Slide 1

Thermoplastie bronchique : indications et efficacité dans l'asthme sévère de l'adulte

Camille Taillé

Service de Pneumologie,

Centre de référence constitutif pour les maladies pulmonaires rares,

Hôpital Bichat, Paris.

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Liens d'intérêt

Période 2012-2019	Industrie pharmaceutique
Coordonnateur études	Bayer, GSK, Sanofi
Investigateur études	GSK, Sanofi, AZ, Novartis, Roche, ALK, Stallergene
Consultant	GSK, Novartis, AstraZeneca, Sanofi
Invitation à des congrès	GSK, Novartis, AstraZeneca, Chiesi
Orateur rémunéré	Novartis, ALK, Teva, GSK, Boeringher, Chiesi
Actionnaire	_

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Slide 3

La technique

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Slide 4
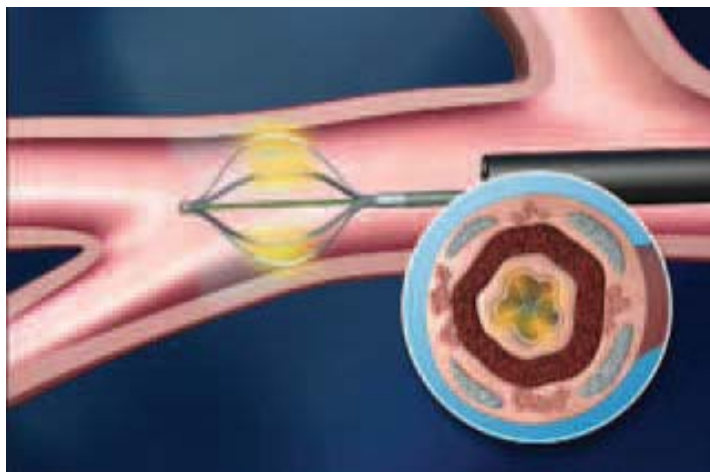
Quels résultats ?

Study	Study population	Study design
Cox et al[21]	16 patients with mild-to-moderate stable asthma	Non-randomized, prospective study
Cox et al[22]	112 patients with moderate-to-severe asthma	Randomized, controlled trial
Pavord et al[23]	32 patients with severe uncontrolled asthma	Randomized, double-blind, parallel-group trial
Castro et al[24]	288 patients with severe, uncontrolled asthma	Randomized, double-blind, controlled, multicenter-based trial
Thomson et al[25]	69 patients enrolled in the AIR trial	Long-term follow-up study
Pavord et al[26]	14 patients enrolled in RISA trial	Long-term follow-up study
Wechsler et al[27]	160 patients enrolled in AIR-2 trial	Long-term follow-up study

3 essais
432 malades traités
Biais
Pas de placebo

Menzella, *Therapeutics and Clinical risk management*, 2017

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Trial	Year published	Study design	Number of patients	Randomization	Age (years)	Pre-BD FEV1 (% predicted)	ICS dose (mg/days) (beclome thasone or equivalent)	OCS dose (mg/days)	Primary endpoint
AIR	2007 (NEJM)	RCT	55 BT, 54 control	1:1 (BT: Control)	18-65	60-85	>200	0	Exacerbations
RISA	2007 (AJRCCM)	RCT	15 BT, 17 control	1:1 (BT: Control)	18-65	>50	>1500	<30	AQLQ
AIR-2	2010 (AJRCCM)	RCT/DB/sham controlled	196 BT, 101 control	2:1 (BT: Sham)	18-65	>60	>1000	<10	AQLQ

RCT=Randomized controlled trial, BT=Bronchial thermoplasty, FEV1=Forced expiratory volume-1 s, ICS=Inhaled corticosteroid, OCS=Oral corticosteroid.
AQLQ=Asthma Quality of Life Questionnaire, BD= Bronchodilator, DB= double bind

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Table 3. Strength of evidence for bronchial thermoplasty interventions

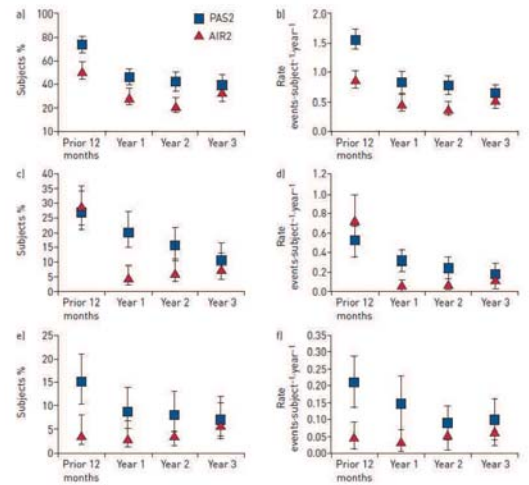| Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
BT and standard care (medical management) vs. standard care alone	Asthma control	Favors BT, but clinical importance unclear: ACQ scores improved in patients who underwent BT compared to those who received standard medical management, but the upper bounds of the confidence interval was less than the MID.	2 RCTs[19,20] n=144	Low (Medium[c] study limitations, Imprecise; MID not met)
	Exacerbations Severe	Inconclusive: Rates of severe exacerbations per patient per week did not vary between treatment conditions. Exacerbations were counted during 2-week periods at 3, 6 and 12 months when LABA were discontinued.	1 RCT[19] n=112	Insufficient (Medium[c] study limitations, Indirect [measured while off LABA], unknown consistency, Imprecise)
	Exacerbations Mild	Favors BT, but clinical importance unclear: Rates of mild exacerbations per patient per week were lower at 3 and 12 months but not at 6 months in patients who received BT and standard care. Exacerbations were counted only during 2-week periods at 3, 6 and 12 months when LABA were discontinued.	1 RCT[19] n=112	Low (Medium[c] study limitations, indirect [measured while off LABA], unknown consistency)
	Hospitalizations (after treatment period)	No difference: Rates of hospitalizations were not different in patients who received BT and standard care versus those treated with standard care alone.	1 RCT n=32	Low (Medium[c] study limitations Imprecise)
	Health care utilization (other than exacerbations)	Favors BT, but clinical importance unclear: Use of rescue medication (puffs per week) was reduced to a greater extent in the BT group than standard care group but does not meet the MID criterion. The overall reduction in oral or inhaled corticosteroid dose was not different between treatment groups in 1 small trial.[20]	2 RCTs[19,20] n=144	Low (Medium[c] study limitations, Imprecise)

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Un effet durable ?

Exacerbations sévères
-45%

Visites aux urgences
-55%

Hospitalisations
-40%

Chupp, *ERJ*, 2017

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Inclusion criteria
  Nonsevere asthmatic with
    Very few patients on oral steroids (3.7%)
    Pre-BD FEV1 >60% predicted
Patient phenotype (Th1/Th2 etc.): Not known
Statistical methods
  Bayesian statistics
  Univariate logistic regression
Primary end-point
  AQLQ unchanged (except emotional component)
Secondary end-point
  No change in airway hyperresponsiveness as measured by
    FEV1 (pre- or post-BD)
    Morning PEF
    Percentage symptom-free days
Post hoc analysis
  Unplanned analysis of health care utilization
  Significant outlier effect
Rescue inhaler usage during and after the AIR-2 trial: Not reported
Characteristics of airway inflammation not assessed
  Lack of
    Bronchial biopsies
    Induced sputum eosinophil counts
    ENO
Lack of Sham group follow up
  5 year report of treatment arm alone
  No follow-up report on Sham arm
Peripheral airways treated with BT: No
Th2 mediated inflammation in asthma: Not addressed by bronchial thermoplasty
BT=Bronchial thermoplasty, ENO=Exhaled oral nitric oxide, FEV1=Forced expiratory volume-1 s, PEF=Peak expiratory flow, AQLQ=Asthma Quality of Life Questionnaire, BD=Bronchodilator

"Given the considerable subjective nature of asthma symptoms, this raises questions about whether the beneficial effects of BT reported in the AIR and RISA trial were the result of a placebo effect.
This point was clearly demonstrated in the AIR-2 trial with the sham arm reporting a significantly improved AQLQ after sham BT (AQLQ increasing from 4.32–5.48 post BT). If one recalls the previous discussion about magnitude of increase in AQLQ; this increase of 1.16 in the sham arm would equate to patients reporting that their asthma was a "good deal better" after undergoing sham BT! "

Nasim, Ann Thorac Med. 2018 Oct-Dec; 13(4): 205–211.

Quels résultats ?

Parameter	Before BT	3 mo after BT	12 mo after BT	P value*
Treatments				
On long-acting β$_2$-agonists (no.)	15	15	15	
Dose of ICS (µg/d beclomethasone equivalents)	2133 ± 516	2000 ± 0	2000 ± 0	.38
On maintenance use of OCS, no. (%)	10 (67)	9 (60)	8 (53)	.15
Dose of oral prednisone (mg/d)	31.5 ± 11.1	20.6 ± 12.4	13.8 ± 5.2‡	.002§
On anti-IgE, no. (%)§	10 (67)	0	0	<.001
Asthma control				
With uncontrolled asthma, no. (%)	15 (100)	6 (40)‡	4 (27)‡	<.001
Score on ACT	8.5 ± 2.8	15.7 ± 4.8‡	16.4 ± 6.9‡	<.001
Score on AQLQ	2.6 ± 0.9	3.7 ± 1.5	4.2 ± 1.5‡	<.001
Annual rate of severe exacerbations	9.7 ± 1.3	0.7 ± 0.3‡	0.7 ± 0.4‡	<.001
Annual rate of hospitalization for asthma	1.7 ± 0.8	0.2 ± 0.1‡	0.2 ± 0.1‡	<.001
Annual rate of visits to emergency department	3.3 ± 1.0	0.5 ± 0.3‡	0.3 ± 0.2‡	<.001
Annual rate of hospitalization in ICU	0.9 ± 0.7	0.2 ± 0.1‡	0.1 ± 0.1‡	.02
Respiratory function				
Prebronchodilator FEV$_1$ (mL)	2068 ± 682	1990 ± 480	2100 ± 680	.66
Postbronchodilator FEV$_1$ (mL)	2250 ± 656	2300 ± 820	2250 ± 670	.93
Prebronchodilator FEV$_1$ (% predicted)	67.1 ± 19.5	63.5 ± 13.4	66.6 ± 16.8	.65
Postbronchodilator FEV$_1$ (% predicted)	71.0 ± 16.6	70.2 ± 13.2	70.8 ± 15.7	.97

Pretolani, *JACI*, 2016[9]

Tolérance

TABLE VIII. AIR2 respiratory adverse events selected AEs with >3% incidence and difference between groups

Adverse event	Treatment period (~12 wk)		Posttreatment period (~46 wk)	
	BT (N = 190) %	Sham (N = 98) %	BT (N = 187) %	Sham (N = 98) %
Asthma (multiple symptom)	52.1	38.8*	27.3*	42.9
Wheezing	15.3	6.1*	4.3	3.1
Atelectasis	4.7	0*	0	0
Hemoptysis	3.2	0*	0	0
Lower respiratory tract infection	7.9	2.0*	3.2	6.1
Upper respiratory tract infection	20.0	11.2*	29.9	25.5
Nasopharyngitis	4.7	7.1	10.7	5.1*
Throat irritation	4.7*	12.2	1.1	3.1

AE, Adverse event; *BT*, bronchial thermoplasty.
*Posterior probability of superiority (PPS) >95.0%.
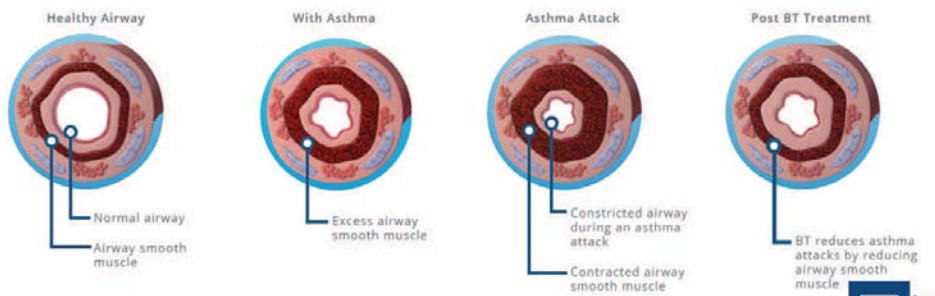
Cas isolés :
Hémoptysie, anévrysme de l'artère pulmonaire
Dilatations des bronches
Pneumothorax

Tan, *JACI*, 2018   10

Quel(s) mécanisme(s) d'action ?

• Diminution de l'épaisseur du muscle lisse et réduction de l'hyperréactivité bronchique ?
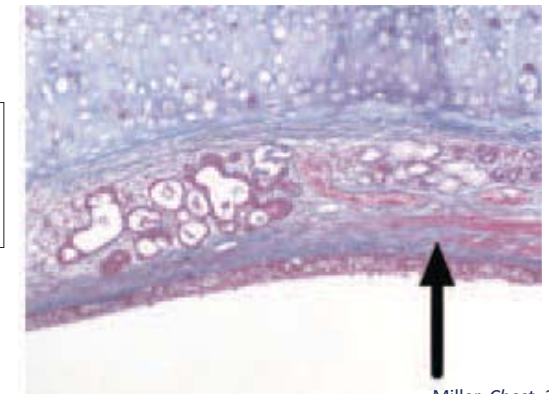

Source : https://btforasthma.com/how-it-works
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Quel(s) mécanisme(s) d'action ?
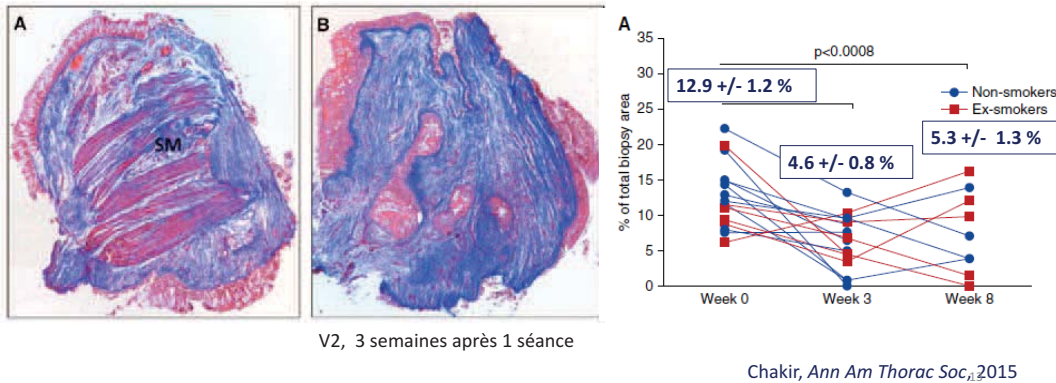
• Diminution du muscle lisse bronchique

• 8 patients opérés
• Thermoplastie 1-3 semaines avant dans la zone à opérer.
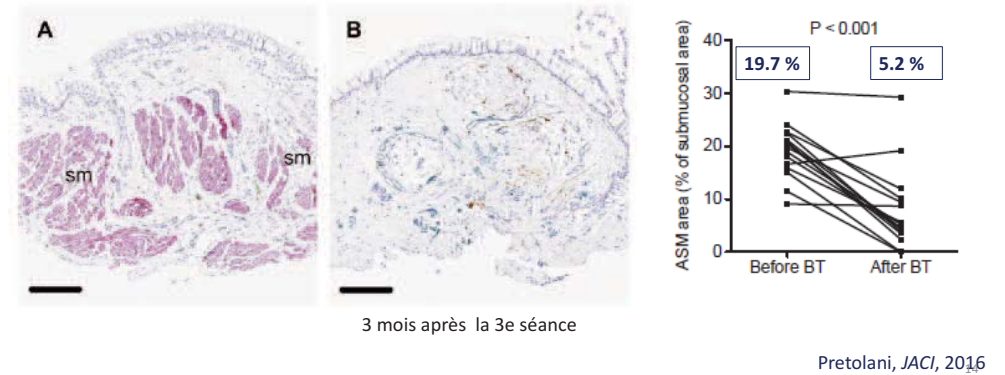• Réduction de 50% de la masse de muscle lisse

Miller, *Chest, 2005*

Quel(s) mécanisme(s) d'action ?

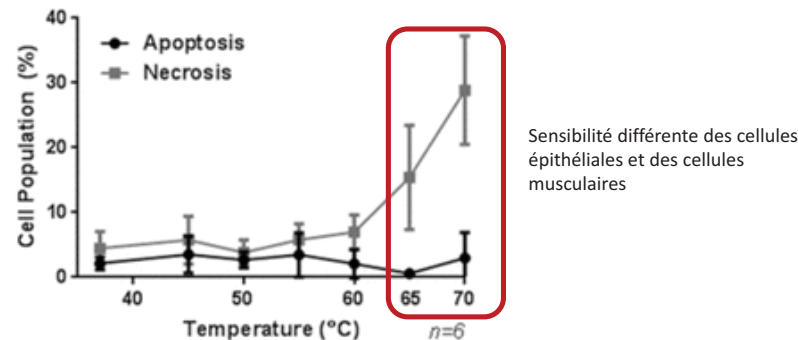- Diminution de la surface de muscle lisse

V2, 3 semaines après 1 séance

Chakir, *Ann Am Thorac Soc*, 2015

Quel(s) mécanisme(s) d'action ?

- Diminution de la surface du muscle lisse

3 mois après la 3e séance

Pretolani, *JACI*, 2016

Quel(s) mécanisme(s) d'action ?

- Effet de la chaleur sur le muscle lisse bronchique

Sensibilité différente des cellules épithéliales et des cellules musculaires

Brook BS, *Am J Respir Crit Care Med*, 193; 2016: A1256

La surface de muscle lisse <u>après thermoplastie</u> est associée à un moins bon contrôle

| Parameter	ACT score		AQLQ score		No. of severe exacerbations		No. of visits to emergency department		No. of hospitalization for asthma		No. of hospitalization in ICU	
	r^*	95% CI	r	95% CI	r	95% CI	r	95% CI	r	95% CI	r	95% CI
Results 3 mo after BT ASM (% of submucosal area)	−0.600‡	−1.00/−0.20	−0.321	−0.73/0.08	0.690§	0.30/1.00	0.616‡	0.21/1.00	0.457†	0.04/0.87	0.309	−0.10/0.72
Results 12 mo after BT ASM (% of submucosal area)	−0.516†	−0.94/−0.09	−0.432†	−0.86/0.00	0.580‡	0.17/0.99	0.572‡	0.16/0.98	0.310	−0.11/0.73	0.189	−0.22/0.60

Pretolani, *JACI*, 2016

La surface de muscle lisse après thermoplastie est associée à un moins bon contrôle

☐ Avant thermoplastie

🟨 Après thermoplastie, bons répondeurs ACT ≥ 15 (n=11)

🟫 Après thermoplastie, non répondeurs ACT<15 (n=4)
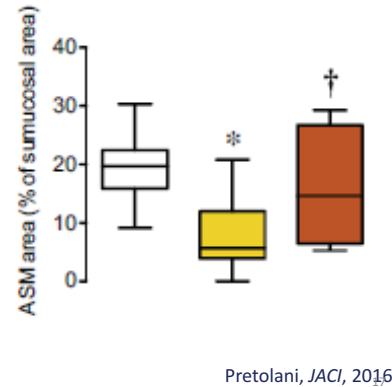
Pretolani, *JACI*, 2016

Pourquoi la réduction du muscle lisse est-elle variable ?

r=0.89
p<0.0001

Chakir, *Ann Am Thorac Soc*, 2015
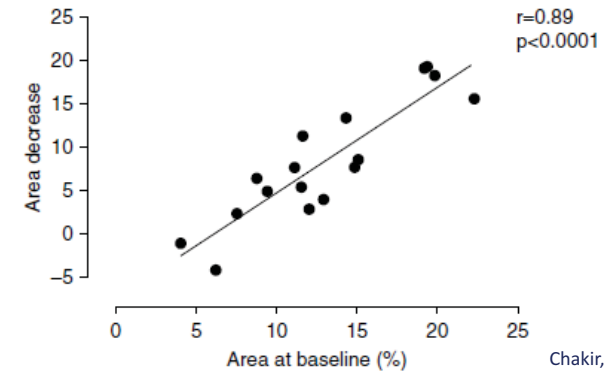
Pourquoi la réduction du muscle lisse est-elle variable selon les patients ?

- Relation avec le nombre d'activations ? (Pretolani, *JACI*, 2016, Langton, *Respir Res* 2017)
- Effet du diamètre bronchique (Brook BS, *Am J Respir Crit Care Med*, 193; 2016: A1256)
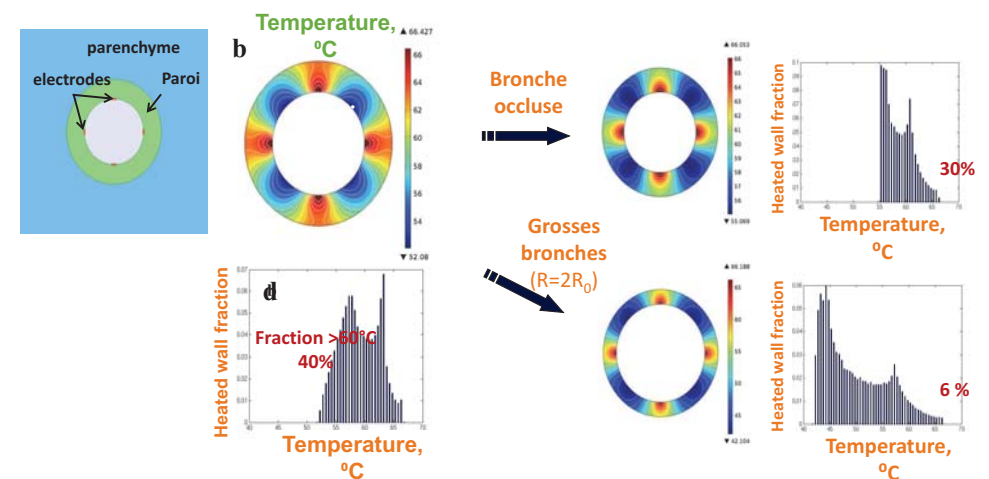
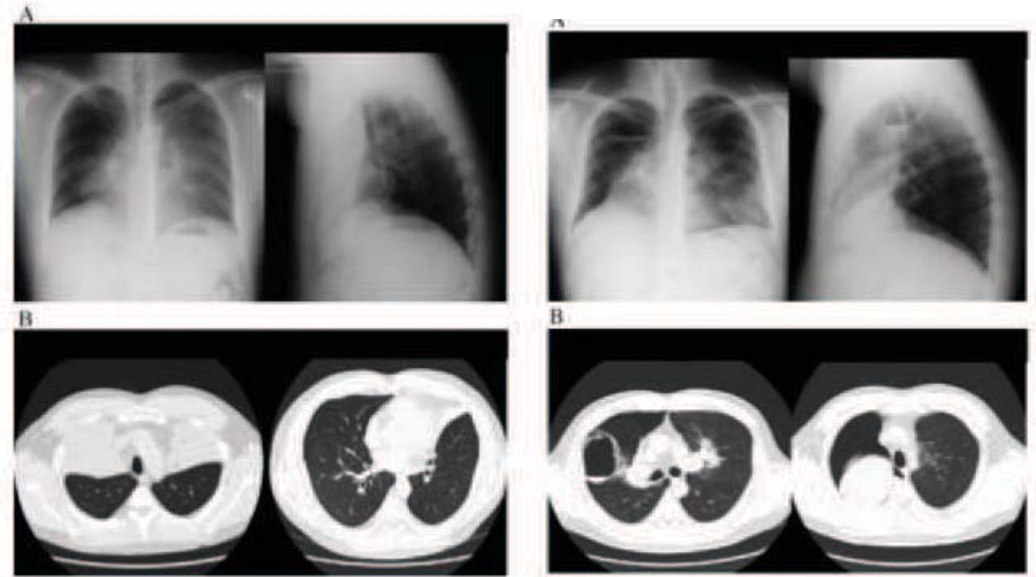Avec l'autorisation de C. Brightling, I. Chernyavsky, R. Russel, B. Brook.

L'effet de la thermoplastie est-il restreint au muscle lisse ?
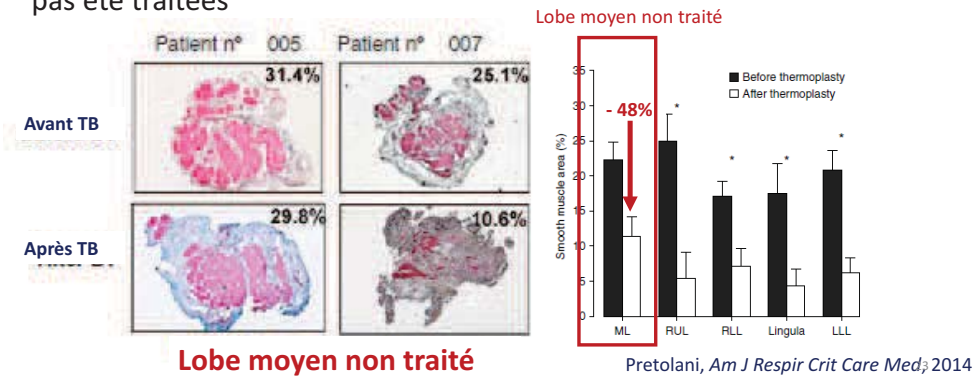
• La chaleur diffuse au-delà de la bronche traitée ?

Debray, *ERJ*, 2016 21
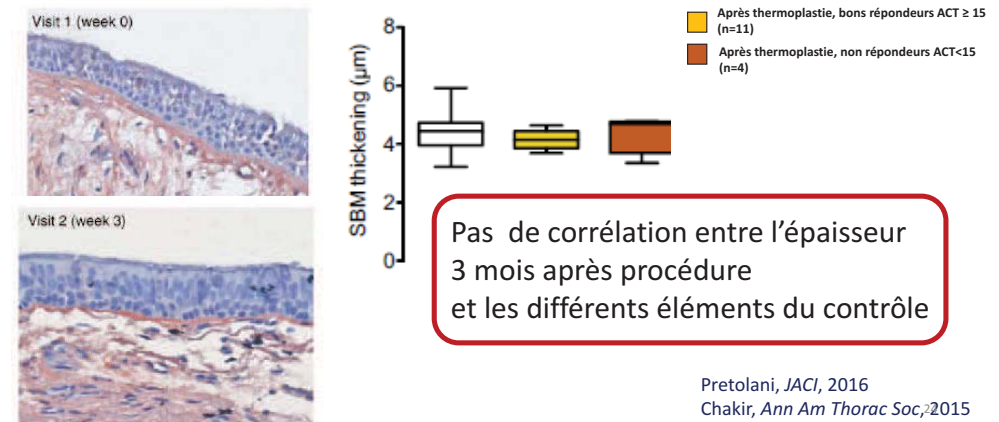

Funatsu, *Respirology Case Report*, 2018.

L'effet de la thermoplastie est-il restreint au muscle lisse ?

• La réduction du muscle lisse est observée dans les bronches qui n'ont pas été traitées

Lobe moyen non traité

Lobe moyen non traité

Pretolani, *Am J Respir Crit Care Med*, 2014

L'effet de la thermoplastie est-il restreint au muscle lisse ?

• Effet sur la membrane basale

Pas de corrélation entre l'épaisseur 3 mois après procédure et les différents éléments du contrôle

Pretolani, *JACI*, 2016
Chakir, *Ann Am Thorac Soc*, 2015

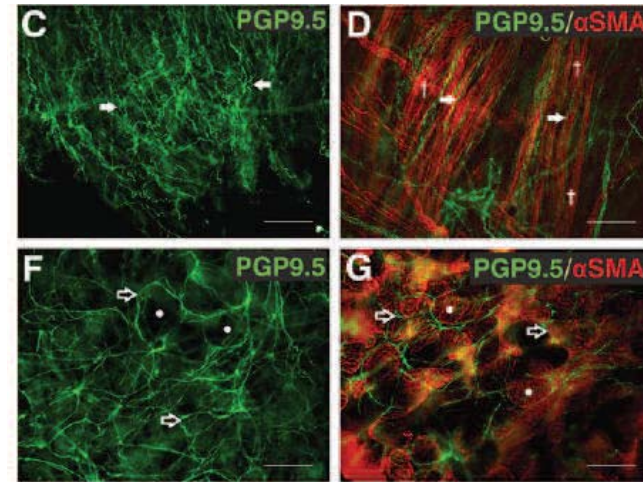# L'effet de la thermoplastie est-il restreint au muscle lisse ?

- Effet sur les terminaisons nerveuses
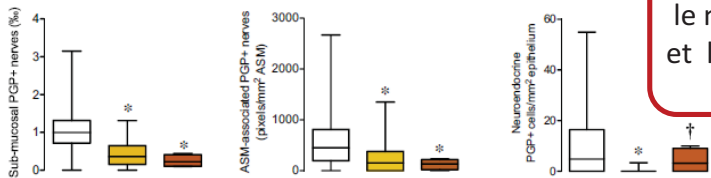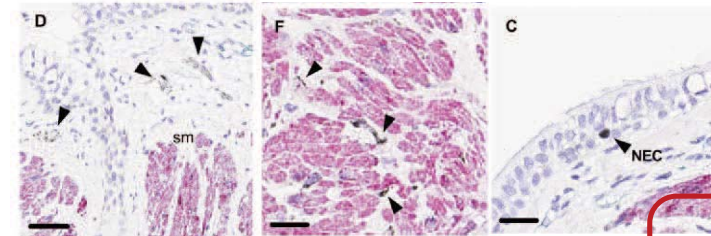
Corrélation entre
le nombre de cellules PGP9 +
et le nombre d'exacerbations
à 3 mois et à 12 mois

Pretolani, *JACI*, 2016

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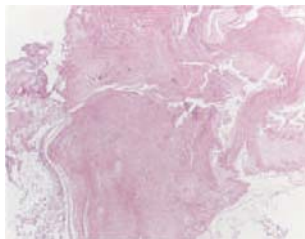# L'innervation du muscle lisse bronchique

West PW, *Am J Respir Crit Care Med*, 2015

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Quel(s) mécanisme(s) d'action ?

- Effet sur les cellules épithéliales : des lésions aigues qui régénèrent ?

AIGU

CHRONIQUE
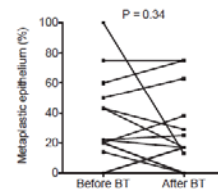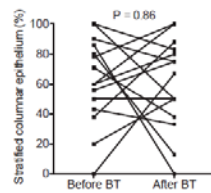
En aigu : mucus, cellules bronchiques desquamées,
Cellules inflammatoires, extravasation
(Facciolono, *Multidisciplinary Respiratory Medicine* 2015)

Biopsies bronchiques
3 mois après la dernière séance
(Pretolani, *JACI*, 2016)

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Quel(s) mécanisme(s) d'action ?

- Effet sur la production de mucus par les cellules épithéliales

Haj Salem, *Am J Respir Crit Care Med*, 2018

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Quel(s) mécanisme(s) d'action ?

• Effet sur les cellules inflammatoires

AIGU

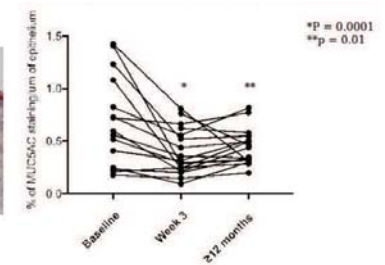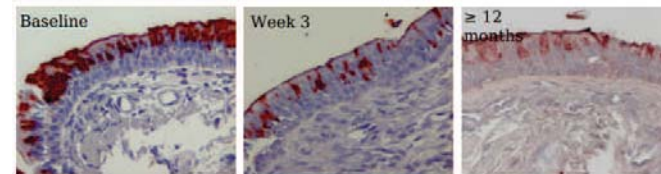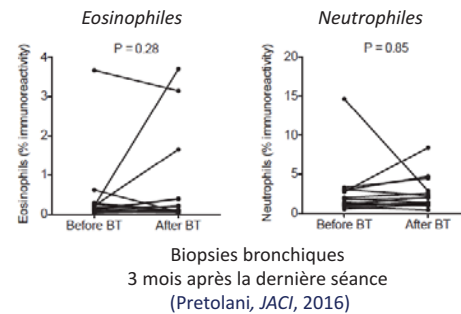| BAL cellular content (%)*	Week 0	Week 3	Week 6
Eosinophils	4 ± 1	1 ± 0†	1 ± 0†
Macrophages	92 ± 2	94 ± 1	92 ± 1
Lymphocytes	3 ± 2	4 ± 1	6 ± 2

Modifications des taux de TGFbeta, TRAIL, RANTES

Lavage alvéolaire
3 et 6 semaines après la 1ere séance
(Denner, *Ann Am Thorac Soc*, 2015)

Augmentation des Lymphocytes T regulateurs ?

CHRONIQUE

Eosinophiles   P = 0.28
Neutrophiles   P = 0.85

Biopsies bronchiques
3 mois après la dernière séance
(Pretolani, *JACI*, 2016)

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Les difficultés de cette recherche

• Variabilité interindividuelles : besoin de nombreux prélèvements (10 biopsies par malade !)

• Comment intégrer les modification des doses de stéroïdes après thermoplastie ?

• Dynamique du remodelage : à quel moment faire les biopsies ?

• Intérêt de développer des méthodes moins invasives +++

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Les questions restantes ?

• Peut-on choisir les zones à traiter ?
• Peut-on améliorer la technique pour réduire davantage le muscle ?

• Comment sélectionner les patients qui vont répondre au traitement ?
➢Sur la taille du muscle ? Sur quelle mesure ? (biopsies ? Épaisseur de la paroi ? VEMS ? ..)
➢Sur l'hyperéractivité ?
➢Sur le nombre d'exacerbations ?
➢Sur l'absence d'inflammation ?

• Quels effets sur l'histoire de la maladie ?
• Effets secondaires à long terme (dilatation des bronches, sténoses) ?

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Quelle place pour la thermoplastie ?

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Slide 33

Consider refractory to Standard Asthma Treatment:
- If ACT < 19 after 3 months, or
- Unable to wean off prednisone, or
- >2 admissions to ED again or hospital within 4 months

Review Check Point Labs

TH2 Low — TH2 High

Paucigranulocytic
Bronchial Thermoplasty
Azithromycin

Atopy with elevated IgE
Omalizumab

Eos ≥150/ µL
Benralizumab
Mepolizumab

Eos ≥400/µL
Reslizumab

Consider BT for those who have failed biologic therapy for 3 months

Tan, *JACI*, 2018

GINA

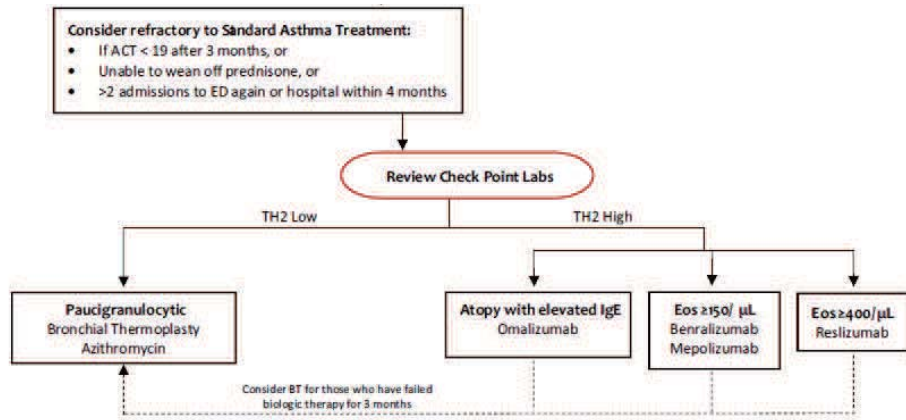| Bronchial thermoplasty | • For highly-selected adult patients with uncontrolled asthma despite use of recommended therapeutic regimens and referral to an asthma specialty center (Step 5), bronchial thermoplasty is a potential treatment option in some countries.
• Caution should be used in selecting patients for this procedure, as the number of studies is small, and people with chronic sinus disease, frequent chest infections or FEV$_1$ <60% predicted were excluded. | B |
| | | D |

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER CHOICE		Low dose ICS	Low dose ICS/LABA**	Med/high ICS/LABA	Refer for add-on treatment e.g. tiotropium,** anti-IgE, anti-IL5*
Other controller options	Consider low dose ICS	Leukotriene receptor antagonists (LTRA) Low dose theophylline*	Med/high dose ICS Low dose ICS+LTRA (or + theoph*)	Add tiotropium**† High dose ICS + LTRA (or + theoph*)	Add low dose OCS
RELIEVER	As-needed short-acting beta$_2$-agonist (SABA)		As-needed SABA or low dose ICS/formoterol#		

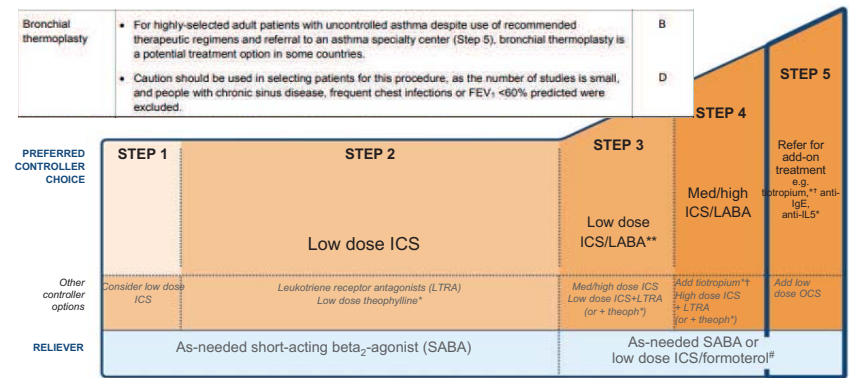## En résumé

- La thermoplastie modifie d'autres structures bronchiques que le muscle, notamment les terminaisons nerveuses.

- Il n'y a pas d'effet clair sur l'inflammation bronchique.

- Actuellement, la thermoplastie est plutôt réservée aux échecs/non indications des biothérapies, compte tenu des interrogations restantes.

Faculté de médecine
Bichat, Paris

INSERM UMR1152
Marina PRETOLANI
Michel AUBIER

Séverine LETUVE
Céline SALLON
Maha-Zohra LADJEMI
Leonarda DI CANDIA
Noëlline GUILLOU
Fatima HAMIDI

CHU Bichat
Claude Bernard, Paris

Services de pneumologie
Bruno CRESTANI
Marie-Christine DOMBRET

Service d'anatomo-pathologie
Aurélie CAZES
Claire DANEL

Service de Radiologie
Marie-Pierre DEBRAY
Antoine KHALIL

Merci !