Asthme sévère
Options thérapeutiques

Capacité Allergologie
DESC Allergologie Immunologie Clinique
DES Allergologie

Lyon, le 04/06/2021

Gilles Devouassoux

Service de Pneumologie, Hôpital de la Croix-Rousse
Hospices Civils de Lyon
Faculté de Médecine Lyon Sud Charles Mérieux
&EA 7426

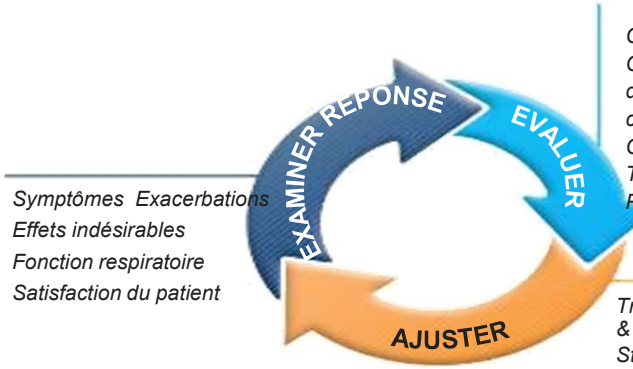
Asthme sévère
GINA 2014

- *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]

Palier 5 → Phénotype → Traitement « ciblé »

Adultes & adolescents ≥ 12 ans

Traitement personnalisé :
Evaluer, Ajuster, Examiner la réponse



Confirmation du diagnostic si nécessaire
Contrôle des symptômes et facteurs de risque modifiables (fonction respiratoire comprise)
Comorbidités
Technique d'inhalation et adhésion
Préférences du patient

Symptômes Exacerbations
Effets indésirables
Fonction respiratoire
Satisfaction du patient

Traitement des facteurs de risque modifiables & des comorbidités
Stratégies non pharmacologiques
ETP
Médicaments de l'asthme

Options thérapeutiques :
Augmenter ou baisser le traitement en fonction des besoins du patient

Traitement de contrôle privilégié
Pour prévenir les exacerbations et contrôler les symptômes

	STADE 1	STADE 2	STADE 3	STADE 4	STADE 5
	CSI-formoterol faible dose à la demande *	Faible dose quotidienne de corticoïdes inhalés (CSI), Ou CSI-formoterol faible dose à la demande *	CSI-LABA Faible dose	CSI-LABA Dose moyenne	Forte dose CSI-LABA Adresser au Spécialiste pour phénotypage ± traitement d'appoint, tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Autres options thérapeutiques	*CSI faible dose à chaque prise de SABA †*	*Antagonistes des récepteurs aux leucotriènes (LTRA), ou CSI faible dose à chaque prise de SABA †*	*Dose moyenne CSI, ou faible dose CSI+LTRA #*	*CSI forte dose, ajout tiotropium, ou ajout LTRA #*	*Ajouter une dose faible de CSO mais surveiller EI*

Traitement de secours privilégié

CSI-formoterol faible dose à la demande * | CSI-formoterol faible dose à la demande ‡

Autres options thérapeutiques : *bêta-2-mimétiques de courte durée d'action (SABA)*

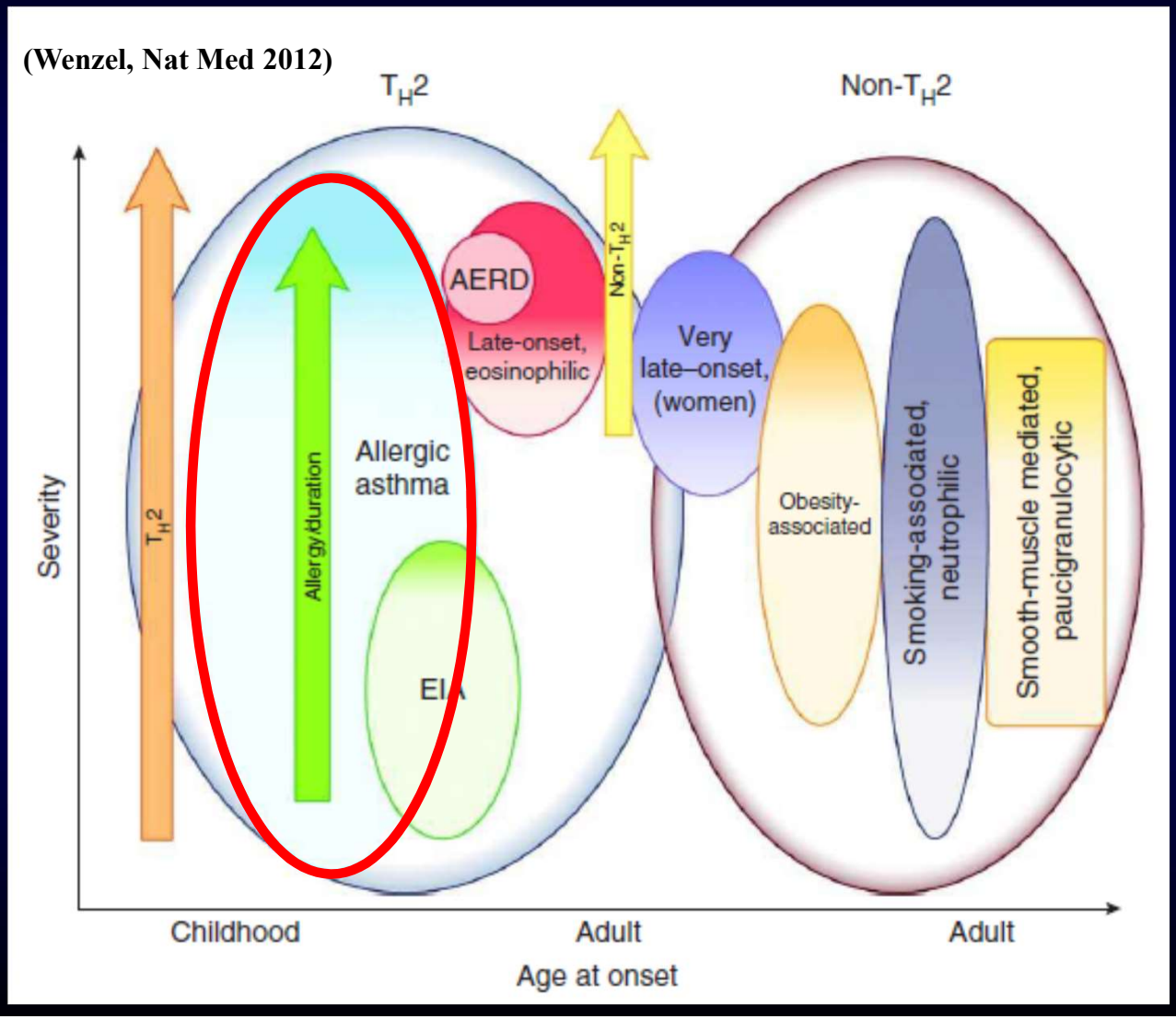
SABA: Short acting B2 Agonist
LABA: Long acting B2 Agonist

* Hors AMM ; données uniquement pour le budesonide-formoterol
† Hors AMM ; Inhalateur avec association fixe ou combiné de CSI et SABA
CSI: corticostéroïdes inhalés
CSO: corticostéroïdes oraux

‡ Faible dose CSI-form est le traitement de secours pour les patients sous bud-form ou BDP-form en traitement de fond ou de secours [1]
# Envisager une immunothérapie allergénique chez les patients sensibilisés et VEMS >70%

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

(Wenzel, Nat Med 2012)



Méthodologie [16,19,24]

Étude INNOVATE

Étude randomisée, multicentrique, en double aveugle, contrôlée *versus* placebo

Patients atteints d'asthme allergique persistant sévère (12 à 79 ans) ayant une réduction de la fonction pulmonaire (VEMS 40-80 % des valeurs prédites) et dont les symptômes de l'asthme étaient mal contrôlés en dépit **d'une corticothérapie inhalée à forte dose + un β_2-agoniste de longue durée d'action** (au moins 2 exacerbations ayant nécessité une corticothérapie systémique ou hospitalisation ou présentation dans un service d'urgences en raison d'une exacerbation sévère de l'asthme au cours de l'année précédente).

n=419

2 groupes : Xolair® (n=209) 1 administration toutes les 2 ou 4 semaines, en fonction de la dose déterminée à partir du poids et du taux d'IgE sériques totales, en addition à un traitement par plus de 1 000 µg de dipropionate de béclométasone (ou équivalent) plus un β_2-agoniste à longue durée d'action. Les traitements de fond par corticoïde oral, théophylline et anti-leucotriènes (si débutés > 4 semaines avant randomisation) étaient autorisés ou un placebo (n=210).

Suivi : 28 semaines.

16. Résumé des Caractéristiques du Produit Xolair®.
19. Avis de la Commission de la Transparence de Xolair®. HAS 4 janvier 2006.
24. Humbert M. *et al.* Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy 2005;60:309-316. Etude retenue lors de l'évaluation de l'AMM et du dossier de transparence.

Xolair omalizumab Solution injectable en seringue prérempliée 75 mg / 150 mg

Critères d'évaluation [16,19,24]

Étude INNOVATE

Critère principal

- Taux d'exacerbations cliniquement significatives de l'asthme au cours de la période de traitement.

Critères secondaires

- Taux d'exacerbations sévères.
- Nombre de recours aux soins d'urgence.
- Score global de qualité de vie (évalué au moyen du questionnaire de qualité de vie JUNIPER).
- DEP.
- VEMS.
- Tolérance.

16. Résumé des Caractéristiques du Produit Xolair®.
19. Avis de la Commission de la Transparence de Xolair®. HAS 4 janvier 2006.
24. Humbert M. *et al.* Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy 2005;60:309-316. Etude retenue lors de l'évaluation de l'AMM et du dossier de transparence.

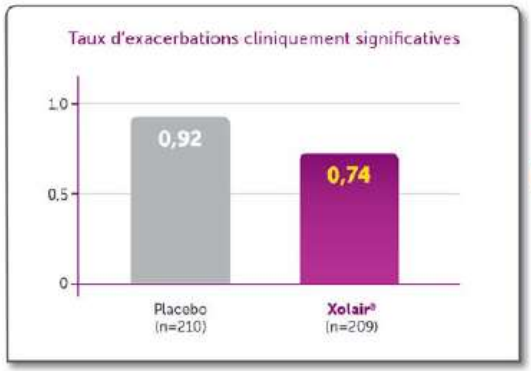
Xolair omalizumab Solution injectable en seringue prérempliée 75 mg / 150 mg

Réduction des exacerbations

Critère principal [16,19,24]

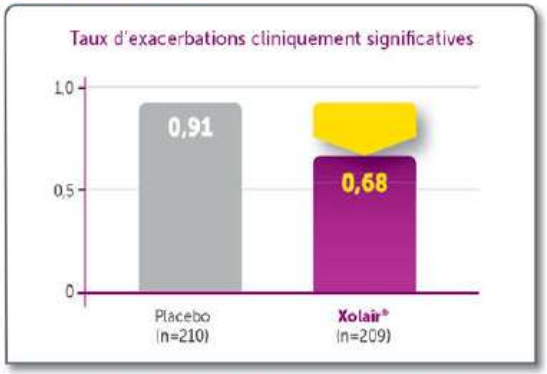
Étude INNOVATE

Réduction des exacerbations cliniquement significatives au cours des 28 semaines de traitement



-19,4%
p=0,153 (NS)

Analyse principale sans ajustement sur les exacerbations à l'entrée de l'étude



-26%
p=0,042
Rapport des taux : 0,738
IC 95 % : [0,552-0,998]

Analyse principale avec ajustement sur les exacerbations à l'entrée de l'étude

Taux d'exacerbations cliniquement significatives :

Nombre d'exacerbations cliniquement significatives (aggravation de l'asthme nécessitant le recours à une corticothérapie systémique) rapporté au nombre de patients inclus.

Ajustement sur le taux d'exacerbations cliniquement significatives :

En raison de la différence constatée, a posteriori, de gravité entre les groupes omalizumab et placebo (fréquence d'exacerbations plus importante dans le groupe Xolair® à l'inclusion), une analyse (modèle de régression de Poisson) avec ajustement sur le taux d'exacerbations au cours des 14 mois précédant l'inclusion a été effectuée pour l'analyse du critère principal.[19]

16. Résumé des Caractéristiques du Produit Xolair®.
19. Avis de la Commission de la Transparence de Xolair®. HAS 4 janvier 2006.
24. Humbert M. *et al.* Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy 2005;60:309-316. Etude retenue lors de l'évaluation de l'AMM et du dossier de transparence.

Xolair omalizumab Solution injectable en seringue préremplie 75 mg / 150 mg

Taux d'exacerbations sévères

Critères secondaires* [16,19,24]

Étude INNOVATE

Taux d'exacerbations sévères

-50%

p=0,002

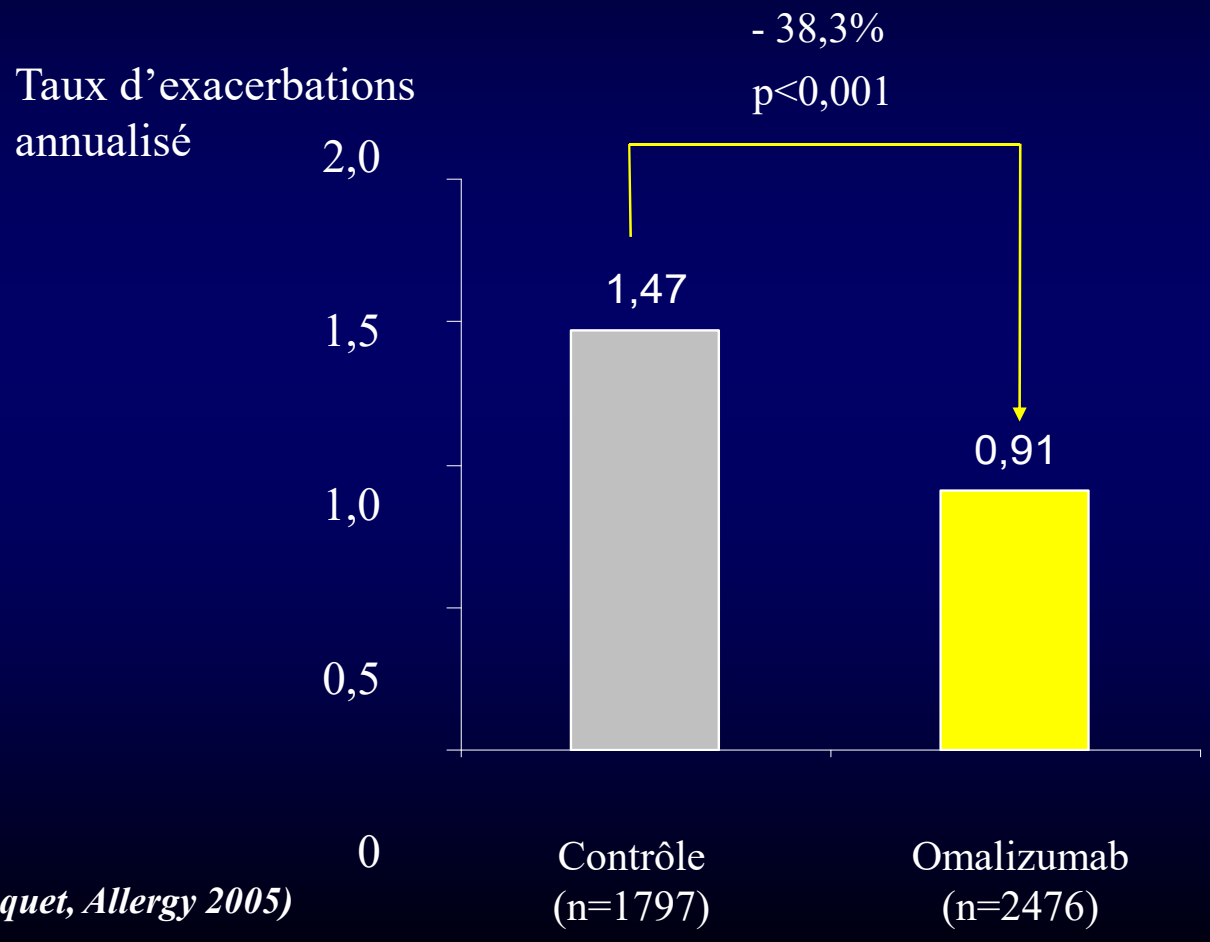
Taux d'exacerbations sévères :
Nombre d'exacerbations sévères rapporté au nombre de patients inclus (DEP ou VEMS < 60% des meilleures valeurs personnelles nécessitant une corticothérapie systémique).

*** Les critères secondaires n'ont pas fait l'objet d'un ajustement.**

16. Résumé des Caractéristiques du Produit Xolair®.
19. Avis de la Commission de la Transparence de Xolair®. HAS 4 janvier 2006.
24. Humbert M. *et al.* Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy 2005;60:309-316. Etude retenue lors de l'évaluation de l'AMM et du dossier de transparence.

Xolair omalizumab Solution injectable en seringue prérempliée 75 mg / 150 mg

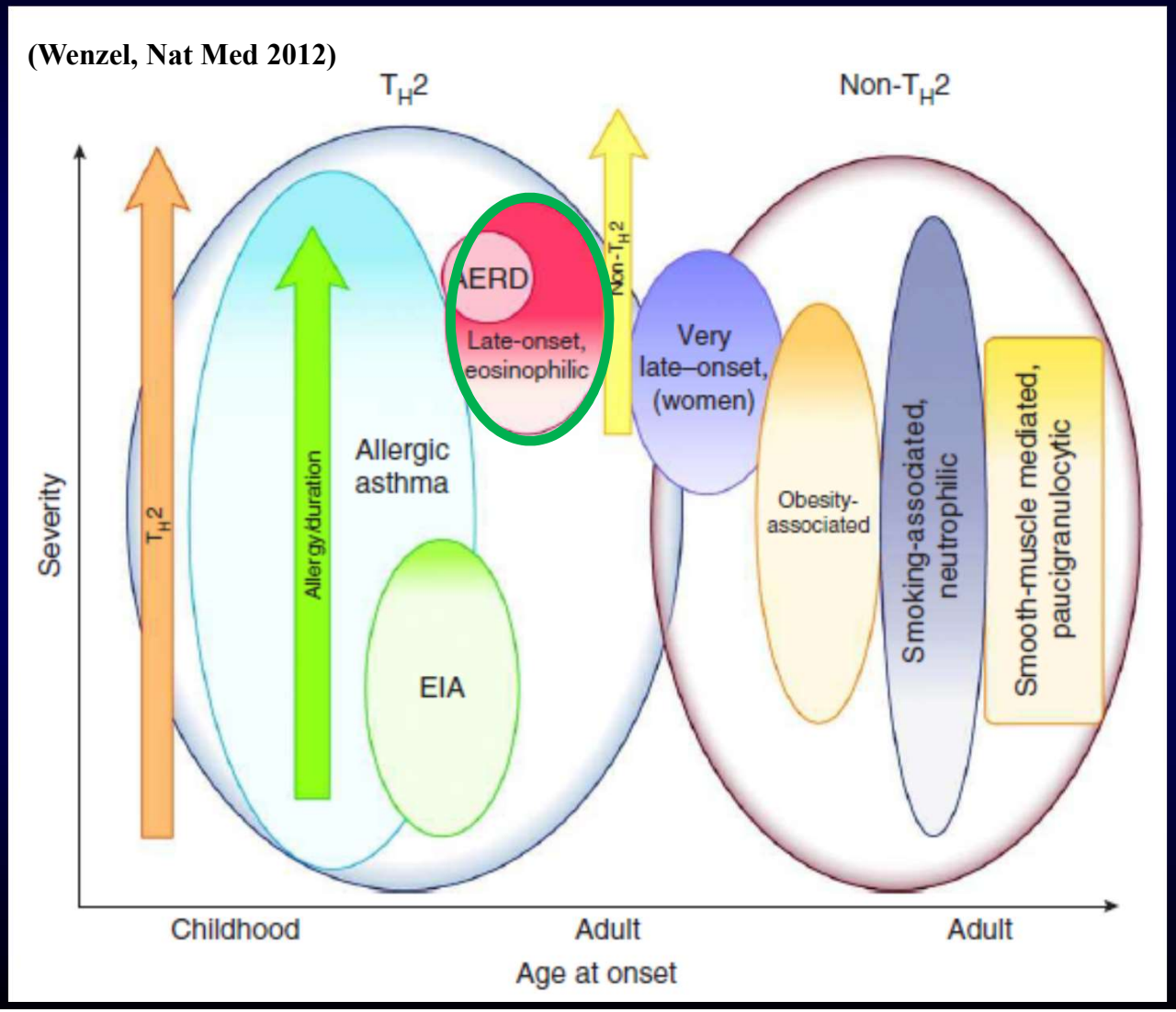
Omalizumab réduit le taux d'exacerbations (Analyse groupée)



(Bousquet, Allergy 2005)

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

(Wenzel, Nat Med 2012)



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

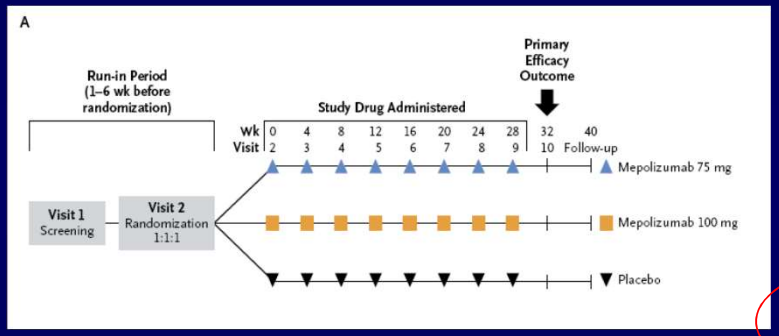
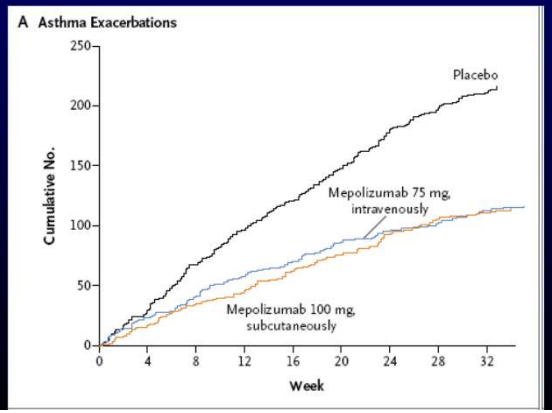
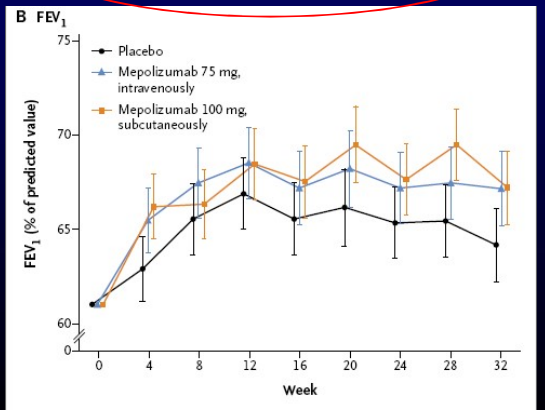


Table 1. Characteristics of the Patients at Baseline in the Intention-to-Treat Population.*

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)





The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 25, 2014 VOL. 371 NO. 13

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

Elisabeth H. Bel, M.D., Ph.D., Sally E. Wenzel, M.D., Philip J. Thompson, M.D., Charlene M. Prazma, Ph.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., Hector G. Ortega, M.D., Sc.D., and Ian D. Pavord, D.M., for the SIRIUS Investigators*

135 asthmatiques éosinophiliques sévères

SIRIUS

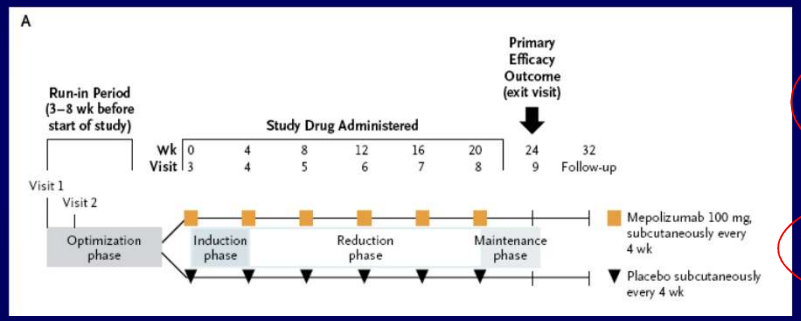
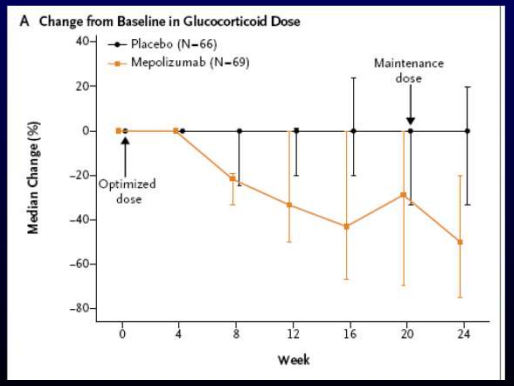
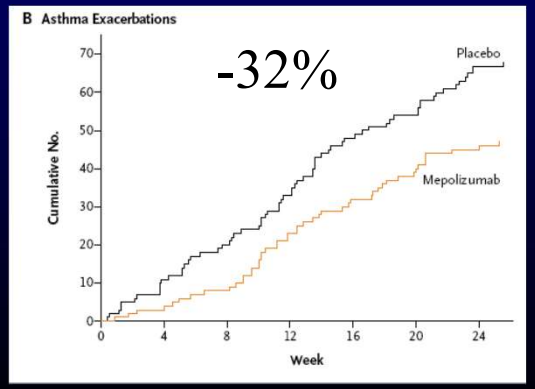
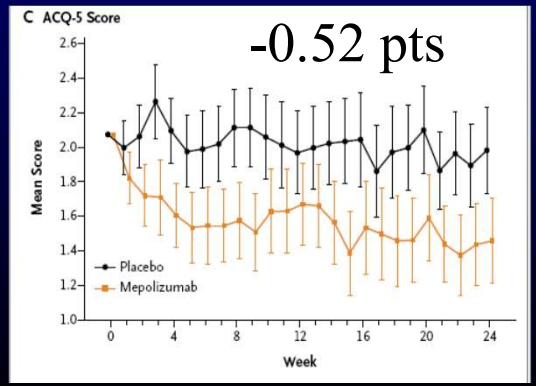


Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

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)





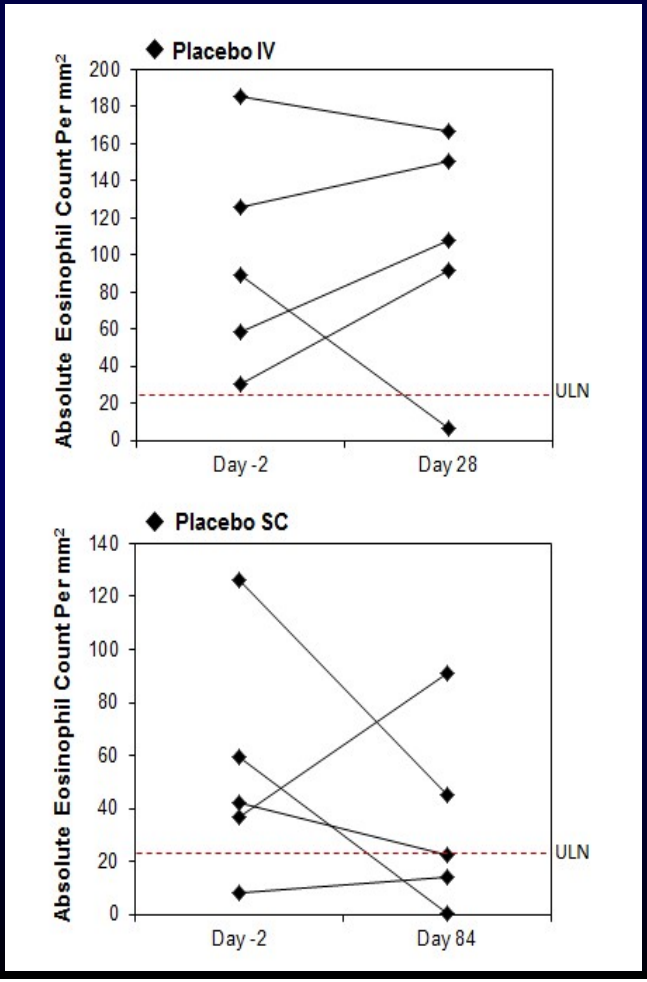


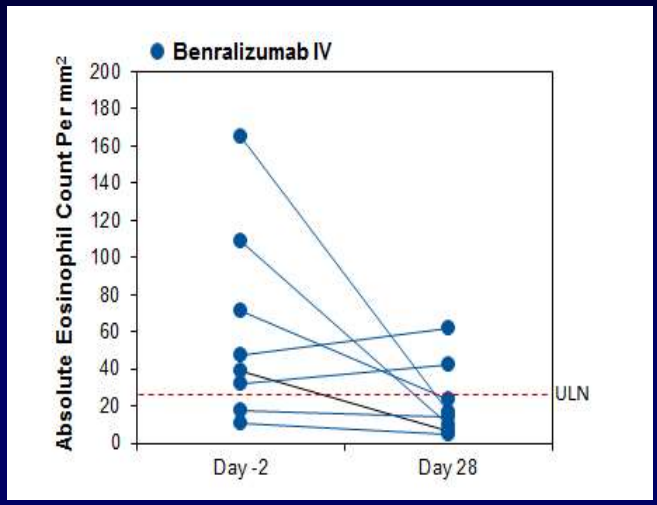
mAc anti-IL-5Rα (Benralizumab)

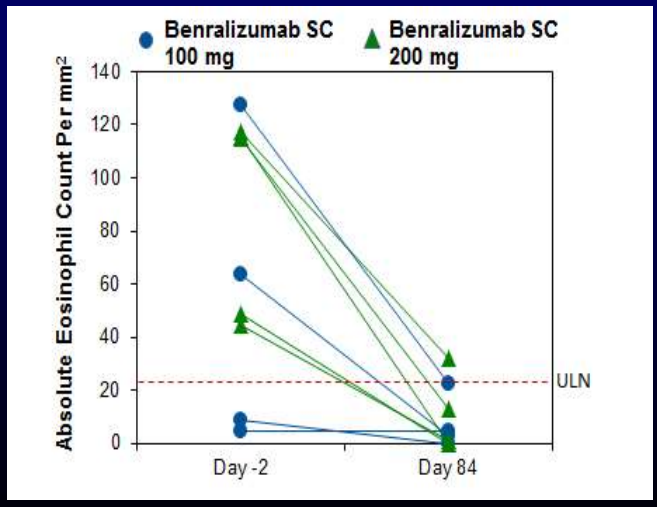
17 asthmatiques traités (IV ou SC vs 10 placebo)

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

Eugene R Bleecker, J Mark FitzGerald, Pascal Chanez, Alberto Papi, Steven F Weinstein, Peter Barker, Stephanie Sproule, Geoffrey Gilmartin, Magnus Aurivillius, Viktoria Werkström, Mitchell Goldman, on behalf of the SIROCCO study investigators*

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 continues 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 (1·1–66·0)	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)

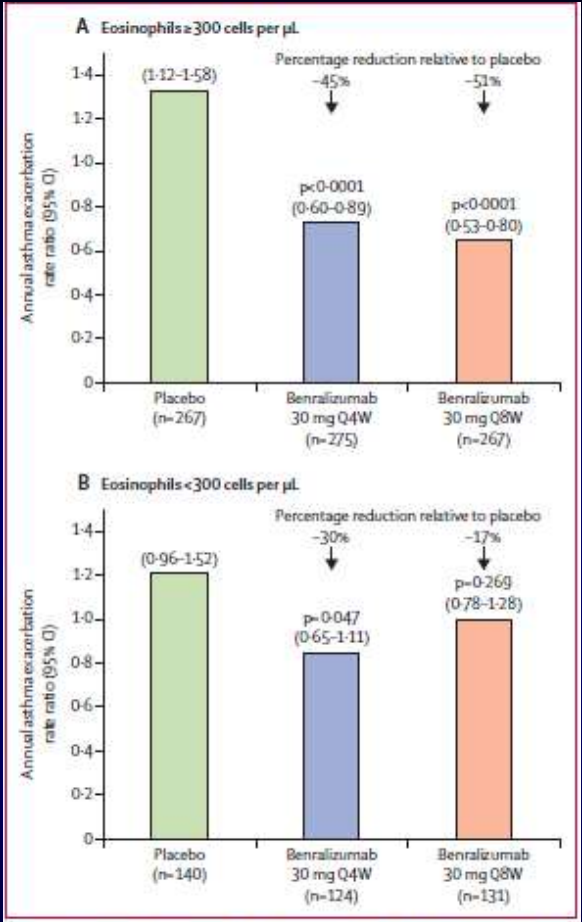


***Figure 2*: Annual asthma exacerbation rate estimates at 48 weeks according to baseline blood eosinophil concentrations**

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).

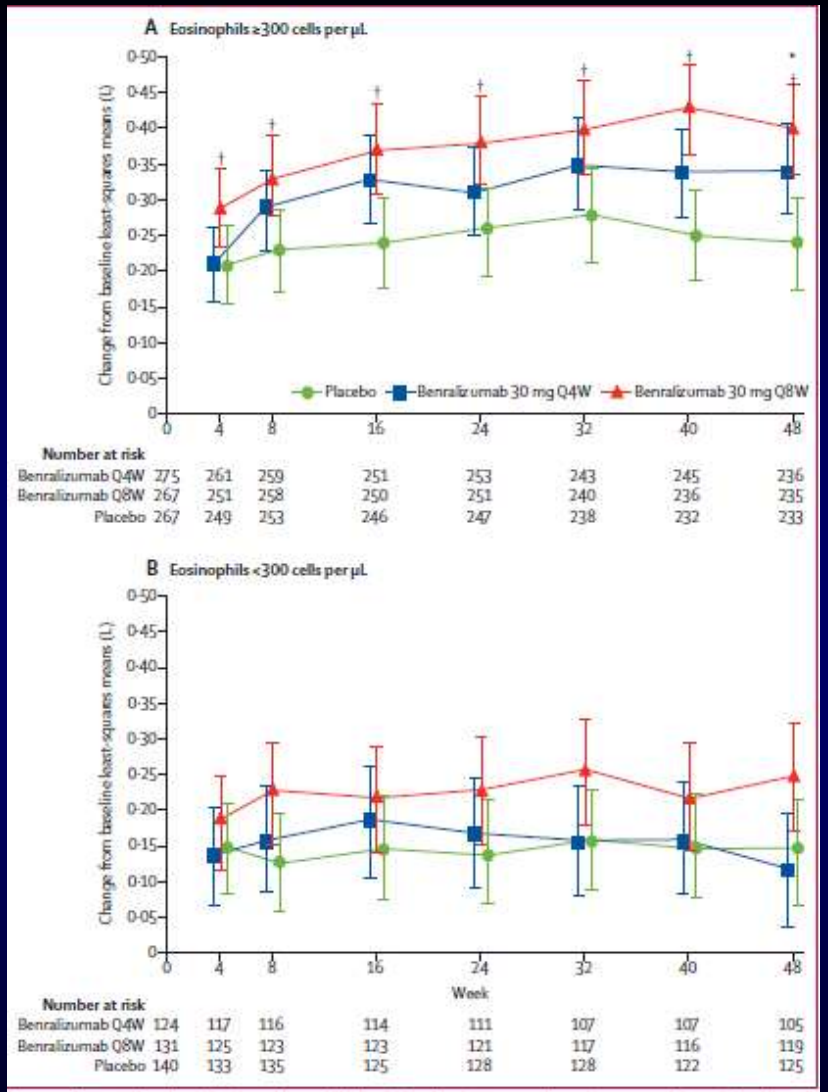


***Figure 3*: Change from baseline in prebronchodilator forced expiratory volume in 1 s according to baseline blood eosinophil concentrations**

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

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*

NEJM 2017

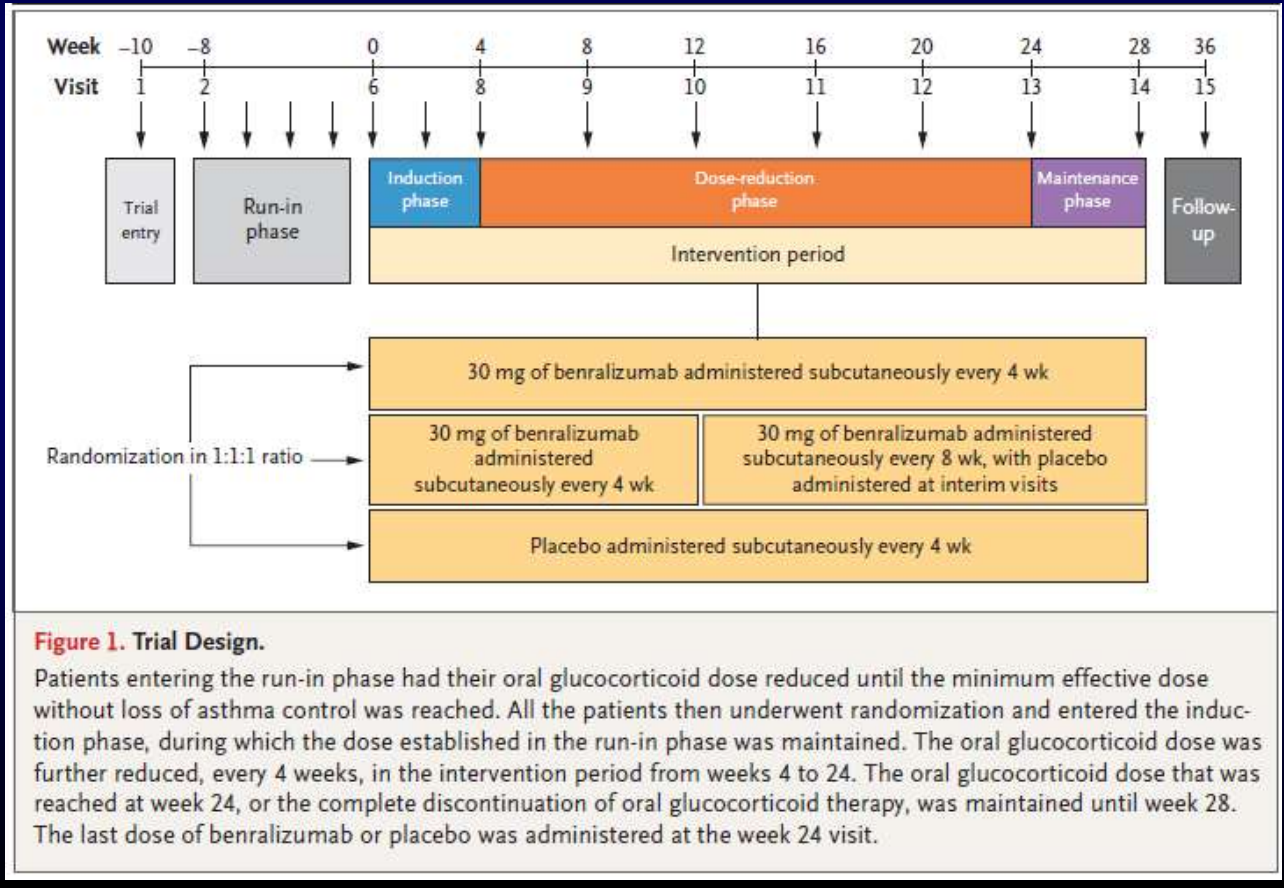


Figure 1. Trial Design.

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)

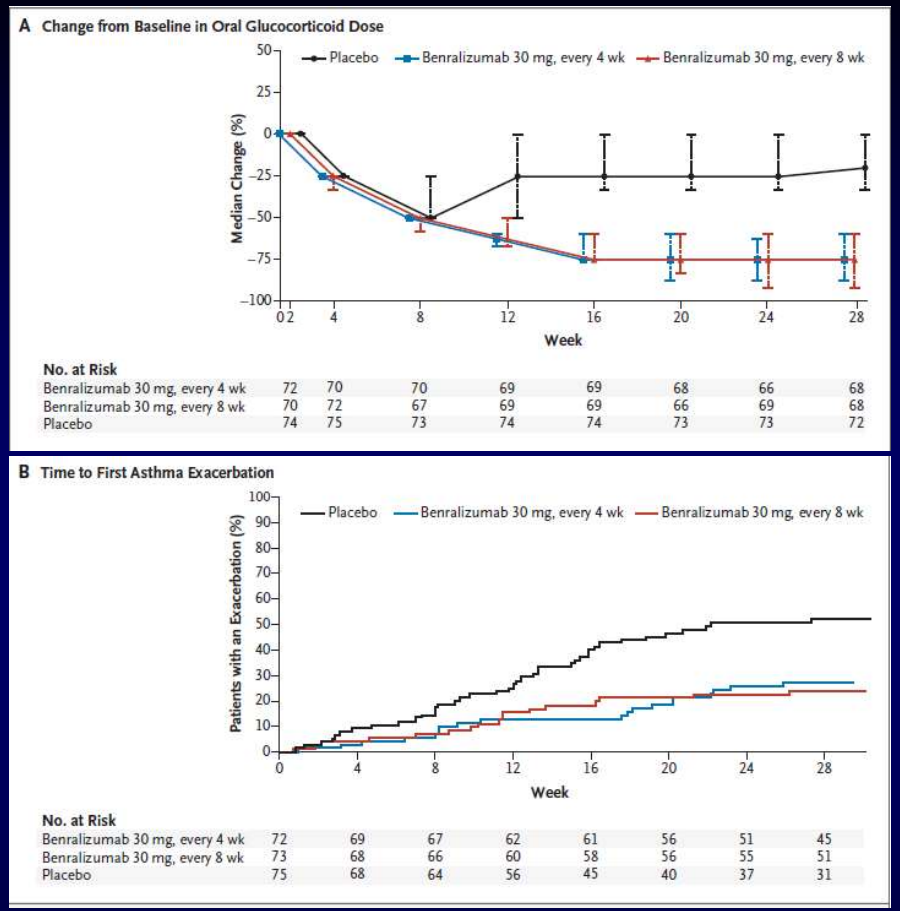
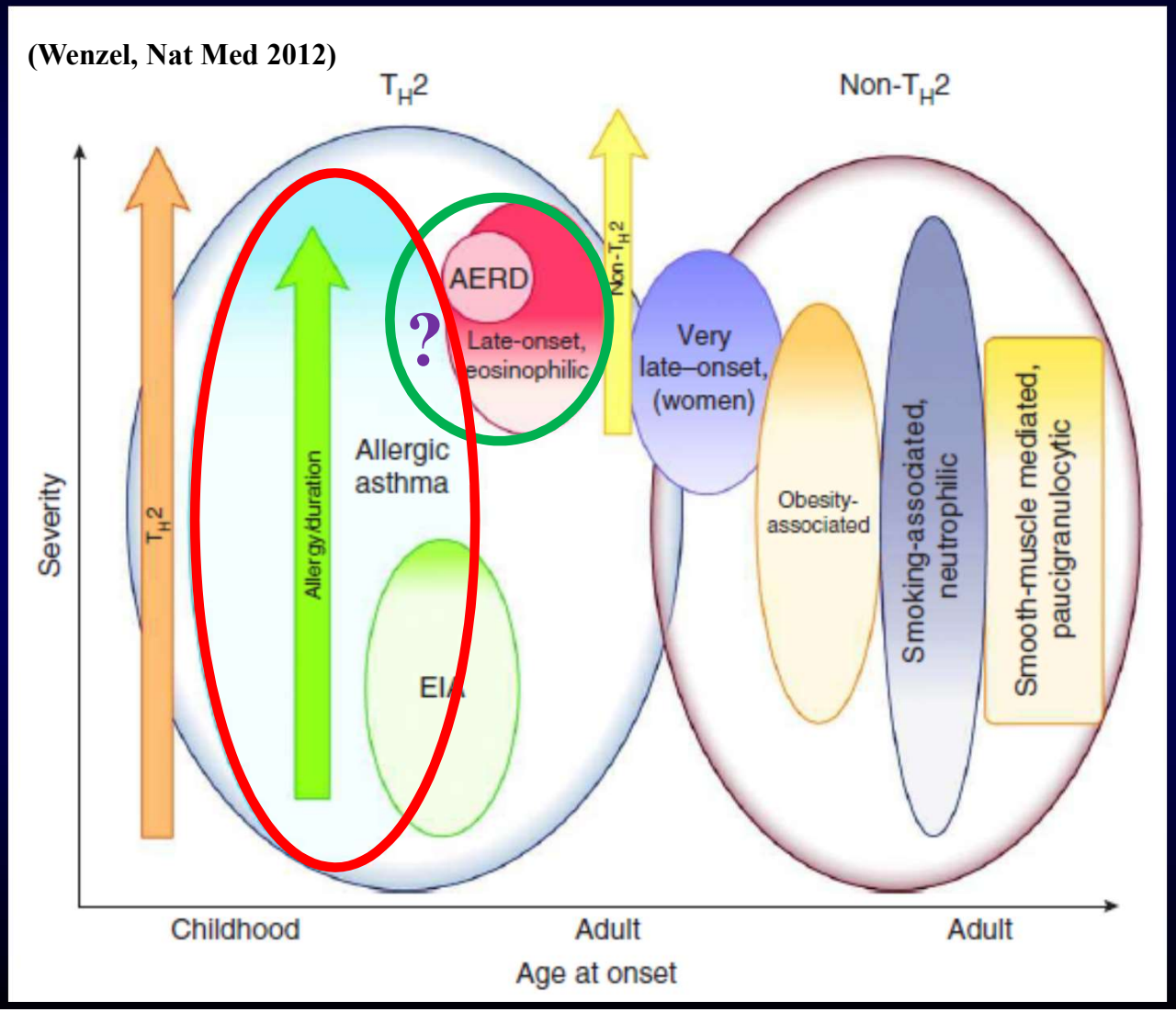


Figure 2. Change from Baseline in the Oral Glucocorticoid Dose and Asthma Exacerbations.

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

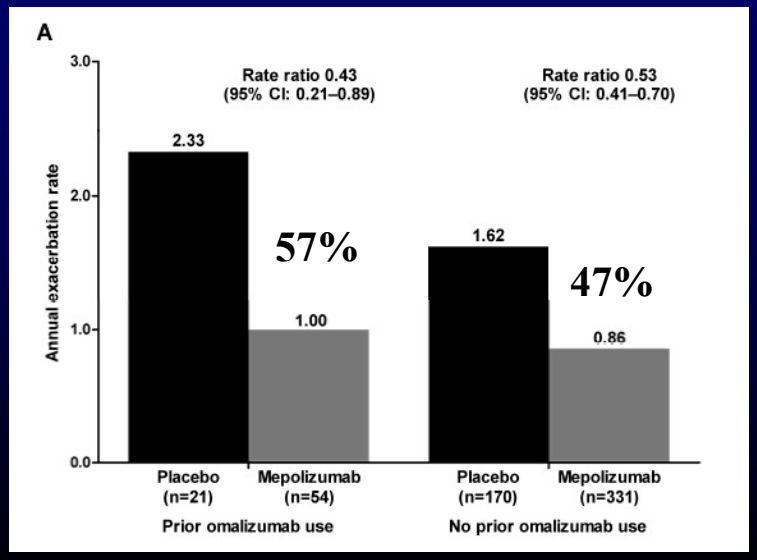
32 S
Mepo 75 mg IV ou 100 mg SC /mois
576 patients
CrP: Réduction Δt exacerbation

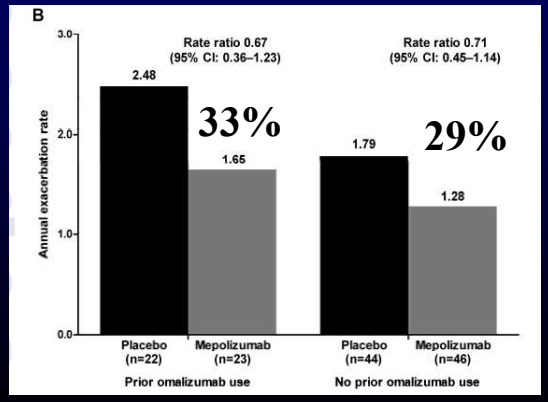
Eo ≥ 150/ml (screening)
Ou
EO ≥ 300 ml (12 mois)

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

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

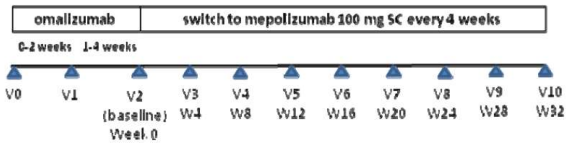
2,15 (0,67-6,90) 2,53 (1,15-5,58)





OSMO study publications

Study Design



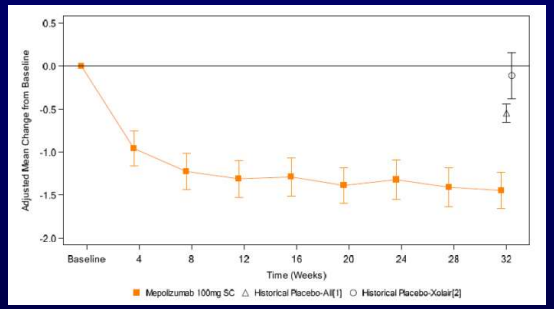
- Subjects not optimally controlled with current omalizumab (Xolair) treatment were switched from omalizumab (Xolair) to mepolizumab
- At Visit 2 subjects discontinued omalizumab (Xolair) and switched to open-label mepolizumab 100 mg SC every 4 weeks for 32 weeks
- Substitution of biologics with no wash-out period expected to reflect clinical practice
- As a single arm study, comparisons made back to baseline

Key Inclusion Criteria

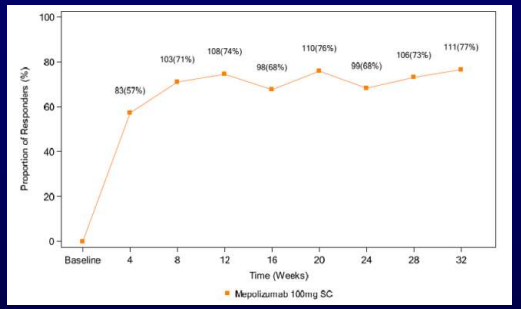
- ACQ-5 score ≥1.5 at both screening (Visit 1) and baseline (Visit 2)
- Documented requirement for regular treatment with high-dose inhaled corticosteroids (ICS)
- Received omalizumab (Xolair), based on weight and IgE levels, for ≥4 months prior to screening (Visit 1)
- Blood eosinophils:
  - eosinophil level ≥300 cells/μL that was related to asthma within the 12 months prior to Visit 1

  or
  - eosinophil level ≥150 cells/μL at Visit 1
- History of ≥2 exacerbations requiring treatment with systemic steroids in previous year
  - Subjects receiving omalizumab for ≥8 months required at least one exacerbation to have occurred while on omalizumab
  - Subjects on maintenance OCS required two-fold or greater increase in dose

ACQ-5 Score



ACQ-5 Responders (≥0.5 Point Reduction from Baseline)

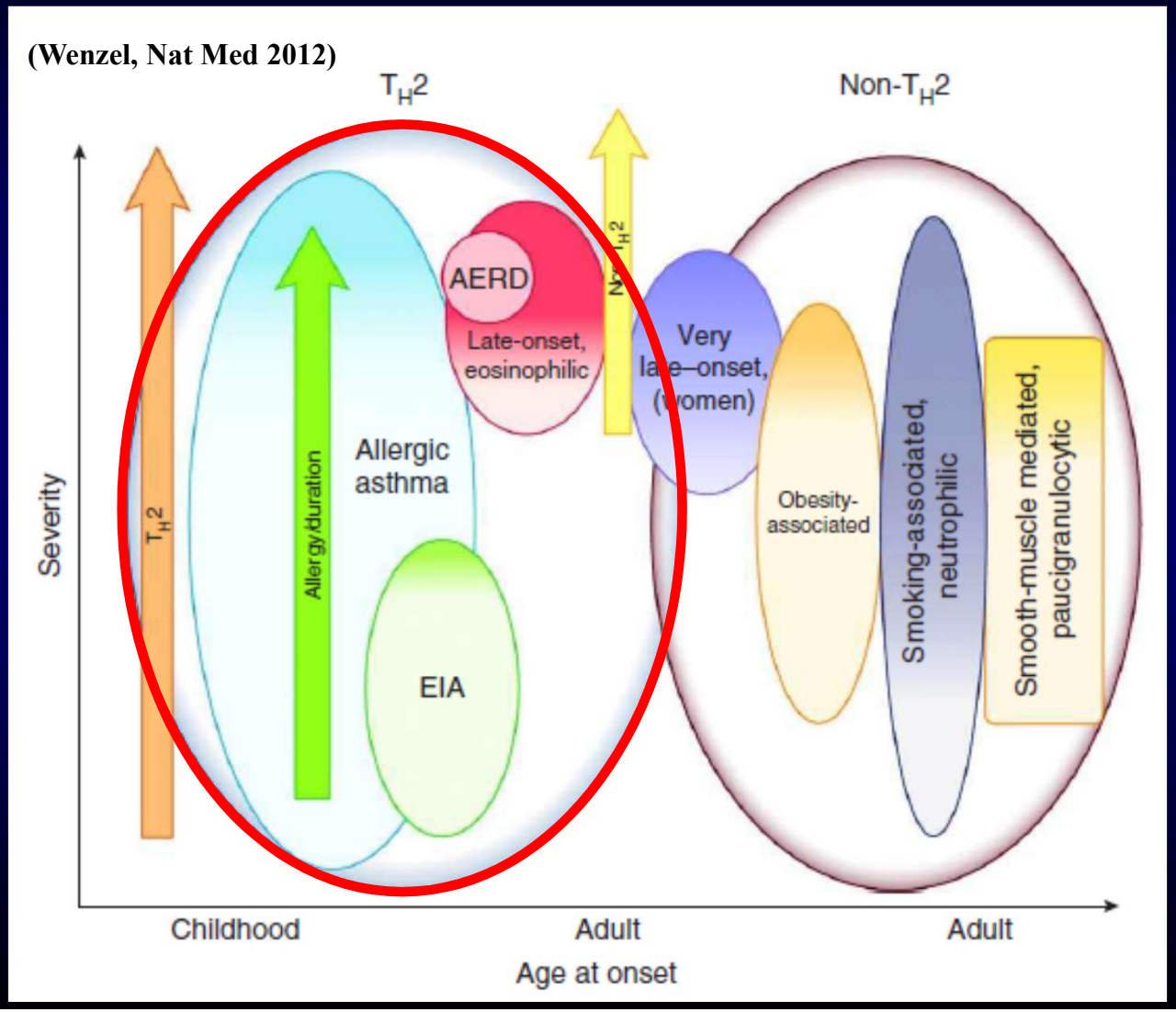


Exacerbations

		Mepolizumab 100g SC N=145
Pre-treatment [1]	Exacerbation rate/year	3.26
On + off treatment [2]	Exacerbation rate/year	1.18
	Rate Ratio ([2] / [1]) 95% CI p-value	0.36 (0.28,0.47) <0.001

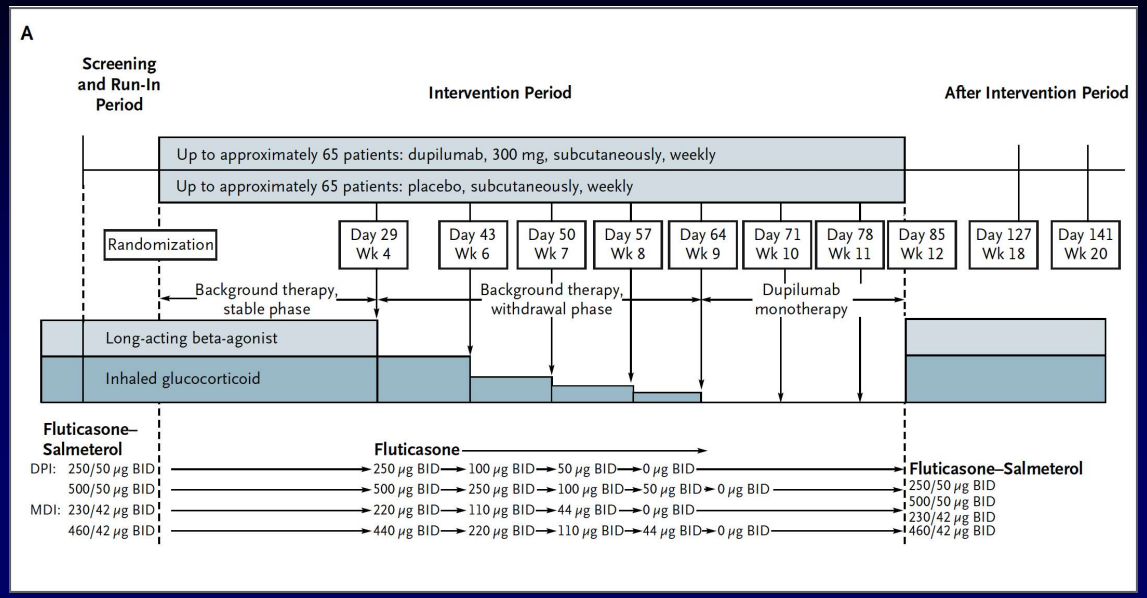
(soumis JACI in practice)

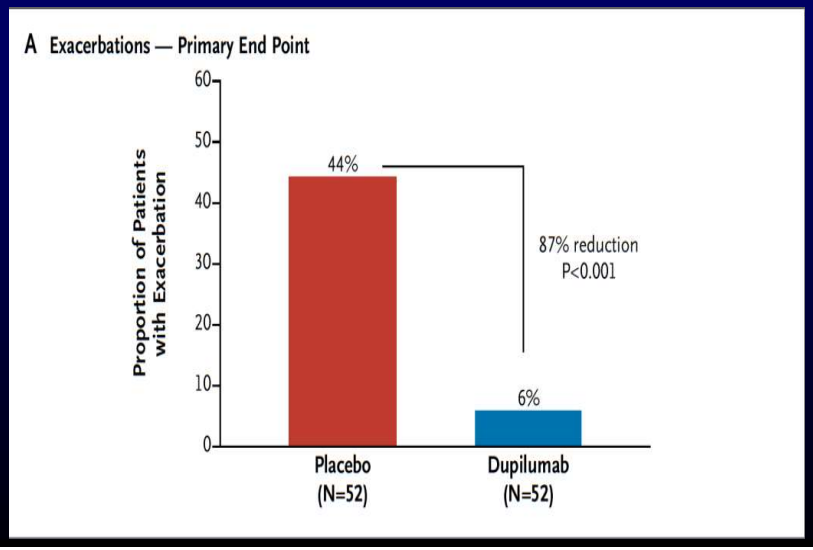
Propositions de phénotypes « théoriques » Th2/nonTH2 et de l'âge de survenue

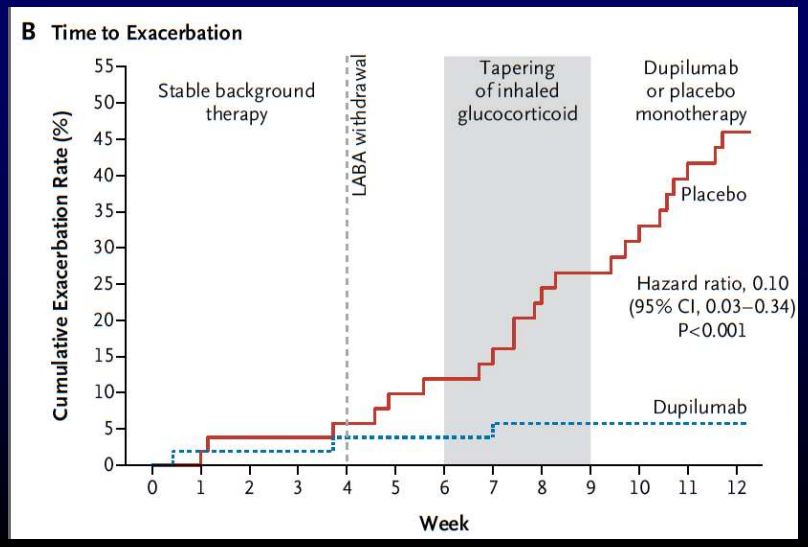


Asthme sévère et anti-IL-4R (Dupilumab)

Wenzel et al. NEJM 2013







ORIGINAL ARTICLE

Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

M. Castro, J. Corren, I.D. Pavord, J. Maspero, S. Wenzel, K.F. Rabe, W.W. Busse, L. Ford, L. Sher, J.M. FitzGerald, C. Katelaris, Y. Tohda, B. Zhang, H. Staudinger, G. Pirozzi, N. Amin, M. Ruddy, B. Akinlade, A. Khan, J. Chao, R. Martincova, N.M.H. Graham, J.D. Hamilton, B.N. Swanson, N. Stahl, G.D. Yancopoulos, and A. Teper

QUEST

Table 1. Selected Baseline Demographic and Clinical Characteristics of the Patients (Intention-to-Treat Population).*

Characteristic	Placebo, 1.14 ml (N=317)	Dupilumab, 200 mg (N=631)	Placebo, 2.00 ml (N=321)	Dupilumab, 300 mg (N=633)	Overall Population (N=1902)
Age — yr	48.2±15.6	47.9±15.3	48.2±14.7	47.7±15.6	47.9±15.3
Female sex — no. (%)	198 (62.5)	387 (61.3)	218 (67.9)	394 (62.2)	1197 (62.9)
Prebronchodilator FEV_1 — liters	1.76±0.61	1.78±0.62	1.75±0.57	1.78±0.60	1.78±0.60
Percent of predicted normal value	58.43±13.22	58.38±13.52	58.35±13.87	58.51±13.52	58.43±13.52
FEV_1 reversibility — %	25.06±18.76	27.39±22.79	26.45±17.65	25.73±23.79	26.29±21.73
No. of exacerbations in past year	2.07±1.58	2.07±2.66	2.31±2.07	2.02±1.86	2.09±2.15
Use of high-dose inhaled glucocorticoid — no. (%)	172 (54.3)	317 (50.2)	167 (52.0)	323 (51.0)	979 (51.5)
ACQ-5 score†	2.71±0.73	2.76±0.80	2.77±0.77	2.77±0.76	2.76±0.77
Ongoing atopic or allergic condition — no. (%)	266 (83.9)	509 (80.7)	266 (82.9)	524 (82.8)	1565 (82.3)
Nasal polyposis or chronic rhinosinusitis — no. (%)	73 (23.0)	141 (22.3)	80 (24.9)	145 (22.9)	439 (23.1)
Former smoker — no. (%)	59 (18.6)	126 (20.0)	67 (20.9)	116 (18.3)	368 (19.3)
No. of pack-yr	3.96±2.81	3.89±2.69	4.07±3.12	4.15±3.04	4.02±2.89
Biomarker levels					
Blood eosinophil count — cells/mm^3					
Mean	370±338	349±345	391±419	351±369	360±366
Median (range)	270 (0–2200)	250 (0–3610)	265 (0–3580)	250 (0–4330)	255 (0–4330)
F_{ENO} — ppb	34.47±28.54	34.45±34.91	38.39±38.00	34.01±29.74	34.97±32.85
Total IgE — IU/ml	394±625	461±818	448±797	415±701	432±747

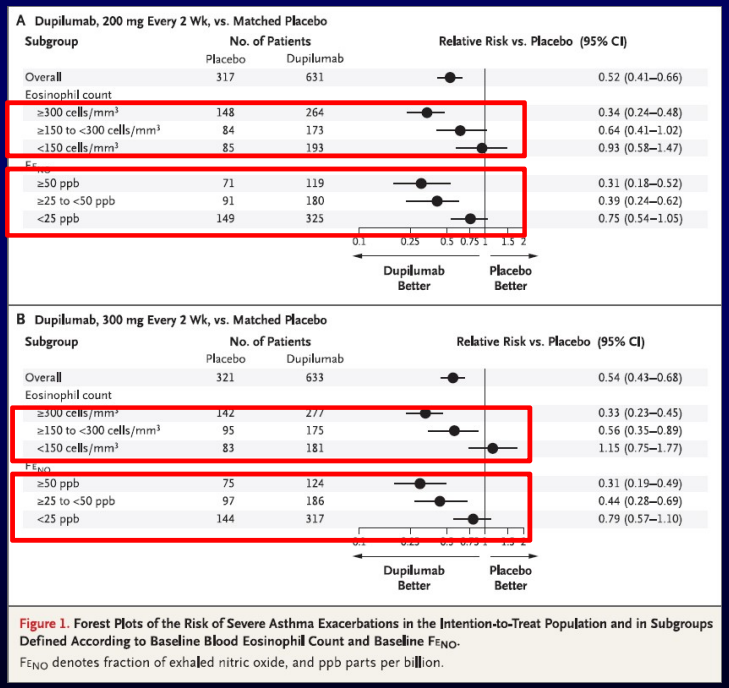
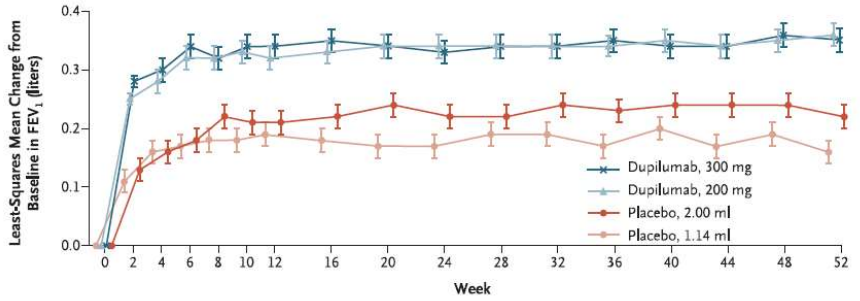


Figure 1. Forest Plots of the Risk of Severe Asthma Exacerbations in the Intention-to-Treat Population and in Subgroups Defined According to Baseline Blood Eosinophil Count and Baseline F_{ENO}.

F_{ENO} denotes fraction of exhaled nitric oxide, and ppb parts per billion.



No. at Risk																
Dupilumab, 300 mg	633	625	614	612	609	598	610	611	593	596	586	579	584	584	570	562	488
Dupilumab, 200 mg	631	610	613	615	604	607	611	605	601	599	589	585	590	577	581	570	477
Placebo, 2.00 ml	321	313	311	313	311	309	313	310	304	296	304	301	301	297	292	290	250
Placebo, 1.14 ml	317	315	307	301	305	301	307	300	303	300	290	286	289	287	288	281	240

Figure 2. Change in the Prebronchodilator FEV_1 from Baseline over the 52-Week Intervention Period in the Intention-to-Treat Population.
Patients received dupilumab at a dose of 200 or 300 mg every 2 weeks or a matched-volume placebo. For the lower dose of dupilumab, the matched placebo had a volume of 1.14 ml. For the higher dose of dupilumab, the matched placebo had a volume of 2.00 ml. P<0.001 for the comparisons of each dupilumab dose with matched placebo at week 12. I bars represent the standard error. FEV_1 denotes forced expiratory volume in 1 second.

Table 2. Adverse Events That Emerged during the Intervention Period (Safety Population).*

Event	Placebo, 1.14 ml (N=313)	Dupilumab, 200 mg (N=631)	Placebo, 2.00 ml (N=321)	Dupilumab, 300 mg (N=632)	Combined Placebo (N=634)	Combined Dupilumab (N=1263)
	number of patients (percent)					
Any adverse event	257 (82.1)	508 (80.5)	270 (84.1)	515 (81.5)	527 (83.1)	1023 (81.0)
Any serious adverse event	26 (8.3)	49 (7.8)	27 (8.4)	55 (8.7)	53 (8.4)	104 (8.2)
Any adverse event leading to death†	3 (1.0)	1 (0.2)	0	4 (0.6)	3 (0.5)	5 (0.4)
Any adverse event leading to permanent discontinuation of the intervention	19 (6.1)	19 (3.0)	10 (3.1)	44 (7.0)	29 (4.6)	63 (5.0)
Adverse events occurring in ≥5% of patients in any group‡						
Viral upper respiratory tract infection	60 (19.2)	119 (18.9)	64 (19.9)	111 (17.6)	124 (19.6)	230 (18.2)
Upper respiratory tract infection	37 (11.8)	69 (10.9)	49 (15.3)	77 (12.2)	86 (13.6)	146 (11.6)
Bronchitis	47 (15.0)	73 (11.6)	42 (13.1)	71 (11.2)	89 (14.0)	144 (11.4)
Influenza	29 (9.3)	36 (5.7)	22 (6.9)	38 (6.0)	51 (8.0)	74 (5.9)
Sinusitis	27 (8.6)	36 (5.7)	29 (9.0)	26 (4.1)	56 (8.8)	62 (4.9)
Urinary tract infection	17 (5.4)	17 (2.7)	12 (3.7)	19 (3.0)	29 (4.6)	36 (2.9)
Headache	26 (8.3)	46 (7.3)	25 (7.8)	40 (6.3)	51 (8.0)	86 (6.8)
Rhinitis allergic	16 (5.1)	21 (3.3)	15 (4.7)	18 (2.8)	31 (4.9)	39 (3.1)
Back pain	16 (5.1)	30 (4.8)	7 (2.2)	25 (4.0)	23 (3.6)	55 (4.4)
Accidental overdose§	16 (5.1)	33 (5.2)	16 (5.0)	33 (5.2)	32 (5.0)	66 (5.2)
Injection-site reaction¶	17 (5.4)	96 (15.2)	33 (10.3)	116 (18.4)	50 (7.9)	212 (16.8)

ORIGINAL ARTICLE

Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma

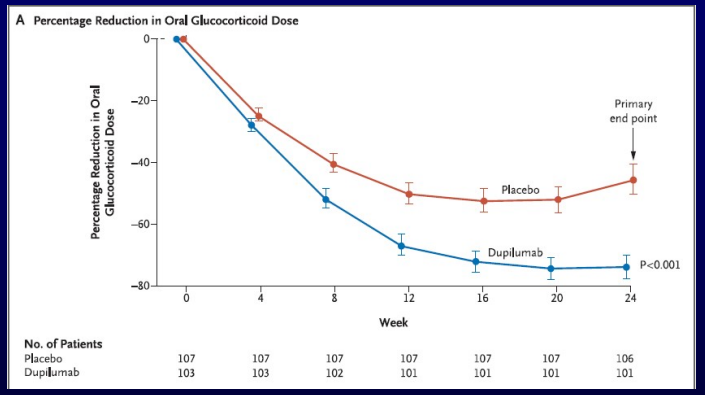
Klaus F. Rabe, M.D., Ph.D., Parameswaran Nair, M.D., Ph.D., Guy Brusselle, M.D., Ph.D., Jorge F. Maspero, M.D., Mario Castro, M.D., Lawrence Sher, M.D., Hongjie Zhu, Ph.D., Jennifer D. Hamilton, Ph.D., Brian N. Swanson, Ph.D., Asif Khan, M.B., B.S., M.P.H., Jingdong Chao, Ph.D., Heribert Staudinger, M.D., Ph.D., Gianluca Pirozzi, M.D., Ph.D., Christian Antoni, M.D., Ph.D., Nikhil Amin, M.D., Marcella Ruddy, M.D., Bolanle Akinlade, M.D., Neil M.H. Graham, M.B., B.S., M.D., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., and Ariel Teper, M.D.

N ENGL J MED 378;26 NEJM.ORG JUNE 28, 2018

VENTURE

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

Characteristic	Placebo Group (N = 107)	Dupilumab Group (N = 103)	Total (N = 210)
Age — yr	50.7±12.8	51.9±12.5	51.3±12.6
Male sex — no. (%)	42 (39)	41 (40)	83 (40)
No. of severe asthma exacerbations in previous year	2.17±2.24	2.01±2.08	2.09±2.16
Time since first oral glucocorticoid prescription — yr	1.64±3.54	1.77±3.52	1.70±3.52
Daily oral glucocorticoid dose — mg/day			
Dose before adjustment phase	11.83±6.02	11.79±6.40	11.81±6.20
Adjusted dose	11.75±6.31	10.75±5.90	11.26±6.12
Prebronchodilator FEV_1 — liters	1.63±0.61	1.53±0.53	1.58±0.57
Prebronchodilator FEV_1 — % of predicted value	52.69±15.14	51.64±15.28	52.18±15.18
FEV_1 reversibility — liters†	0.28±0.32	0.29±0.31	0.28±0.31
Any relevant medical history — no. (%)‡	86 (80)	76 (74)	162 (77)
Nasal polyposis	38 (36)	33 (32)	71 (34)
Food allergy	10 (9)	10 (10)	20 (10)
Former smoker — no. (%)	17 (16)	24 (23)	41 (20)
Time since cessation of smoking — yr	16.98±11.01	13.99±10.96	15.23±10.94
ACQ-5 score§	2.58±1.09	2.42±1.24	2.50±1.16
Blood eosinophil count — cells/mm^3	325±298	370±316	347±307
FE_{NO} — ppb	39.62±34.12	35.55±28.34	37.61±31.38



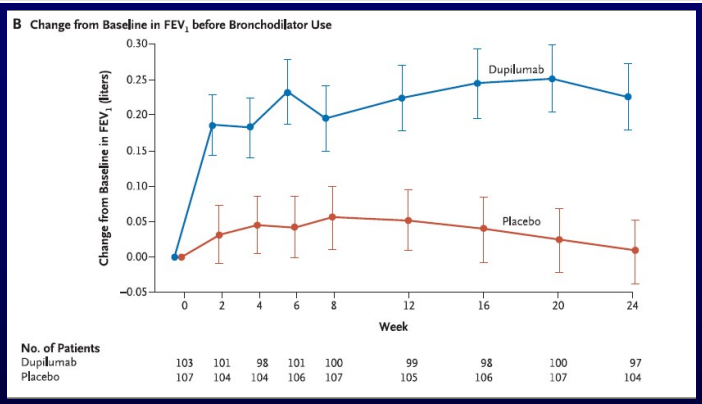
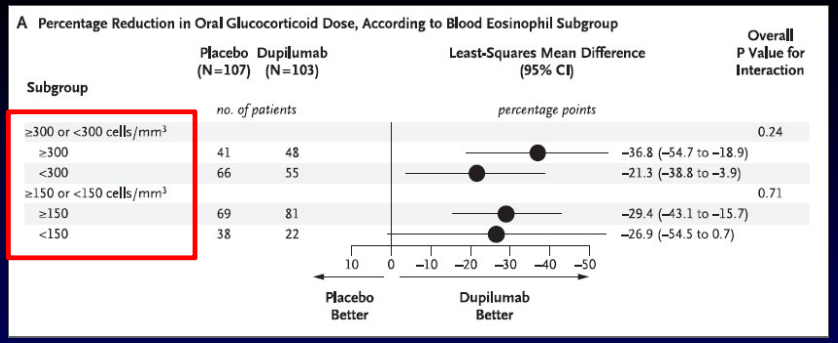


Figure 1. Primary End Point at Week 24 and Change in Prebronchodilator FEV_1 during the 24-Week Intervention Period (Intention-to-Treat Population).

The primary end point was the percentage reduction in the oral glucocorticoid dose at week 24. Values are least-squares means, and I bars represent the standard error. Values are slightly offset from each other at each time point for clarity. The dashed line in each panel indicates baseline. The intention-to-treat population included all the patients who underwent randomization; data were analyzed according to the assigned trial group, regardless of the trial regimen received. FEV_1 denotes forced expiratory volume in 1 second.



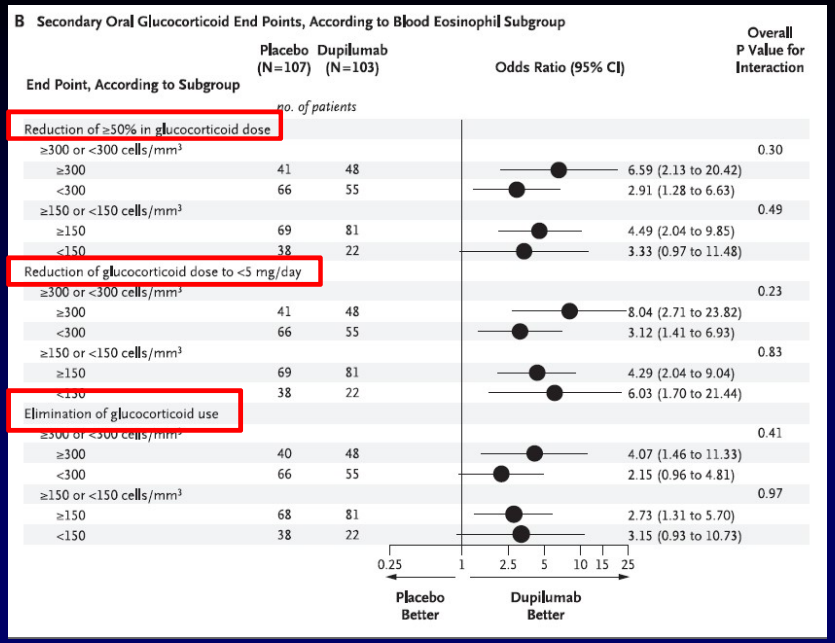


Figure 2. Primary End Point and Secondary Oral Glucocorticoid End Points at Week 24, According to Baseline Blood Eosinophil Subgroup.

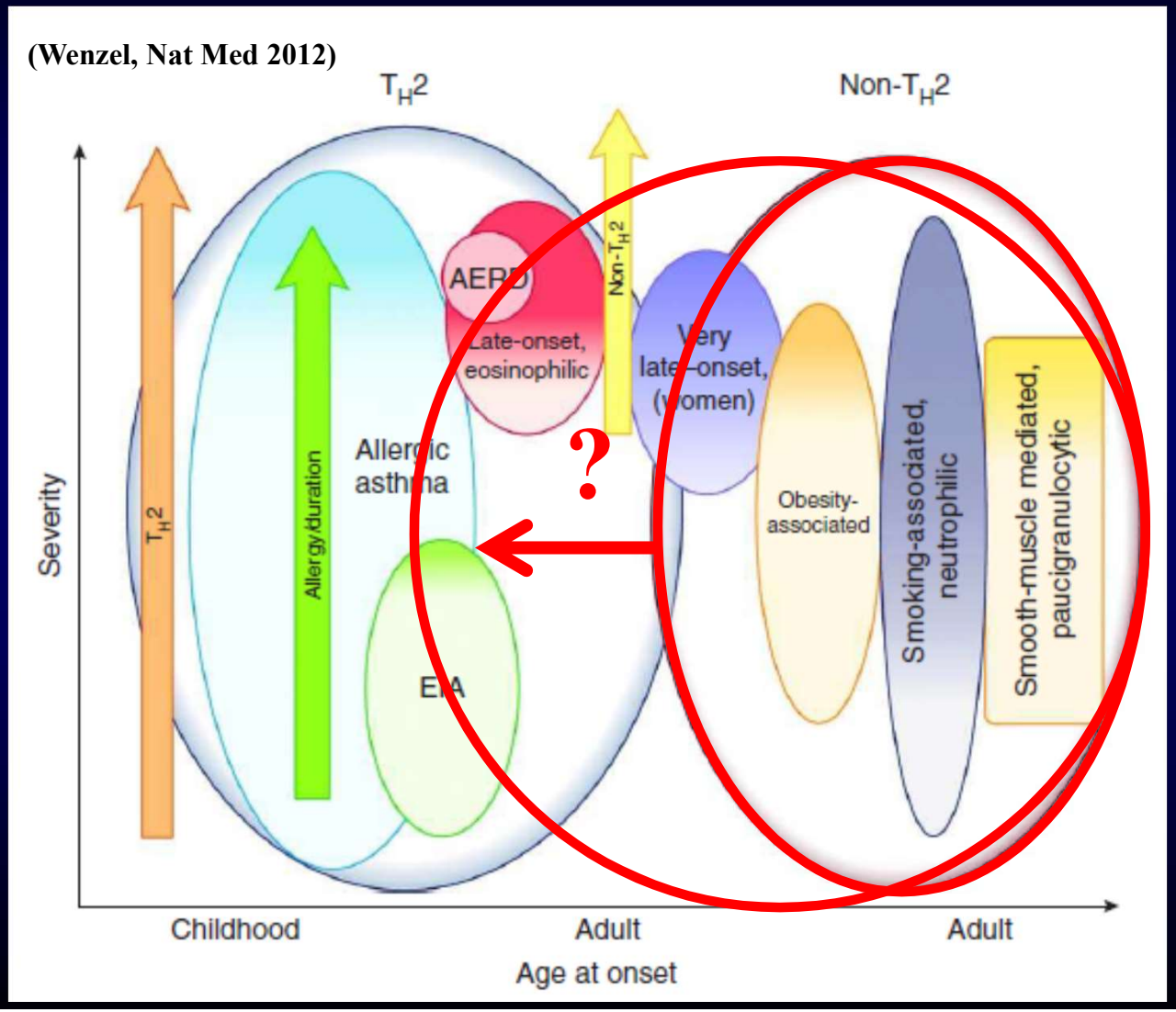
These data have not been controlled for multiple comparisons. Only the patients whose glucocorticoid dose was 30 mg per day or less at baseline were included in the analysis of the end point regarding the elimination of glucocorticoid use.

Table 2. Overview of Adverse Events during 24-Week Intervention Period and Injection-Site Reactions (Safety Population).*

Event	Placebo Group (N = 107)	Dupilumab Group (N = 103)
	number (percent)	
Any adverse event	69 (64)	64 (62)
Any serious adverse event	6 (6)	9 (9)
Any adverse event leading to death	0	0
Any adverse event leading to permanent discontinuation of trial regimen	4 (4)	1 (1)
Adverse event occurring in ≥5% of patients in either group†		
Viral upper respiratory tract infection	19 (18)	9 (9)
Bronchitis	6 (6)	7 (7)
Sinusitis	4 (4)	7 (7)
Influenza	6 (6)	3 (3)
Eosinophilia‡	1 (1)	14 (14)
Injection-site reaction§	4 (4)	9 (9)
≥1 measurement of blood eosinophil count >3000 cells/mm³	1 (1)	13 (13)

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

(Wenzel, Nat Med 2012)

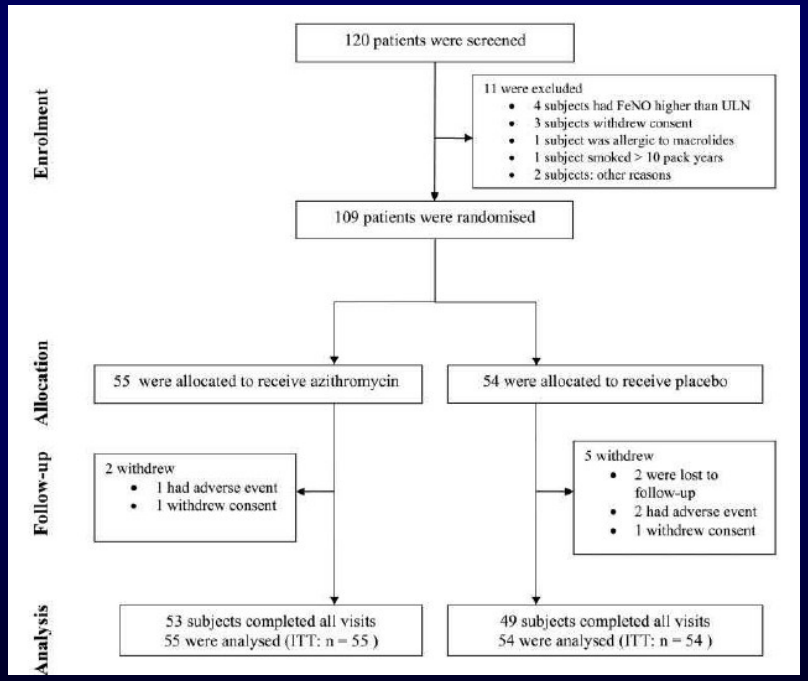


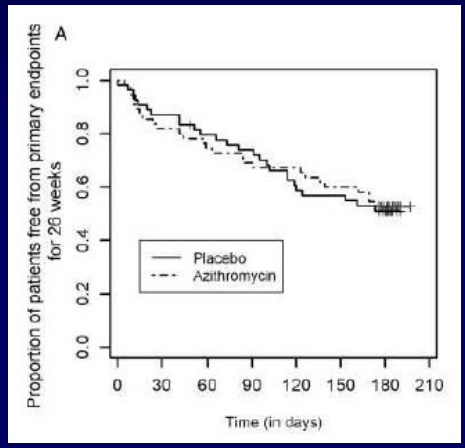
THORAX

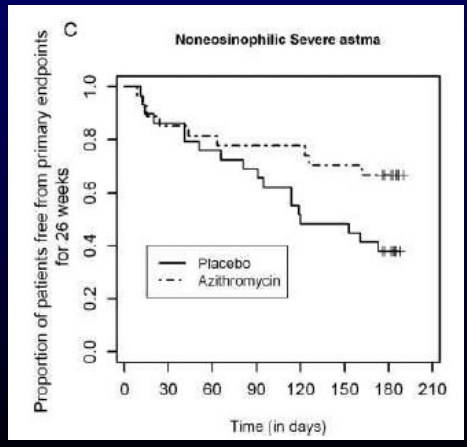
Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial

Thorax 2013

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







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

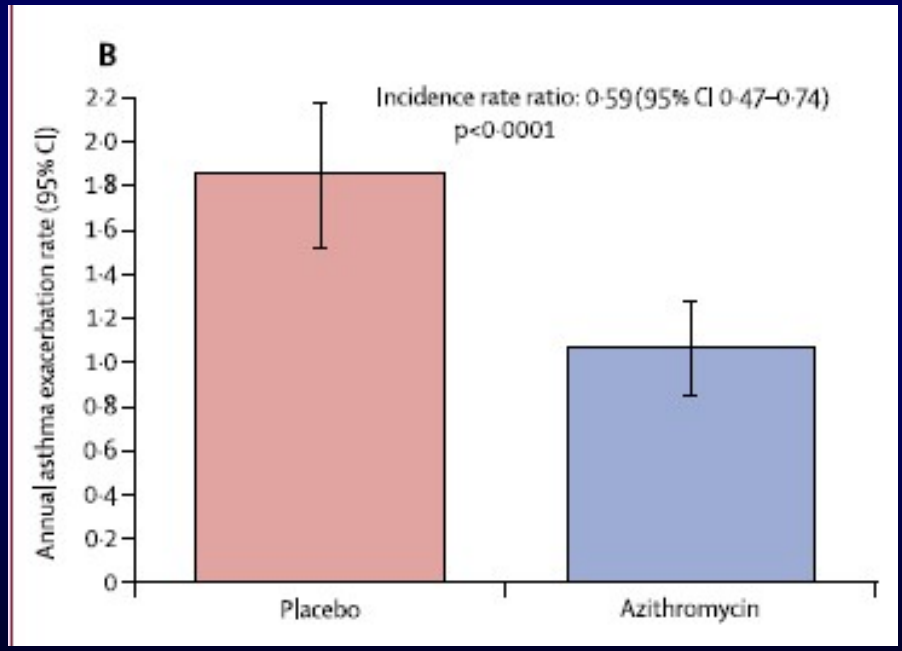
Peter G Gibson, Ian A Yang, John W Upham, Paul N Reynolds, Sandra Hodge, Alan L James, Christine Jenkins, Matthew J Peters, Guy B Marks, Melissa Baraket, Heather Powell, Steven L Taylor, Lex E X Leong, Geraint B Rogers, Jodie L Simpson

Lancet 2017; 390: 659–68

	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%)	156 (74%)
Ex-smoker	81 (39%)	80 (38%)
Pack years	7·5 (1·5–18·0)	7·6 (1·75–26·0)
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)	17 (5–40)
Age asthma diagnosed	20 (5–44)	21 (5–42)
ACQ6 score	1·55 (0·79)	1·56 (0·79)
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 B2 spirometry	n=205	n=210
Pre B2 FEV_1%	73·58 (18·83)	72·33 (20·70)
Pre B2 FVC%	82·95 (15·14)	82·74 (16·06)
Pre B2 FEV_1/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 (2·34–7·29)
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)

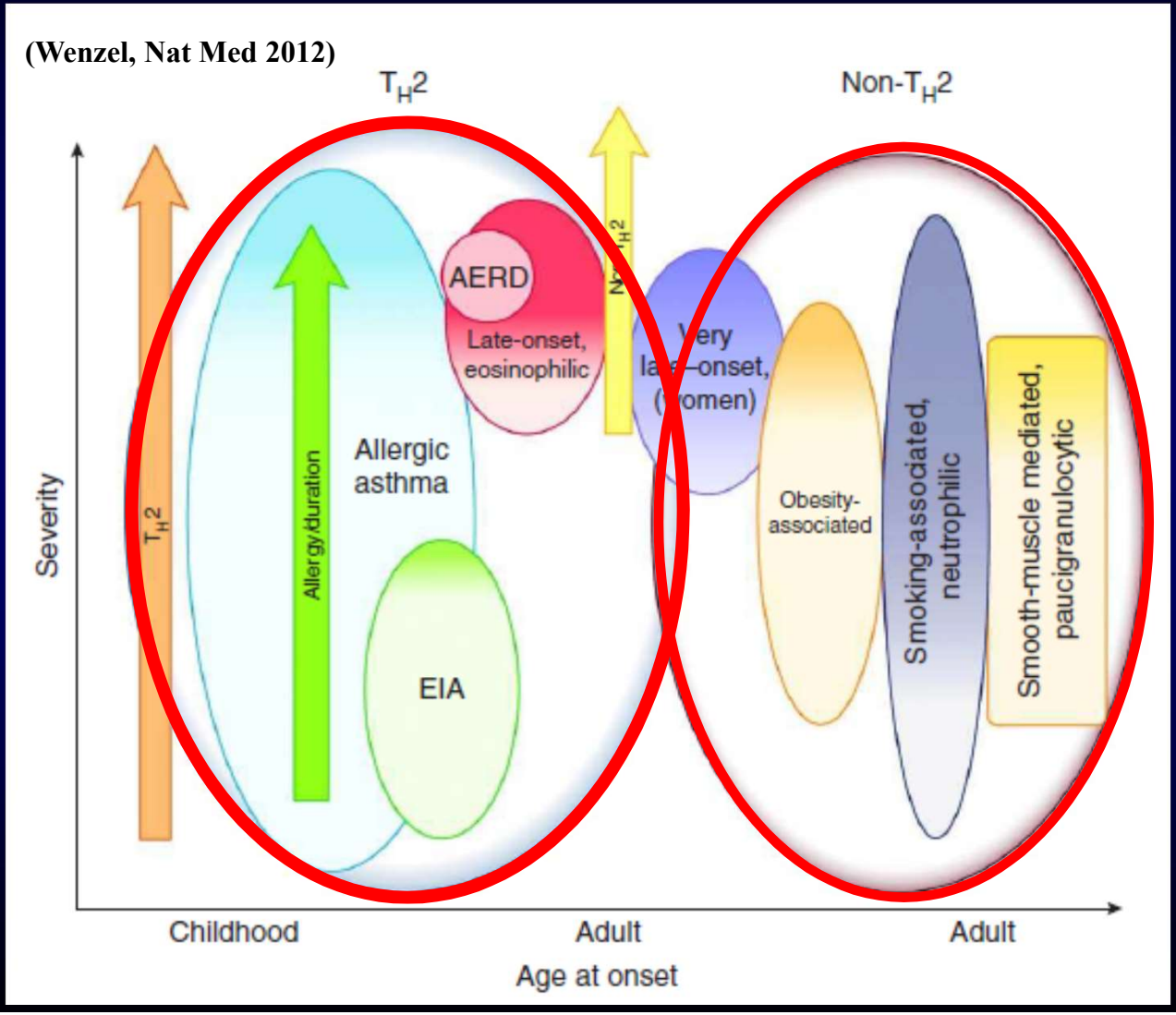
Data are median (IQR), mean (SD), or n (%). AQLQ=Asthma Quality of Life Questionnaire. ACQ6=Asthma Control Questionnaire. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity.

Table 1: **Characteristics of patients at baseline**



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

(Wenzel, Nat Med 2012)



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)

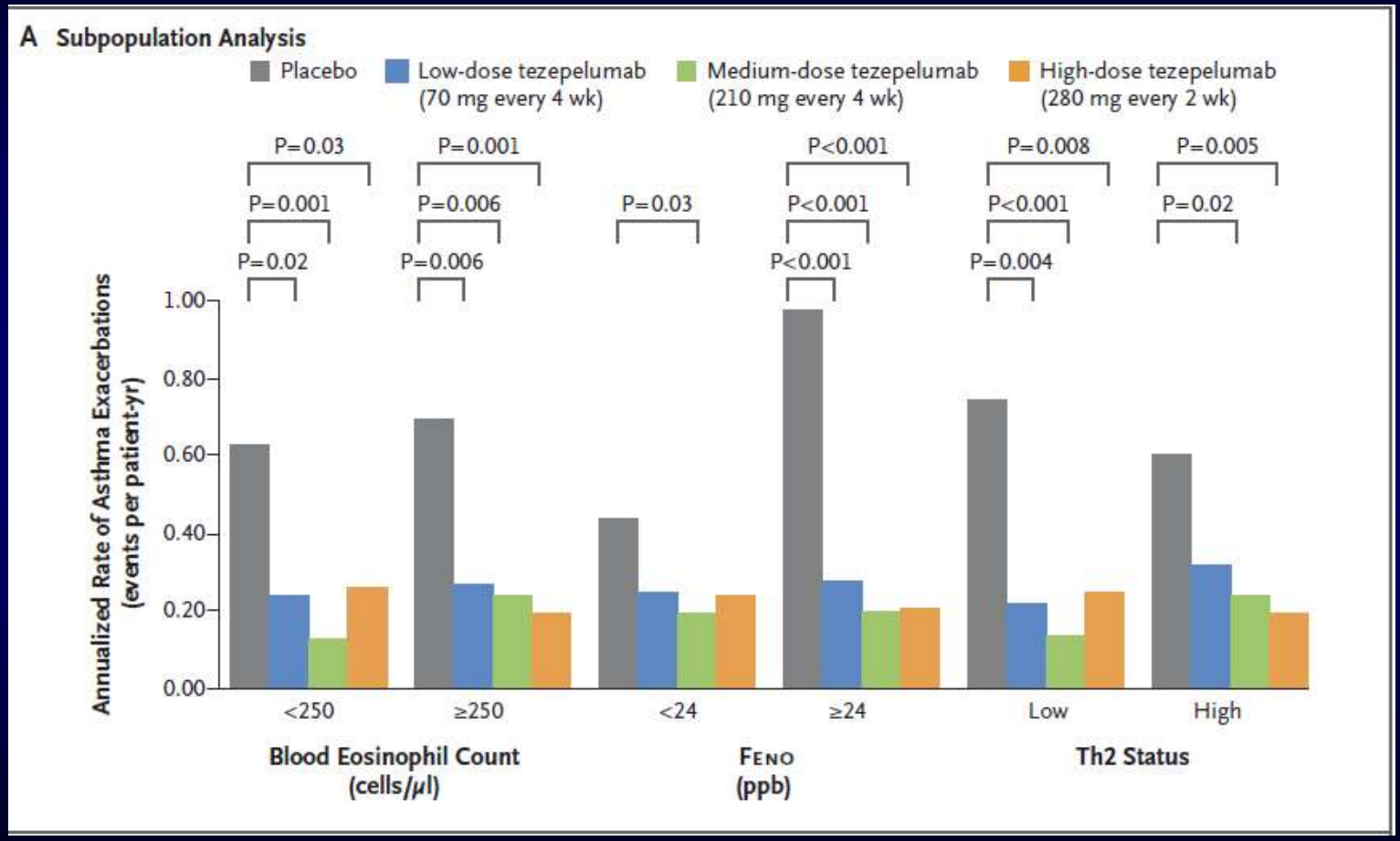
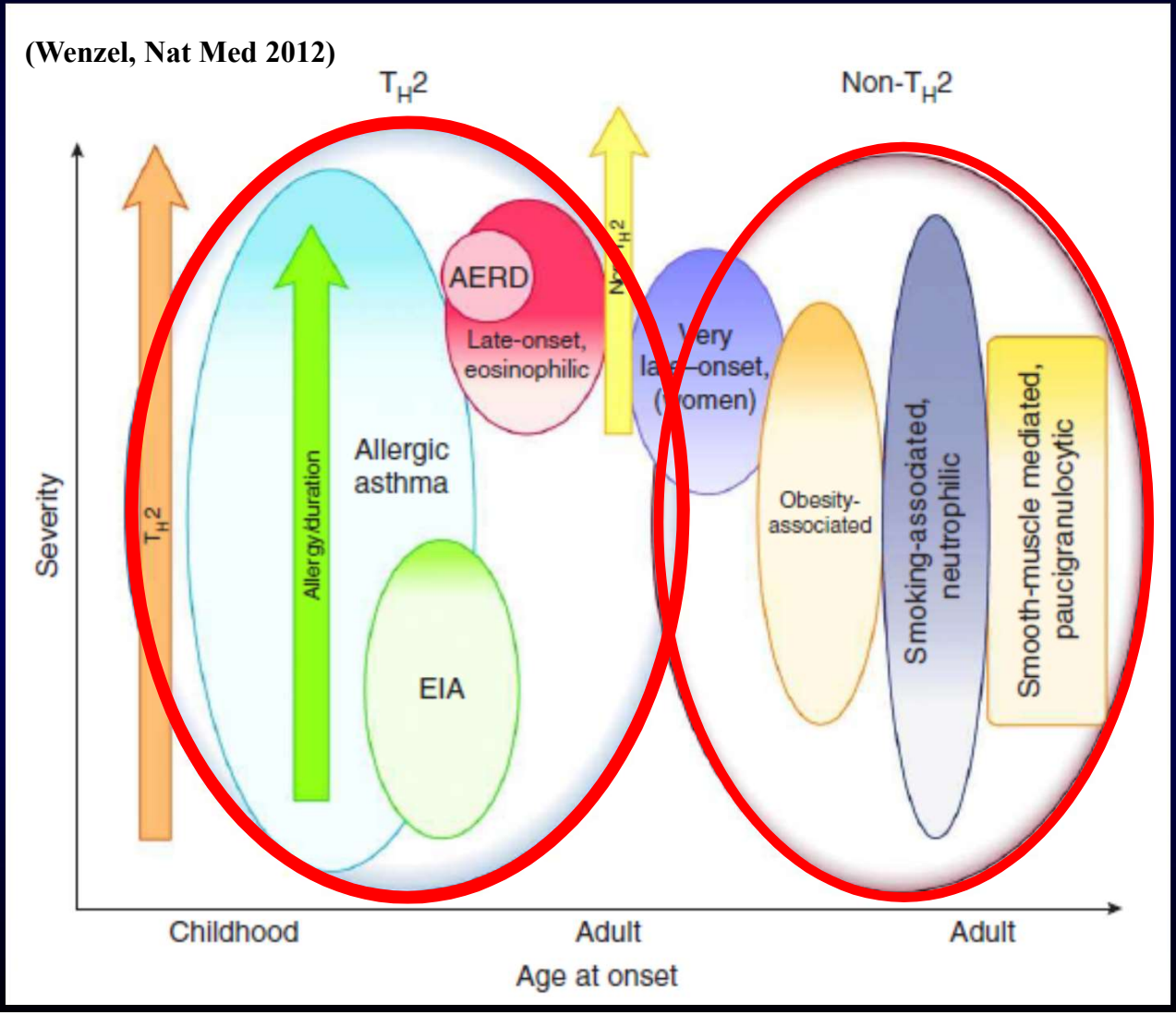

A Subpopulation Analysis
Placebo
Low-dose tezepelumab (70 mg every 4 wk)
Medium-dose tezepelumab (210 mg every 4 wk)
High-dose tezepelumab (280 mg every 2 wk)
P=0.03
P=0.001
P=0.02
P=0.001
P=0.006
P=0.006
P=0.03
P<0.001
P<0.001
P<0.001
P=0.008
P<0.001
P=0.004
P=0.005
P=0.02
Annualized Rate of Asthma Exacerbations (events per patient-yr)
1.00
0.80
0.60
0.40
0.20
0.00
<250
≥250
<24
≥24
Low
High
Blood Eosinophil Count (cells/μl)
FENO (ppb)
Th2 Status

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)	

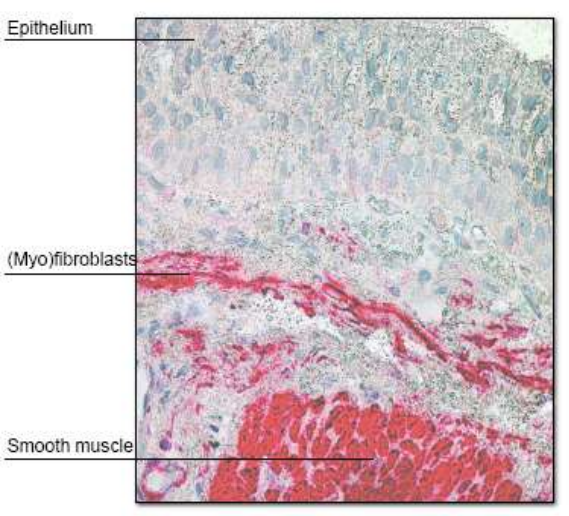
Propositions de phénotypes « théoriques » Th2/nonTH2 et de l'âge de survenue

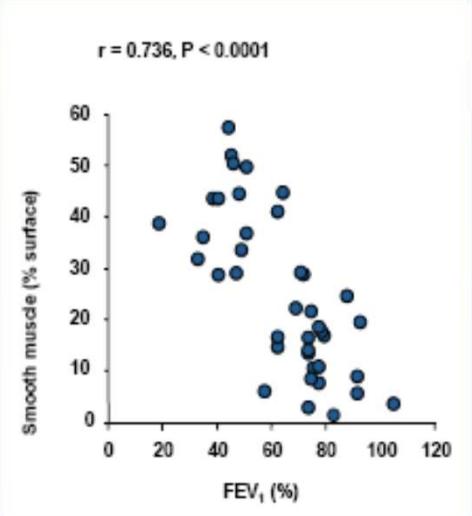
(Wenzel, Nat Med 2012)

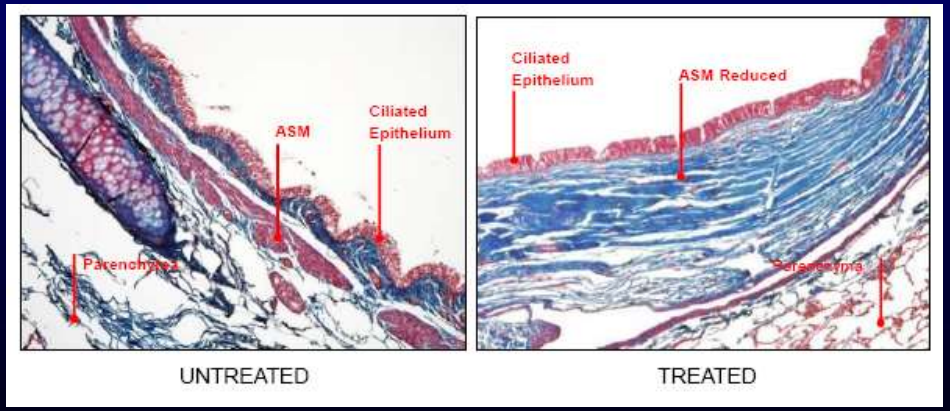


Thermoplastie bronchique

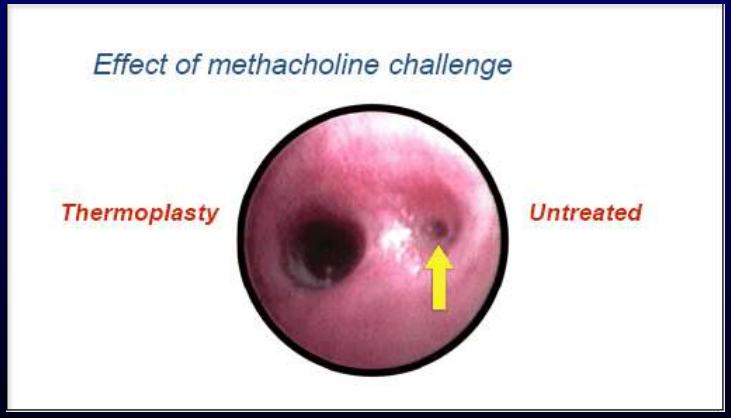
Radio frequencies to “cook” the smooth muscle in airways







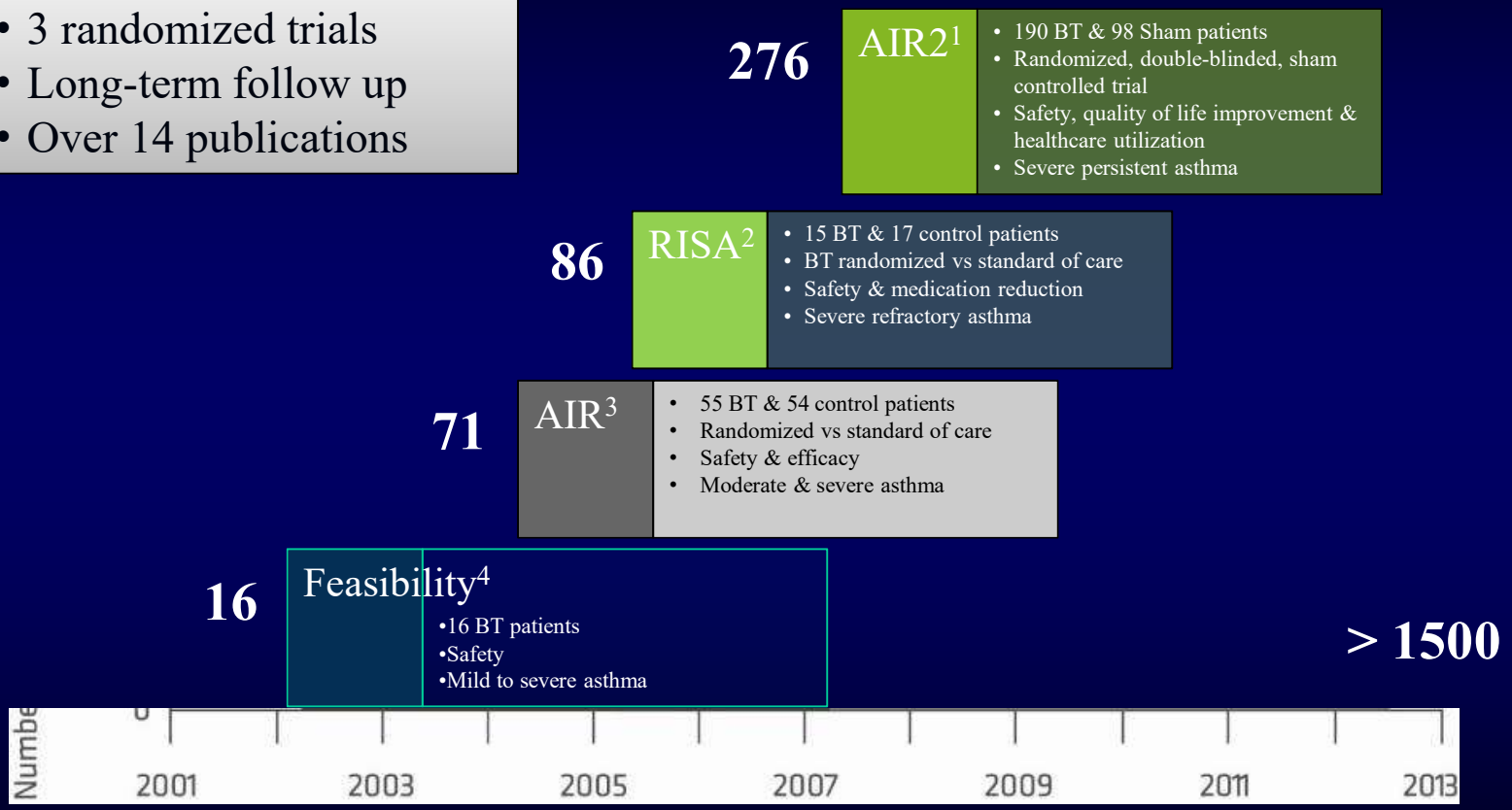
(Danek, J Appl Physiol 2004)



(Cox, ERJ 2004)

Background
Clinical Studies of Bronchial Thermoplasty

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

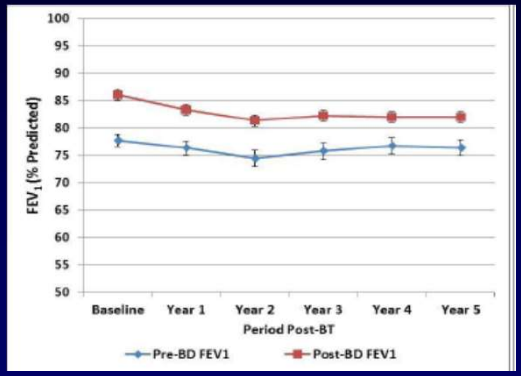


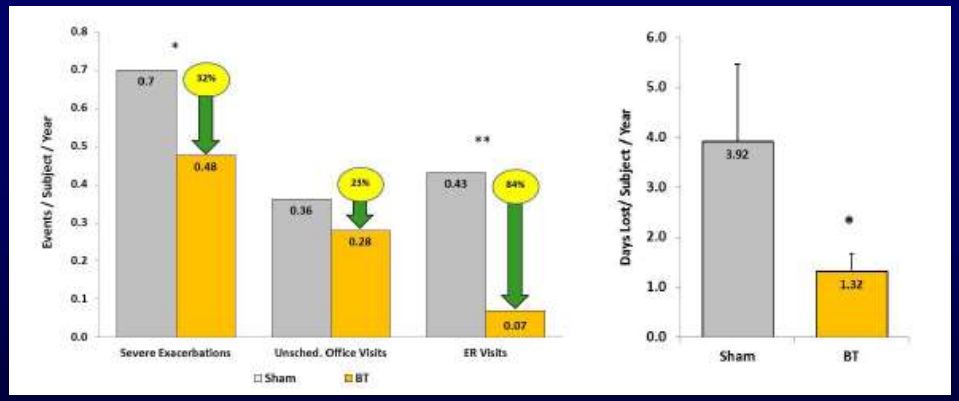
1 Castro et al., AJRCCM 2010; Castro et al., AnnAAI 2011
2 Pavord et al., AJRCCM 2007; Pavord et al.,AJRCCM 2011
3 Cox et al., NEJM 2007; Thomson et al., BMC Pulmonary Medicine 2011
4 Cox et al., AJRCCM 2006; Cox et al., AJRCCM 2010

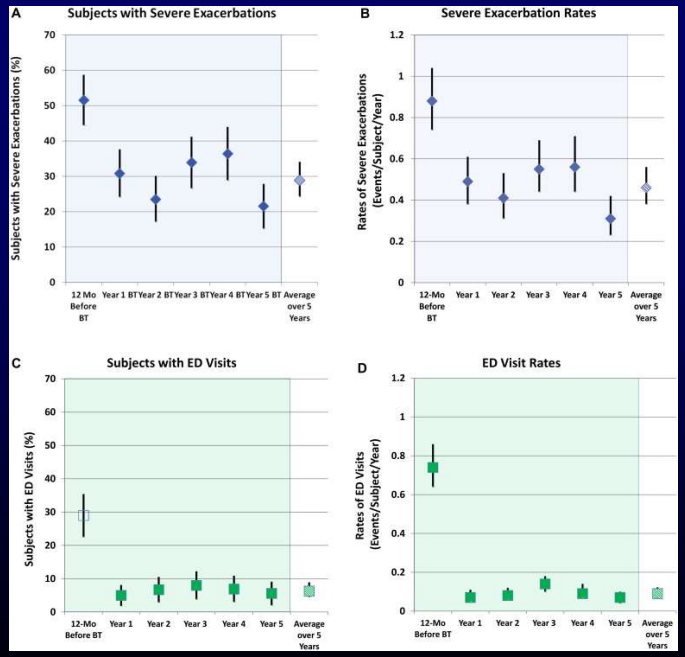
Principaux résultats cliniques

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)

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) Omalizumab, Mepolizumab, Benralizumab, Dupilumab disponibles

5) Quelques candidats sérieux en développement actuel

Tezepelumab, anti-IL-33…

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

7) Autres biothérapies candidates

Nombreuses, dont beaucoup peu ou pas évaluées

Anti-IL-17…

8) Autres alternatives: Azithromycine ?

Autres molécules (anti-CRTH2, TKI …) ?, TB ?…