (SD), number (%), or median (range). Some percentages do not add up to 100 because of rounding. ICS=inhaled corticosteroids. LABA=long-acting β_2-agonists. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). ACQ-6=Asthma Control Questionnaire, six-question version. AQLQ(S)+12=Standardised Asthma Quality of Life Questionnaire for 12 years and older. ED=emergency department. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. *Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, or other. †Low numbers represent better symptom control. ‡High numbers suggest better quality of life. §Current smoker or former smoker with a smoking history of ≥10 packs per year.

Table 1: **Baseline demographics and clinical characteristics** (full analysis set)

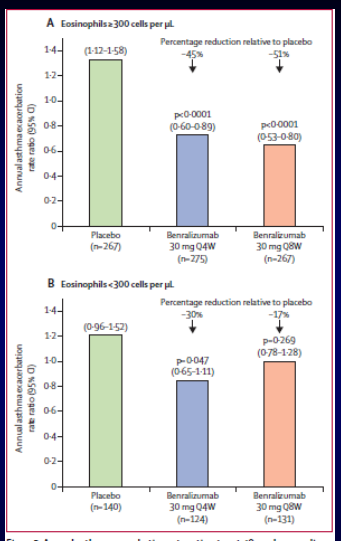


Figure 2: **Annual asthma exacerbation rate estimates at 48 weeks according to baseline blood eosinophil concentrations**
Data for patients with baseline blood eosinophils (A) ≥300 cells per μL and (B) <300 cells per μL in the full analysis set are shown. Estimates were calculated using a negative binomial model, with adjustment for treatment, region, oral corticosteroid use at time of randomisation, and previous exacerbations. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W).

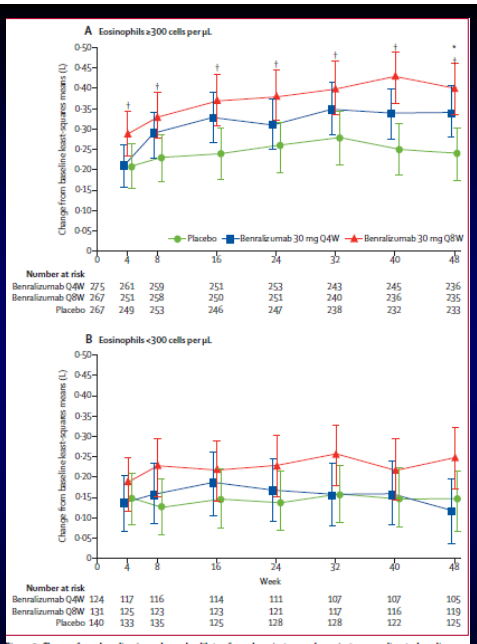


Figure 3: **Change from baseline in prebronchodilator forced expiratory volume in 1 s according to baseline blood eosinophil concentrations**
Data for patients with baseline blood eosinophils (A) ≥300 cells per μL and (B) <300 cells per μL in the full analysis set are shown. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). *p<0·05 for benralizumab 30 mg Q4W vs placebo. †p<0·05 for benralizumab 30 mg Q8W vs placebo.

ZONDA

NEJM 2017

Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma

Parameswaran Nair, M.D., Ph.D., Sally Wenzel, M.D., Klaus F. Rabe, M.D., Ph.D., Arnaud Bourdin, M.D., Ph.D., Njira L. Lugogo, M.D., Piotr Kuna, M.D., Ph.D., Peter Barker, Ph.D., Stephanie Sproule, M.Math., Sandhia Ponnarambil, M.D., and Mitchell Goldman, M.D., for the ZONDA Trial Investigators*

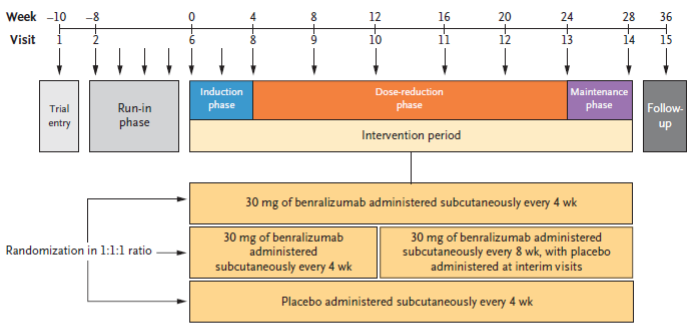


Figure 1. Trial Design.
Patients entering the run-in phase had their oral glucocorticoid dose reduced until the minimum effective dose without loss of asthma control was reached. All the patients then underwent randomization and entered the induction phase, during which the dose established in the run-in phase was maintained. The oral glucocorticoid dose was further reduced, every 4 weeks, in the intervention period from weeks 4 to 24. The oral glucocorticoid dose that was reached at week 24, or the complete discontinuation of oral glucocorticoid therapy, was maintained until week 28. The last dose of benralizumab or placebo was administered at the week 24 visit.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=75)	Benralizumab, Every 4 Wk (N=72)	Benralizumab, Every 8 Wk (N=73)
Age — yr	49.9±11.7	50.2±12.0	52.9±10.1
Female sex — no. (%)	48 (64)	40 (56)	47 (64)
Body-mass index†	28.7±5.2	29.8±6.8	30.2±6.5
Median smoking history (range) — pack-yr	6.0 (1 to 9)	5.5 (2 to 9)	5.0 (1 to 8)
Median time since asthma diagnosis (range) — yr	10.5 (1.1 to 54.5)	13.3 (1.2 to 52.3)	16.3 (1.3 to 53.0)
Median oral glucocorticoid dose (range) — mg/day			
At trial entry‡	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)
At end of run-in phase	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)
Mean inhaled glucocorticoid dose (range) — μg/day	1232 (250 to 5000)	1033 (250 to 3750)	1192 (100 to 3250)
Leukotriene-receptor antagonist — no. (%)	25 (33)	28 (39)	29 (40)
No. of exacerbations in previous 12 mo	2.5±1.8	2.8±2.0	3.1±2.8
FEV_1 before bronchodilation			
Value — liters	1.931±0.662	1.850±0.741	1.754±0.635
Percent of predicted normal value	62.0±16.5	57.4±18.0	59.0±17.9
FEV_1:FVC ratio before bronchodilation — %	62±13	59±13	59±12
Median percent reversibility of FEV_1 (range)§	16.4 (−5.4 to 93.4)	18.2 (−3.0 to 126.0)	22.6 (−3.4 to 88.0)
Total asthma symptom score¶	2.4±1.0	2.5±1.0	2.3±1.1
ACQ-6 score‖	2.7±1.0	2.6±1.1	2.4±1.2
AQLQ(S)+12 score**	4.1±1.1	4.2±1.1	4.4±1.2
Blood eosinophil count			
Median count (range) — cells/mm^3††	535 (160 to 4550)	462 (160 to 1740)	437 (154 to 2140)
Distribution — no. (%)			
≥150 to <300 cells/mm^3	11 (15)	10 (14)	12 (16)
≥300 cells/mm^3	64 (85)	62 (86)	61 (84)

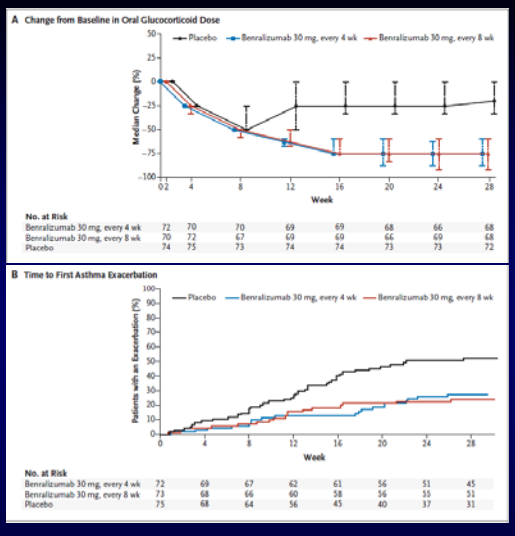
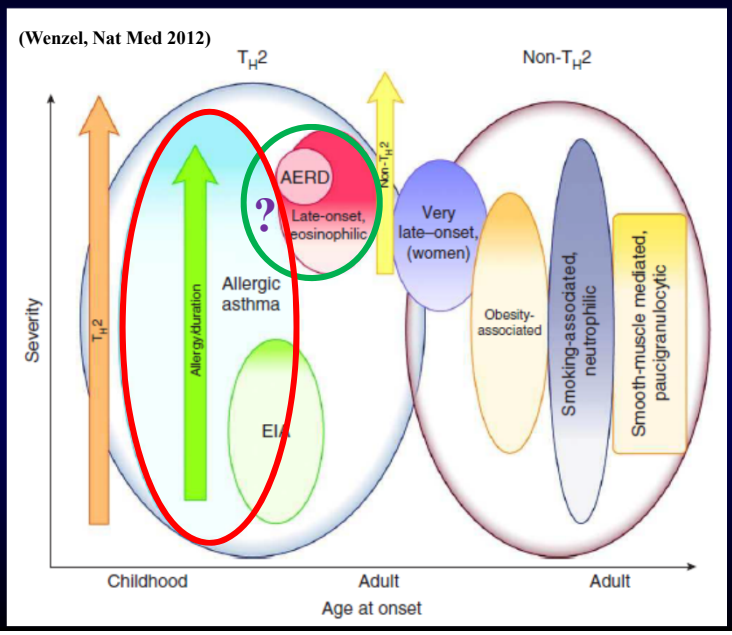


Figure 2. Change from Baseline in the Oral Glucocorticoid Dose and Asthma Exacerbations.
Panel A shows the median percentage change from baseline to week 28 in the oral glucocorticoid dose in patients who received benralizumab or placebo. Error bars represent 95% confidence intervals. Values are slightly offset from each other at each time point for clarity. Panel B is a Kaplan–Meier cumulative incidence curve for the time to the first exacerbation in patients who received benralizumab as compared with those who received placebo. Benralizumab administered every 4 weeks was associated with a longer time to the first exacerbation than was placebo (hazard ratio, 0.39; 95% confidence interval [CI], 0.22 to 0.66; P<0.001), and benralizumab administered every 8 weeks was also associated with a longer time to the first exacerbation than was placebo (hazard ratio, 0.32; 95% CI, 0.17 to 0.57; P<0.001).

Propositions de phénotypes « théoriques » Th2/nonTH2 et de l'âge de survenue

(Wenzel, Nat Med 2012)



Treatment response with mepolizumab in severe eosinophilic asthma patients with previous omalizumab treatment

Allergy 71 (2016) 1335–1344

A. Magnan[1], A. Bourdin[2], C. M. Prazma[3], F. C. Albers[3], R. G. Price[4], S. W. Yancey[3] & H. Ortega[3,*]

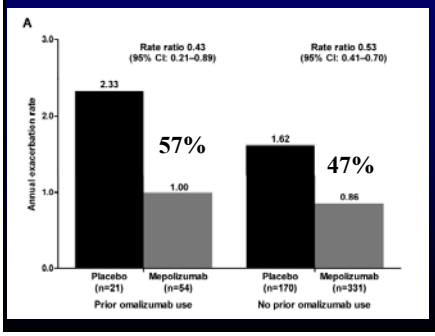
MENSA — **SIRIUS**

Analyse post-hoc de l'impact du Mépolizumab chez des asthmatiques sévères éosinophiliques, précédemment traités ou non par omalizumab

32 S
Mepo 75 mg IV ou 100 mg SC /mois
576 patients
CrP: Réduction Δt exacerbation

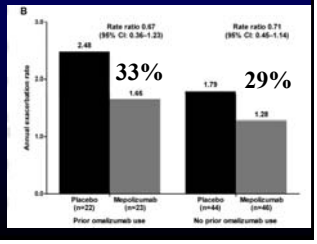
Eo ≥ 150/ml (screening)
Ou
EO ≥ 300 ml (12 mois)

24S
Mepo 100 mg SC/mois
135 patients
CrP: % réduction CO

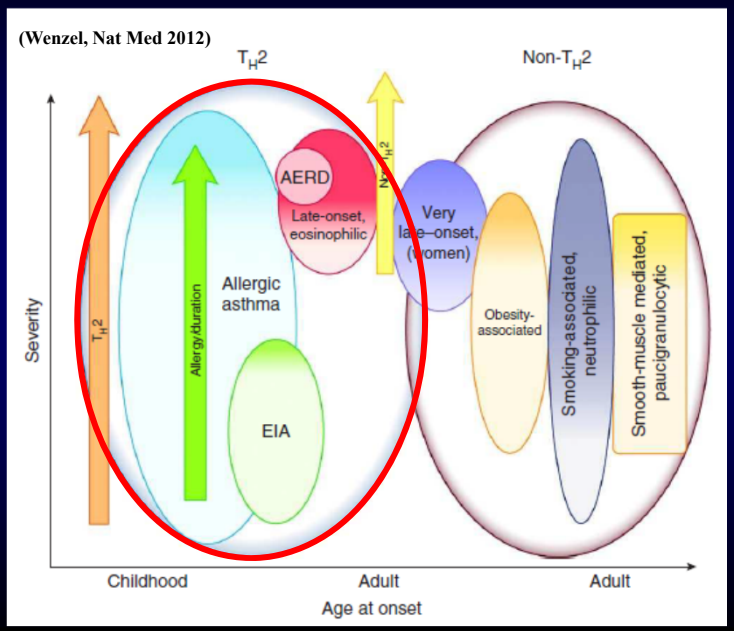


% Réduction CO OR Mepo/placebo (95% CI)

2,15 (0,67-6,90) 2,53 (1,15-5,58)

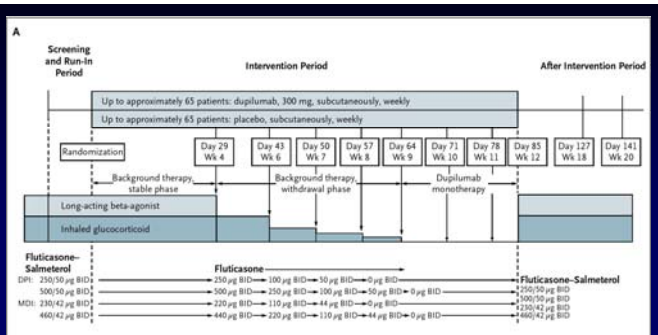


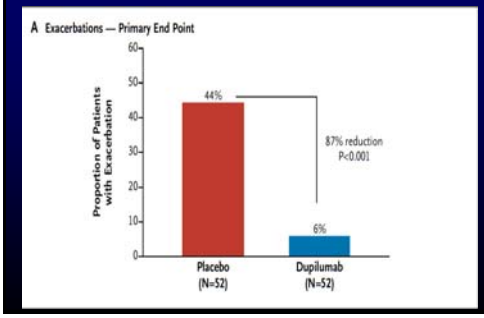
Propositions de phénotypes « théoriques » Th2/nonTH2 et de l'âge de survenue

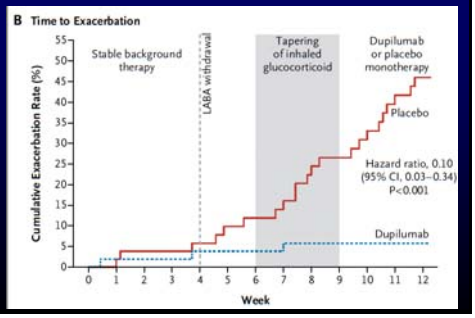


Asthme sévère et anti-IL-4R (Dupilumab)

Wenzel et al. NEJM 2013







Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial

(S Wenzel, Lancet 2016)

769 patients
Eosinophilie < ou ≥ 300/µl)
(158/611)
200 ou 300 mg/ 2 ou 4 semaines

174 sites
16 pays
52
52 semaines

Critère principal: modification VEMS à 12 semaines

→ Différence significative à S12 S2 pour 200 et 300 mg
Eosinophilie < ou ≥ 300/µl
→ Résultat maintenu à S24

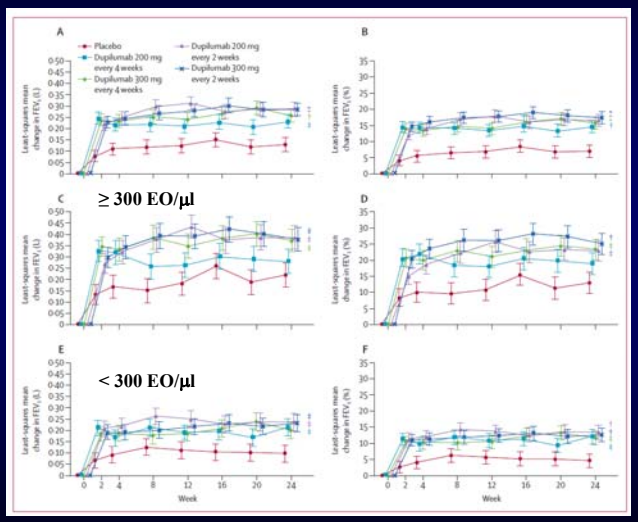
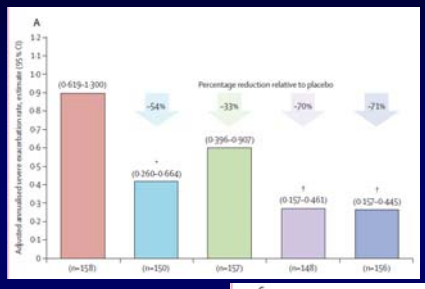
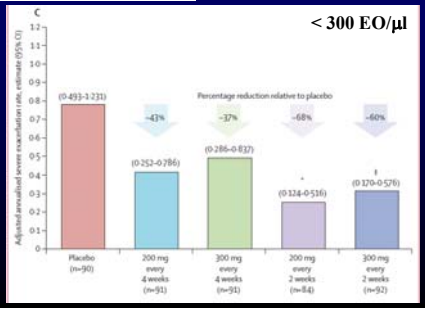


Figure 2: Improvement in FEV_1 in L (A, C, E) and percentage change (B, D, F) from baseline to week 24
Data are in the overall population (A, B), patients with baseline blood eosinophil counts of at least 300 eosinophils per µL (C, D), and patients with counts lower than 300 eosinophils per µL (E, F). FEV_1=forced expiratory volume in 1 s. *p<0·001. †p<0·01. ‡p<0·05. Error bars indicate SE.

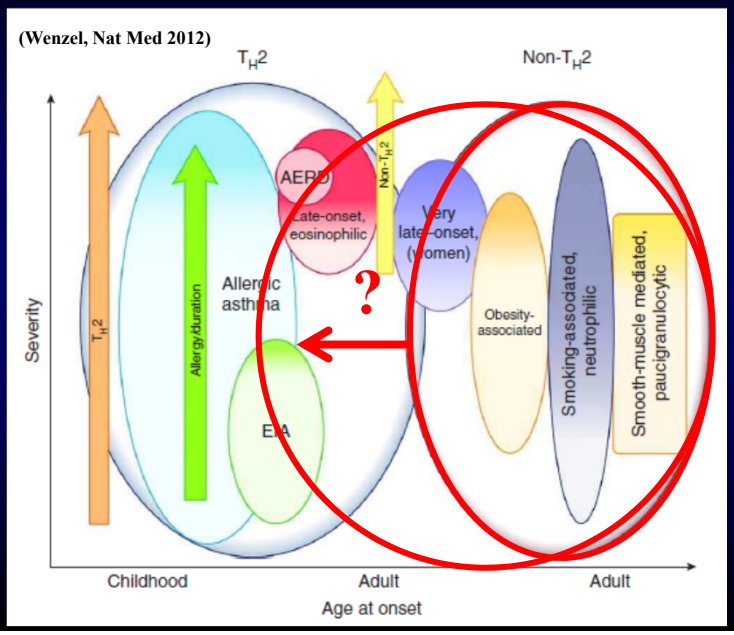
Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial

(S Wenzel, Lancet 2016)





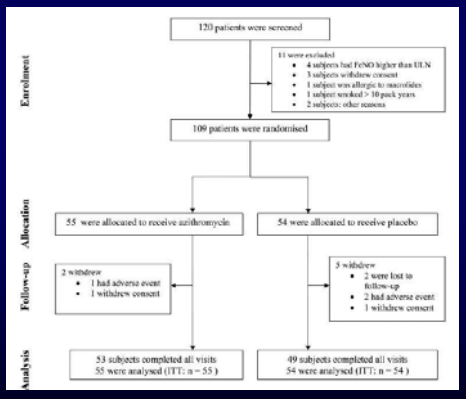
Propositions de phénotypes « théoriques » Th2/nonTH2 et de l'âge de survenue

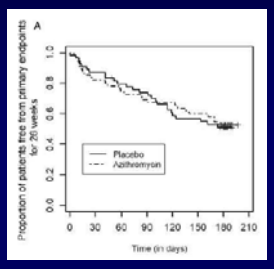


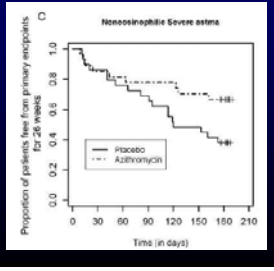
THORAX

Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial *Thorax* 2013

Guy G Brusselle, Christine VanderStichele, Paul Jordens, et al.







	Placebo (n=207)	Azithromycin (n=213)
Age (years)	60·01 (49·58–67·98)	61·02 (50·62–68·74)
Sex		
Female	121 (58%)	134 (63%)
Male	86 (42%)	79 (37%)
Atopy	163 (80%)	158 (74%)
Ex-smoker	81 (39%)	80 (38%)
Pack years	7·5 (3·5–18·0)	7·6 (3·75–26·0)
Body-mass index (kg/m²)	28·81 (25·48–33·11)	29·90 (25·81–34·86)
Asthma history		
Age asthma symptoms began	13 (4–40)	12 (5–40)
Age asthma diagnosed	20 (5–44)	21 (5–47)
ACQ6 score	1·55 (0·79)	1·56 (0·75)
AQLQ score	5·35 (0·89)	5·36 (0·93)
Asthma history past year		
Emergency room visit or hospital admission	0 (0–0)	0 (0–0)
Unscheduled doctor visits	1 (0–3)	1 (0–2)
Oral corticosteroid courses	1 (0–2)	1 (0–2)
Medications		
Inhaled corticosteroid daily dose, beclomethasone equivalent		
Low dose (<400 µg/day)	4 (2%)	5 (2%)
Moderate dose (400–<800 µg/day)	26 (13%)	23 (11%)
High dose (≥800 µg/day)	176 (85%)	185 (87%)
Long-acting beta agonist	205 (99%)	208 (98%)
Leukotriene modifier	6 (3%)	8 (4%)
Long-acting anti-muscarinic	33 (16%)	40 (19%)
Theophylline (slow-release)	6 (3%)	7 (3%)
Oral corticosteroid	6 (3%)	8 (4%)
Pre BD spirometry	n=205	n=210
Pre BD FEV₁, %	73·58 (18·83)	72·33 (20·70)
Pre BD FVC %	82·55 (15·14)	82·74 (16·06)
Pre BD FEV₁/FVC%	68·26 (11·90)	67·46 (12·90)
Sputum cell counts	n=166	n=165
Total cell count (×10⁶) per mL	4·05 (2·16–8·90)	4·05 (2·34–7·79)
Neutrophils (%)	33·25 (16·25–55·0)	36·75 (17·25–56·75)
Eosinophils (%)	2·38 (0·50–10·5)	1·75 (0·50–7·50)
Sputum phenotype		
Eosinophilic	77 (46%)	67 (41%)
Neutrophilic	25 (15%)	21 (13%)
Paucigranulocytic	55 (33%)	70 (42%)
Mixed	9 (5%)	7 (4%)
Blood eosinophils (×10⁹) per L	0·28 (0·16–0·41)	0·20 (0·11–0·40)

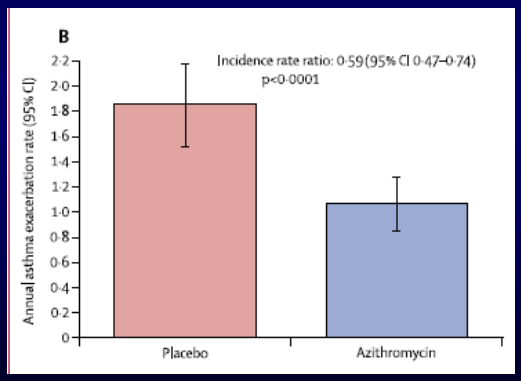
Data are medians (IQR), mean (SD), or n (%). AQLQ=Asthma Quality of Life Questionnaire. ACQ6=Asthma Control Questionnaire. FEV₁=forced expiratory volume in 1 s. FVC=forced vital capacity.

Table 1: Characteristics of patients at baseline

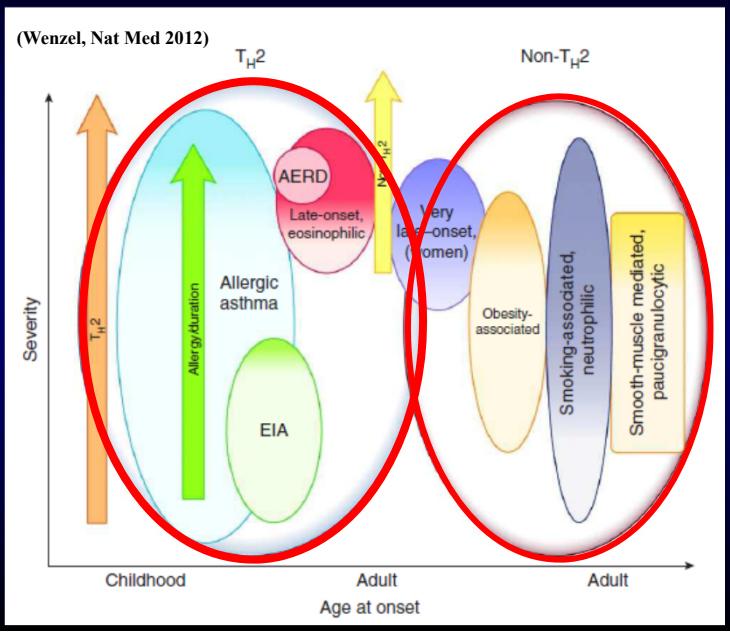
Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial

Peter G Gibson, Ian A Yang, John W Upham, Paul N Reynolds, Sandra Hodge, Alan L James, Christine Jenkins, Matthew J Peters, Guy B Marks, Melissa Baraket, Heather Powell, Steven L Taylor, Lex E X Leong, Geraint B Rogers, Jodie L Simpson

Lancet 2017; 390: 659–68



Propositions de phénotypes « théoriques » Th2/nonTH2 et de l'âge de survenue



Tezepelumab in Adults with Uncontrolled Asthma

Jonathan Corren, M.D., Jane R. Parnes, M.D., Liangwei Wang, Ph.D., May Mo, M.S., Stephanie L. Roseti, A.P.N., M.S.N., Janet M. Griffiths, Ph.D., and René van der Merwe, M.B., Ch.B.

N Engl J Med 2017;377:936-46.

Thymic stromal lymphopoietin
→ Induit par Th2 (Ag)
→ Induit par non TH2 (tabac, DEP, virus)

Phase II
Tezepelumab 3 posologies vs placebo
SC , / 4 semaines
52 semaines
436/148

→ Exacerbations

Table 1. Baseline Demographic and Clinical Characteristics in the Intention-to-Treat Population.*

Characteristic	Placebo (N=148)	Low-Dose Tezepelumab (N=145)	Medium-Dose Tezepelumab (N=145)	High-Dose Tezepelumab (N=146)	Total Tezepelumab (N=436)
Age — yr	52.2±11.5	50.6±12.4	52.6±12.5	50.1±12.2	51.1±12.4
Male sex — no. (%)	48 (32.4)	50 (34.5)	54 (37.2)	53 (36.3)	157 (36.0)
White race — no. (%)†	133 (89.9)	138 (95.2)	136 (93.8)	129 (88.4)	403 (92.4)
Body-mass index‡	28.5±5.5	28.3±5.1	28.4±4.9	27.7±5.0	28.1±5.0)
FEV_1 before bronchodilation — liters	1.83±0.58	1.91±0.66	1.83±0.58	1.87±0.60	1.87±0.61
ACQ-6 score§	2.66±0.67	2.76±0.80	2.71±0.81	2.63±0.75	2.70±0.78
AQLQ(S)+12 score¶	4.06±0.86	4.14±0.94	4.19±0.90	4.09±0.90	4.14±0.91
Asthma symptom score‖	1.72±0.58	1.70±0.63	1.76±0.57	1.68±0.61	1.72±0.60
Dose level of inhaled glucocorticoids — no. (%)					
Medium	73 (49.3)	71 (49.0)	70 (48.3)	72 (49.3)	213 (48.9)
High	75 (50.7)	74 (51.0)	75 (51.7)	74 (50.7)	223 (51.1)
Blood eosinophil count — cells/μl					
Mean	366±323	345±284	359±347	378±423	361±356
Median (range)	270 (0–1870)	270 (10–1600)	275 (0–3180)	255 (0–3990)	270 (0–3990)
Total serum IgE — IU/ml					
Mean	447±1232	314±870	464±1366	344±579	374±992
Median (range)	135 (4–11,860)	109 (2–7423)	135 (2–11,430)	138 (2–3814)	127 (2–11,430)
FENO					
No. of patients evaluated	146	144	143	141	428
Mean — ppb	36.3±38.9	34.5±46.9	30.4±29.4	32.6±33.9	32.5±37.5
Median (range) — ppb	21.5 (3.5–276.3)	22.0 (2.5–349.0)	20.5 (4.0–152.5)	19.7 (2.0–217.5)	21.0 (2.0–349.0)

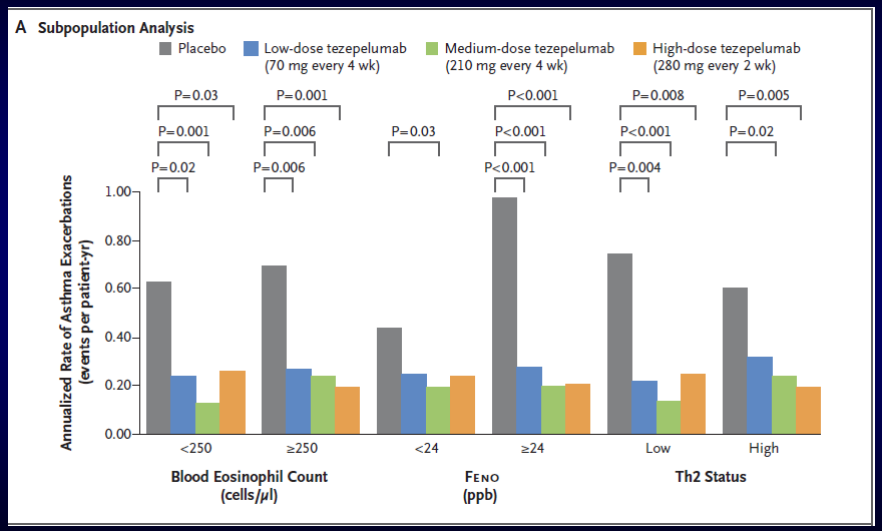
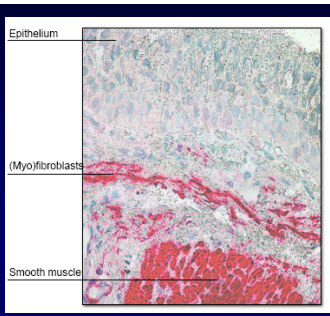


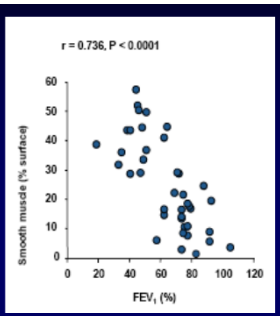
Table 3. Summary of Adverse Events, with and without Inclusion of Asthma-Related Events.*

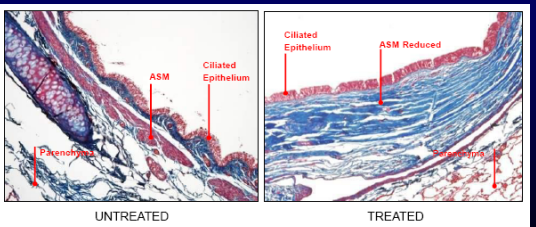
Event	Placebo (N=148)		Low-Dose Tezepelumab (N=145)		Medium-Dose Tezepelumab (N=145)		High-Dose Tezepelumab (N=146)		Total Tezepelumab (N=436)	
	All Events	Asthma-Related Events Excluded	All Events	Asthma-Related Events Excluded	All Events	Asthma-Related Events Excluded	All Events	Asthma-Related Events Excluded	All Events	Asthma-Related Events Excluded
	number of patients (percent)									
≥1 Event	92 (62.2)	83 (56.1)	96 (66.2)	86 (59.3)	94 (64.8)	90 (62.1)	90 (61.6)	83 (56.8)	280 (64.2)	259 (59.4)
≥1 Event of grade 3–5 severity†	28 (18.9)	16 (10.8)	26 (17.9)	20 (13.8)	29 (20.0)	23 (15.9)	21 (14.4)	13 (8.9)	76 (17.4)	56 (12.8)
Death†	0	0	1 (0.7)	1 (0.7)	0	0	0	0	1 (0.2)	1 (0.2)
≥1 Serious event‡	18 (12.2)	11 (7.4)	17 (11.7)	13 (9.0)	13 (9.0)	12 (8.3)	18 (12.3)	15 (10.3)	48 (11.0)	40 (9.2)
≥1 Serious event or event of grade 3–5 severity†‡	34 (23.0)	21 (14.2)	32 (22.1)	24 (16.6)	31 (21.4)	26 (17.9)	29 (19.9)	20 (13.7)	92 (21.1)	70 (16.1)
≥1 Event leading to discontinuation of trial agent	1 (0.7)	1 (0.7)	0	0	2 (1.4)	2 (1.4)	3 (2.1)	3 (2.1)	5 (1.1)	5 (1.1)
Most common events of any grade§										
Bronchitis	7 (4.7)		8 (5.5)		5 (3.4)		9 (6.2)		22 (5.0)	
Nasopharyngitis	17 (11.5)		21 (14.5)		19 (13.1)		15 (10.3)		55 (12.6)	
Headache	7 (4.7)		8 (5.5)		11 (7.6)		5 (3.4)		24 (5.5)	
Asthma	50 (33.8)		35 (24.1)		27 (18.6)		38 (26.0)		100 (22.9)	

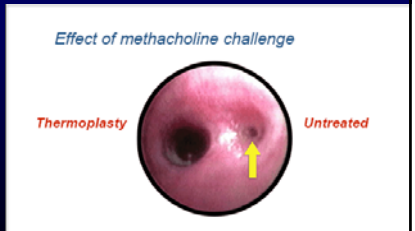
Thermoplastie bronchique

Radio frequencies to "cook" the smooth muscle in airways









(Danek, J Appl Physiol 2004)

(Cox, ERJ 2004)

Background
Clinical Studies of Bronchial Thermoplasty

- 3 randomized trials
- Long-term follow up
- Over 14 publications

276 AIR2[1]
- 190 BT & 98 Sham patients
- Randomized, double-blinded, sham controlled trial
- Safety, quality of life improvement & healthcare utilization
- Severe persistent asthma

86 RISA[2]
- 15 BT & 17 control patients
- BT randomized vs standard of care
- Safety & medication reduction
- Severe refractory asthma

71 AIR[3]
- 55 BT & 54 control patients
- Randomized vs standard of care
- Safety & efficacy
- Moderate & severe asthma

16 Feasibility[4]
- 16 BT patients
- Safety
- Mild to severe asthma

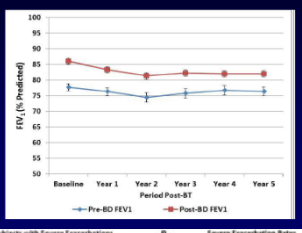
> 1500

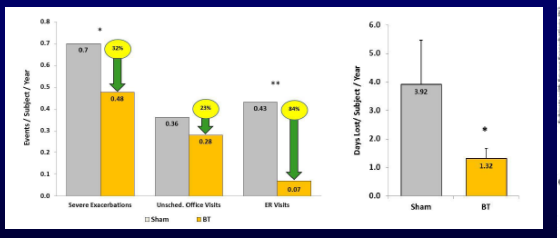
1 Castro et al., AJRCCM 2010; Castro et al., AnnAAI 2011
2 Pavord et al., AJRCCM 2007; Pavord et al.,AJRCCM 2011
3 Cox et al., NEJM 2007; Thomson et al., BMC Pulmonary Medicine 2011
4 Cox et al., AJRCCM 2006; Cox et al., AJRCCM 2010

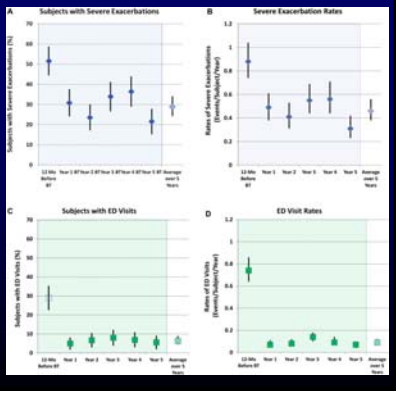
Principaux résultats cliniques

Suivi à 5 ans de 190 asthmatiques sévères traités par TB vs sham
Evaluation efficacité **et** tolérance ++

85.3 % des patients ont été suivis (162 patients)
Globalement
44% de réduction des exacerbation
78% de réduction des consultations en urgence
Réduction de18% de la CI
Evaluation TDM sans anomalies attribuables à TB







Persistance à long terme des résultats cliniques de la TB
Contrôle de l'asthme & Sécurité

(Wechsler, JACI 2013)

Eur Respir J 2017

Long-term outcomes of bronchial thermoplasty in subjects with severe asthma: a comparison of 3-year follow-up results from two prospective multicentre studies

Geoffrey Chupp[1], Michel Laviolette[2], Lauren Cohn[1], Charlene McEvoy[3], Sandeep Bansal[4], Adrian Shifren[5], Sumita Khatri[6], G. Mark Grubb[7], Edmund McMullen[7], Racho Strauven[7] and Joel N. Kline[8]

TABLE 2 Baseline demographics and characteristics for subjects enrolled in the PAS2 (Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma) study and AIR2 (Asthma Intervention Research 2) trial

	PAS2	AIR2, bronchial thermoplasty	p-value
Subjects	190	190	
Demographics			
Age years	45.87±11.39 [190] [18.00–66.00]	40.69±11.89 [190] [18.00–63.00]	<0.0001
Female	61.6 (117/190)	57.4 (109/190)	0.4032
BMI kg·m^{-2}	32.50±7.72 [190] [18.48–61.27]	29.29±6.16 [190] [17.63–52.77]	<0.0001
Baseline medication usage			
ICS dose µg·day^{-1}	2301.04±807.46 [189] [750.00–4480.00]	1960.74±765.19 [190] [880.00–4000.00]	<0.0001
LABA dose µg·day^{-1}	106.87±39.36 [189] [75.00–416.67]	116.8±34.39 [189]	0.0031
SABA puffs·day^{-1}	2.38±1.48 [182] [1.00–18.00]	2.24±1.29 [168] [1.00–8.00]	0.3451
Other asthma medications			
OCS	18.9 (36/190)	4.2 (8/190)	<0.0001
Dose mg·day^{-1}	9.13±2.66 [35] [5.00–17.00]	11.88±15.51 [8] [5.00–50.00]	0.3125
Methylxanthines	4.2 (8/190)	2.6 (5/190)	0.3972
Leukotriene modifier	44.2 (84/190)	0.0 (0/190)	<0.0001
Omalizumab	15.8 (30/190)	1.1 (2/190)	<0.0001
Dose mg·day^{-1}	266.83±88.67 [30] [150.00–405.00]	350.00±35.36 [2] [325.00–375.00]	0.2026
Other	40.5 (77/190)	31.1 (59/190)	0.0541
Any of the above maintenance medications	70.5 (134/190)	33.7 (64/190)	<0.0001
Quality of life measurement: AQLQ	4.17±1.33 [190] [1.56–6.59]	4.30±1.17 [190] [1.63–6.28]	0.2936
ERS/ATS guidelines: modified definition of severe asthma[#]	94.7 (180/190)	82.1 (156/190)	0.0001
Spirometry			
Pre-bronchodilator FEV$_1$ % pred	79.63±13.10 [190] [59.52–125.93]	77.83±15.65 [190] [50.15–120.27]	0.2255
Post-bronchodilator FEV$_1$ % pred	86.82±12.90 [190] [65.09–130.69]	86.04±15.76 [190] [56.09–130.29]	0.4009
Pre-bronchodilator FEV$_1$ L	2.54±0.65 [190] [1.28–4.93]	2.59±0.73 [190] [1.31–5.68]	0.4517
Post-bronchodilator FEV$_1$ L	2.70±0.66 [190] [1.40–5.18]	2.87±0.79 [190] [1.34–5.83]	0.0225
Medical history: how long the subject has been diagnosed with asthma years	25.62±14.46 [190] [1.00–60.00]	22.91±13.37 [190] [1.00–59.00]	0.0591
Prior 12 months			
Subjects			
Severe exacerbations	74.2 (141/190)	51.6 (98/190)	<0.0001
Hospitalisations for asthma	15.3 (29/190)	4.2 (8/190)	0.0003
Emergency department visits for asthma	27.4 (52/190)	28.9 (55/190)	0.7322
Events			
Severe exacerbations	1.57±1.15 [190] [0.00–3.00]	0.88±1.03 [190] [0.00–3.00]	<0.0001
Hospitalisations for asthma	0.21±0.53 [190] [0.00–2.00]	0.05±0.27 [190] [0.00–2.00]	0.0003
Emergency department visits for asthma	0.52±1.16 [190] [0.00–10.00]	0.74±1.71 [190] [0.00–10.00]	0.1409

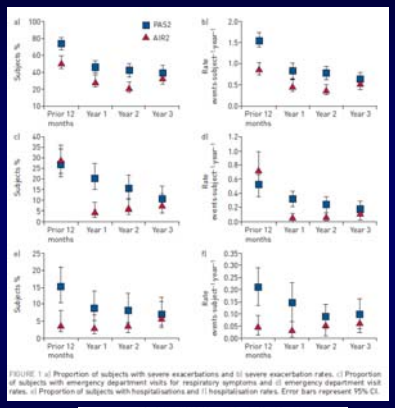
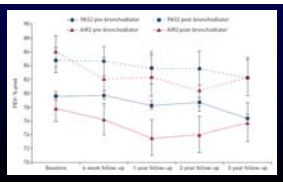


FIGURE 1 a) Proportion of subjects with severe exacerbations and b) severe exacerbation rates. c) Proportion of subjects with emergency department visits for respiratory symptoms and d) emergency department visit rates. e) Proportion of subjects with hospitalisations and f) hospitalisation rates. Error bars represent 95% CI.



AS: Thérapies ciblées: Conclusions

1) Proposer des alternatives thérapeutiques aux AS (paliers IV/V GINA)

2) Nombreux phénotypes AS

3) Caractérisation des mécanismes (endotype)
→ Thérapeutiques ciblées

4) L'anti-IgE est la seule biothérapie disponible à ce jour (+ mépolizumab)

5) Quelques candidats sérieux en développement actuel
autres Anti-IL-5, anti-IL-5R et éosinophilie
Anti-IL-13 ?, Anti-IL-4R et Th2

6) Place respective des uns par rapport aux autres ? Stratégie future ?

7) Autres biothérapies candidates
Nombreuses, dont beaucoup peu ou pas évaluées
Anti-TSLP, Anti-IL-17, anti-IL-33…

8) Autres alternatives: Azithromycine ?
Autres molécules (anti-CRTH2, TKI …) ?, TB ?…