Journées Pharmaceutiques Internationales de Paris
Paris, 7 décembre 2018

Aspects médico-économique et Efficience des biothérapies dans la Polyarthrite Rhumatoïde

Bruno Fautrel, MD PhD

Sorbonne Université, GRC 08

AP-HP, Service de Rhumatologie,
Groupe hospitalier Pitié Salpêtrière, Paris, France

Institut Pierre Louis d'Epidémiologie et Santé publique

CRI-IMIDIATE, F-CRIN clinical research network

CRMR CEREMAIA, Filière Maladie Rare FAI2R

Conflits d'intérêts

- **Intérêts financiers**
  - Néant
- **Liens durables ou permanents**
  - Néant
- **Interventions ponctuelles**
  - AbbVie, Biogen, BMS, Celgene, Fresenius Kabi, Janssen-Cilag, Lilly, Medac, MSD, NORDIC Pharma, Novartis, Pfizer, Roche, Sanofi-Aventis, SOBI, UCB
- **Intérêts indirects**
  - Subventions de recherche: AbbVie, Lilly, MSD, Pfizer

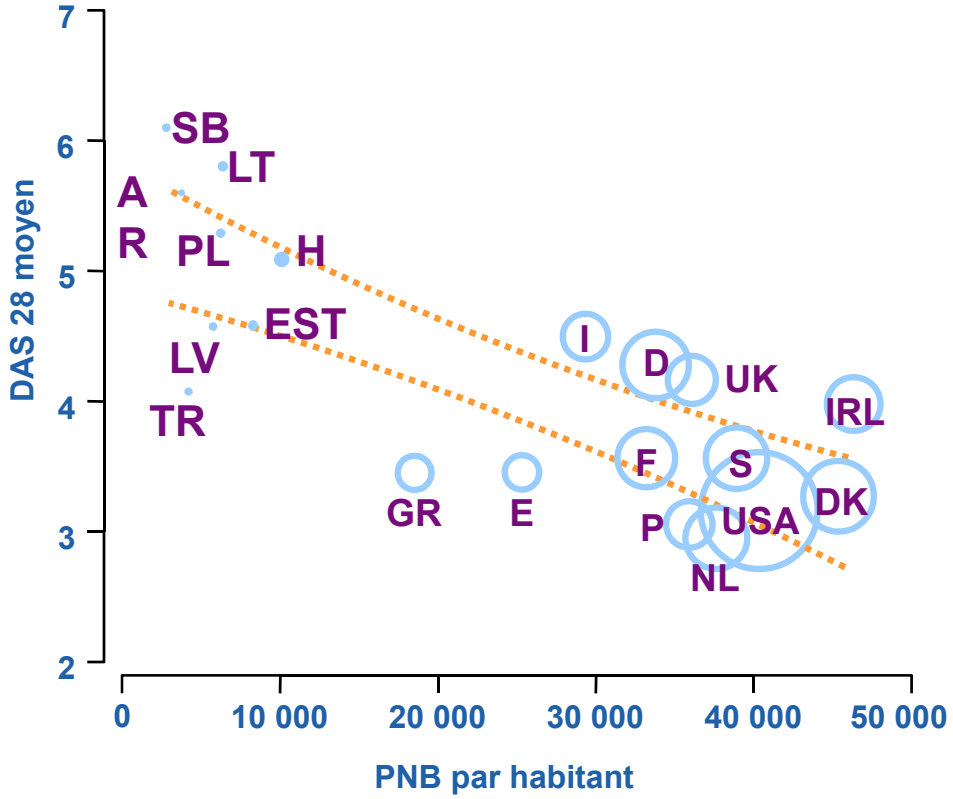
Organisation de la présentation

- **Réalité économique de la PR**
- **Evaluation médico-économique**
  - Balance entre coûts – bénéfices
- **Application à la rhumatologie et ses conséquences**
  - « Inflationnisme » du système
- **France : l'heure de la « Décroissance »**
  - Quelles sont nos marges?

Réalité économique de la PR

Bien traiter la PR a un coût

- **Etude QUEST-RA**
  - 22 pays, 62 centres
  - 5 519 PR
  - Age moyen 57 ans
  - Ancienneté PR 11 ans



Sokka T, ARD 2009

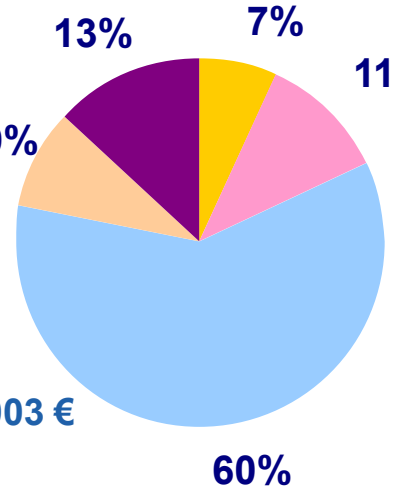
Revue systématique de la littérature

"CoI studies"

	Weighted mean [IQR] (Euros - €)
Direct costs	
Health care costs	**4,170** [2756-4561]
. Outpatient costs	2,981 [1754-3660]
. Inpatients costs	1,243 [446-1649]
Patient & family costs	**2,284** [628-3092]
Costs of paid productivity loss	
Costs sick-leave	**2770** [855-2378]
Productivity costs (HCA)	**8452** [4144-11,566]
Productivity costs (FCA)	**1441** [702-1307]

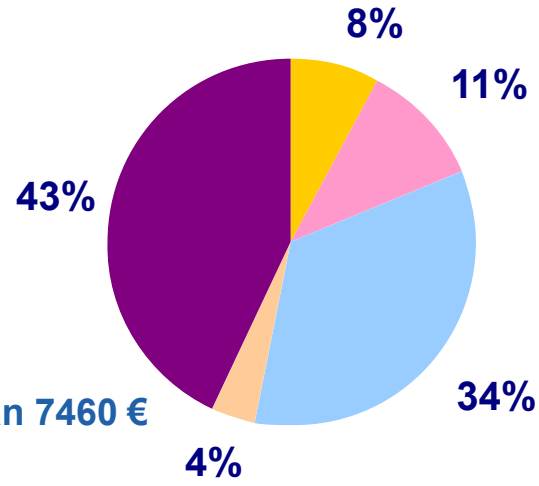
Evolution des coûts de la PR en France

PRACTIS



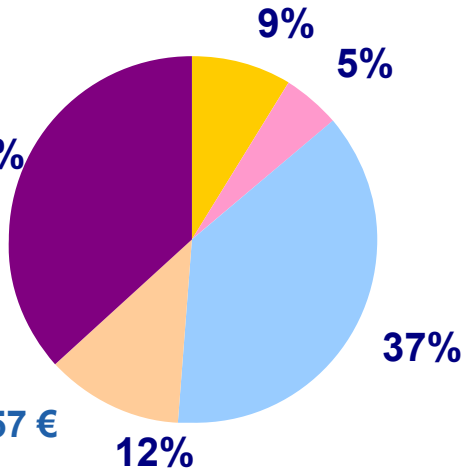
2000
1003 PR
aTNF 0%
Coût moy. an 4003 €

EURIDISS



2004
125 PR
aTNF 19%
Coût moy. an 7460 €

EcoPR



2005
1487 PR
aTNF 27%
Coût moy. an 11757 €

Cs | Ex. compl. | Hosp. | Divers | Médicaments

France : analyse base EGB

- **1234 PR, années 2009 – 2010**

Comparison of annual total per patient reimbursed health expenditures

Cost category $n = 1234$	RA patients $n = 1234$ Cost/patient (mean ± SD)	% of total cost
Outpatient care	4198 ± 5310	65.6
Drugs	*2327 ± 4106*	*36.3*
Hospitalisations	2207 ± 5552	34.4
Total	**6404 ± 8316**	**100**

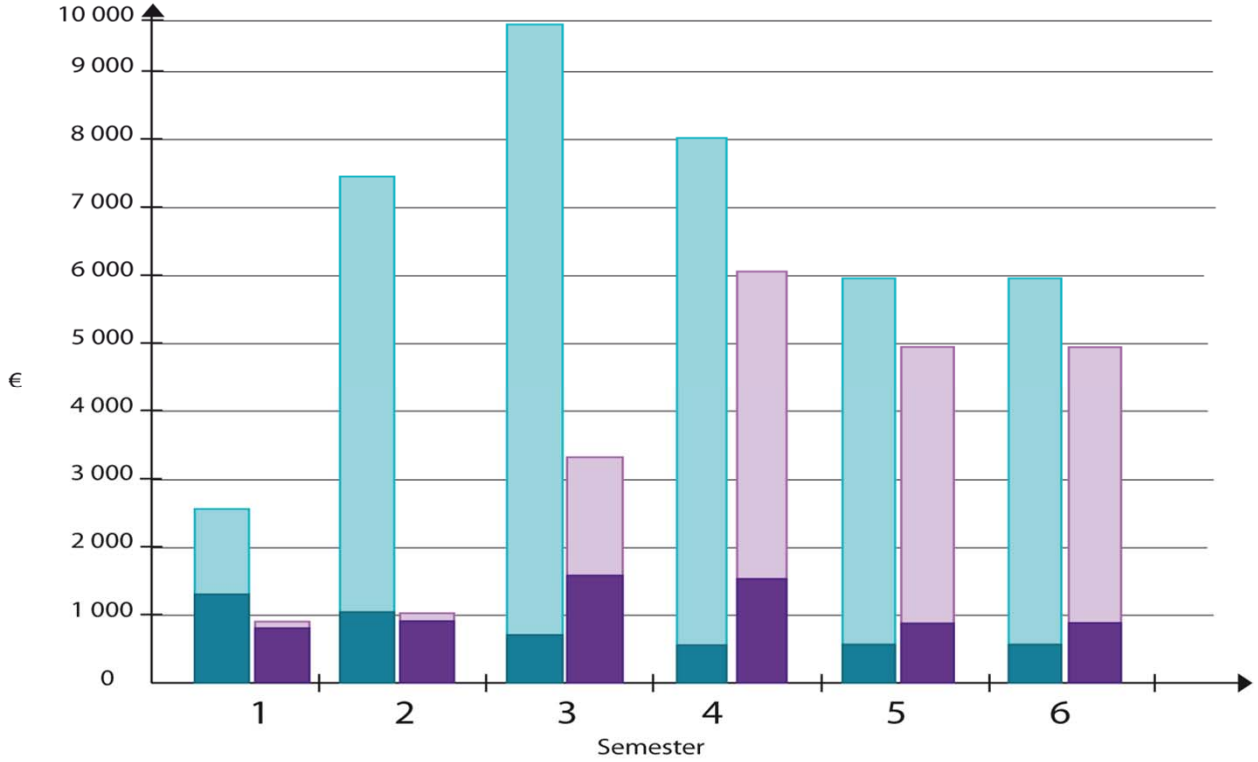
Cost category $n = 1234$	Control $n = 3810$ Cost/patient (mean ± SD)	% of total cost
Outpatient care	1791 ± 3367	57.8
Drugs	*640 ± 1500*	*20.7*
Hospitalisations	1304 ± 4883	42.1
Total	**3095 ± 6979**	**100**

Cost category $n = 1234$	Difference Cost/patient (mean)
Outpatient care	2407
Drugs	*1687*
Hospitalisations	903
Total	**3308**

Focus sur BioTx dans ESPOIR

Initiation dans ou après la 1ère année

- 50 “early starters” *vs*. 42 “late starters”
- Mean direct costs, adjusted on HAQ



Early starters

- RA Tx
- Other costs

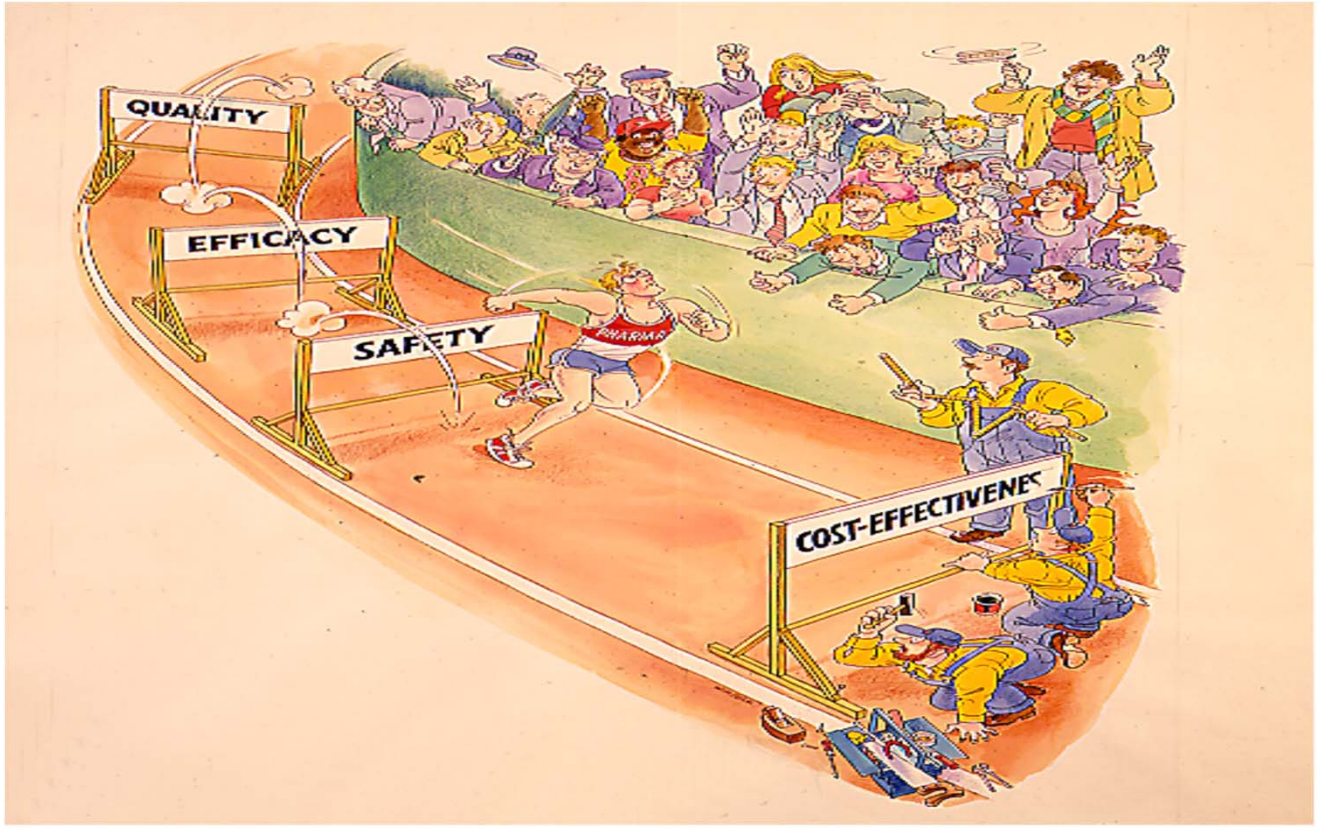
Late starters

- RA Tx
- Other costs

Evaluations médico-économiques

Evaluations médico économiques

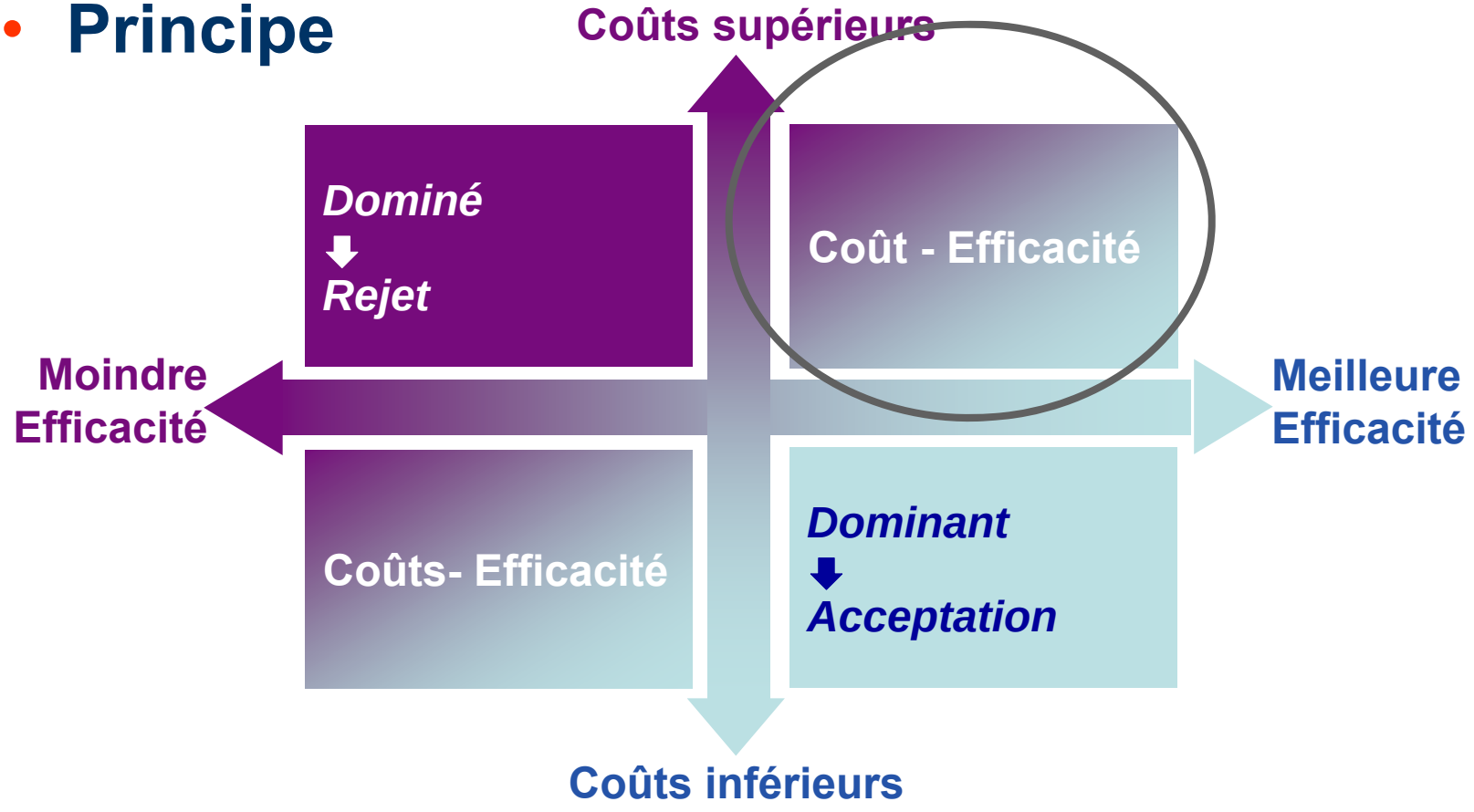
- ***Health Technology Assessment***
  - Balance entre la valeur de l'innovation
  - Et la bonne gestion de la richesse publique



Remerciements
Pr J Hans Severens

Rapport coût – efficacité : ICER

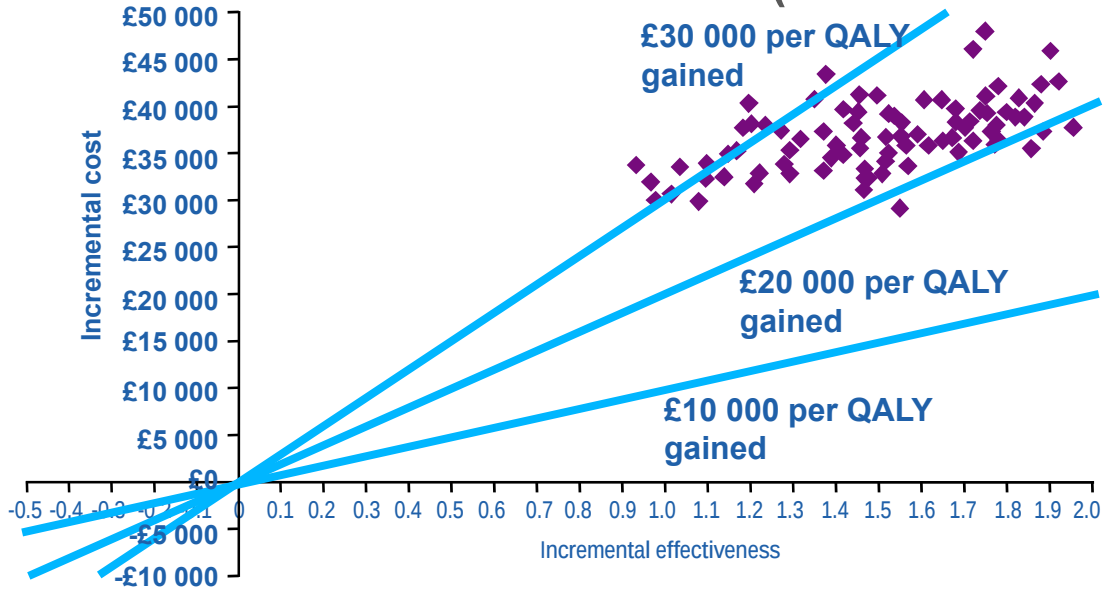
- **Principe**



ICER des anti-TNFs

PR en échec de DMARD conventionnel

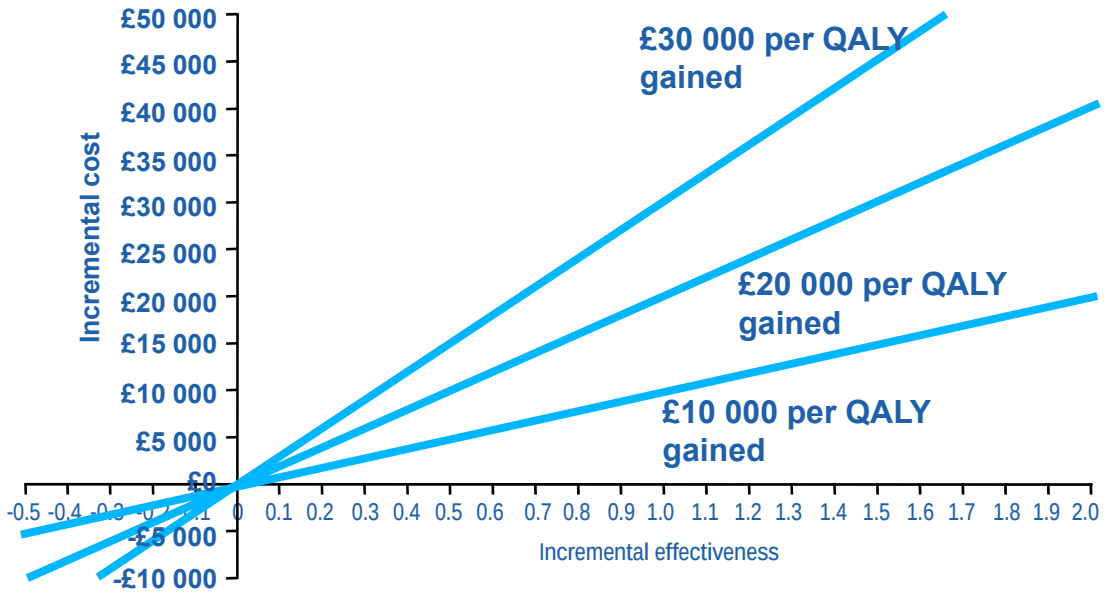
- **Modélisation à partir du registre britanniques des biothérapies (BSR BR) : 7 083 PR sous anti-TNF - 870 PR témoins**
  - Modélisation fondée sur
    - la réponse en termes de HAQ (transformé en QALY)
    - et la consommation de soins (coûts directs)



Brennan, *Rheumatology 2007*

ICER bDMARD

- **PR en 1ère ligne de traitement**



Van den Hout, Arthritis Care Res 2009

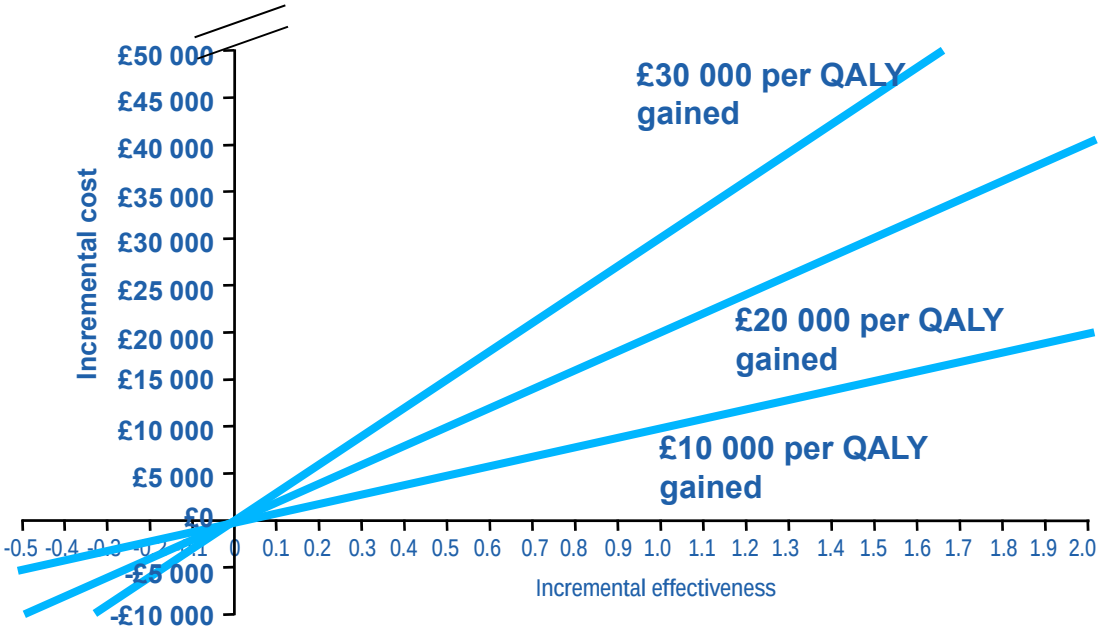
ICERs TTT

ETA d'emblée

MTX puis ETA Step-up

- **Triple association csDMARDs**

MTX + TriTx Step-up



Van den Hout, Arthritis Care Res 2009

Limites des évaluations médico-économiques

Dilemme Hépatite C: ICER Sofosbuvir

Annals of Internal Medicine ORIGINAL RESEARCH

Cost-Effectiveness of Novel Regimens for the Treatment of Hepatitis C Virus

Mehdi Najafzadeh, PhD; Karin Andersson, MD; William H. Shrank, MD, MSHS; Alexis A. Krumme, MS; Olga S. Matlin, PhD; Troyen Brennan, MD, JD, MPH; Jerry Avorn, MD; and Niteesh K. Choudhry, MD, PhD

Table 2. Base-Case Results*

Treatment Strategy, by Genotype	Cost, $	Effectiveness, *QALYs*	Incremental Cost Relative to Usual Care, *change in $*
Genotype 1			
BOC–RBV–PEG (usual care)	100 926 (94 766 to 108 470)	11.28 (10.66 to 11.98)	Reference
SOF–RBV–PEG	120 648 (115 949 to 125 548)	12.19 (11.55 to 12.85)	19 722 (13 651 to 24 185)
SOF–SMV (PEG-free regimen)	171 023 (166 580 to 176 401)	12.26 (11.62 to 12.95)	70 097 (64 063 to 74 878)
SOF–DCV (PEG-free regimen)	169 747 (165 406 to 174 669)	12.36 (11.71 to 13.11)	68 821 (62 574 to 73 859)
SOF–LDV (PEG-free regimen)	115 358 (111 095 to 120 379)	12.40 (11.77 to 13.08)	14 432 (8396 to 19 489)
Genotype 2			
RBV–PEG (usual care)	54 005 (48 633 to 60 897)	11.86 (11.20 to 12.61)	Reference
SOF–RBV (PEG-free regimen)	109 958 (105 544 to 114 729)	12.37 (11.70 to 13.09)	55 953 (50 878 to 59 769)
SOF–DCV (PEG-free regimen)	316 845 (311 645 to 322 857)	12.24 (11.53 to 12.99)	262 840 (257 326 to 267 722)
Genotype 3			
RBV–PEG (usual care)	58 323 (52 027 to 65 999)	11.50 (10.90 to 12.23)	Reference
SOF–RBV (PEG-free regimen)	207 872 (201 623 to 215 794)	11.37 (10.74 to 12.09)	149 549 (145 381 to 154 820)
SOF–DCV (PEG-free regimen)	317 830 (312 217 to 325 029)	12.16 (11.43 to 12.94)	259 507 (253 615 to 265 813)
SOF–LDV–RBV (PEG-free regimen)	120 464 (115 543 to 125 573)	12.35 (11.68 to 13.07)	62 141 (53 101 to 70 163)

BOC = boceprevir; DCV = daclatasvir; LDV = ledipasvir; PEG = pegylated interferon; QALY = quality-adjusted life-year; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir.
* Numbers in parentheses are 95% credible intervals, which reflect the results of probabilistic sensitivity analysis.

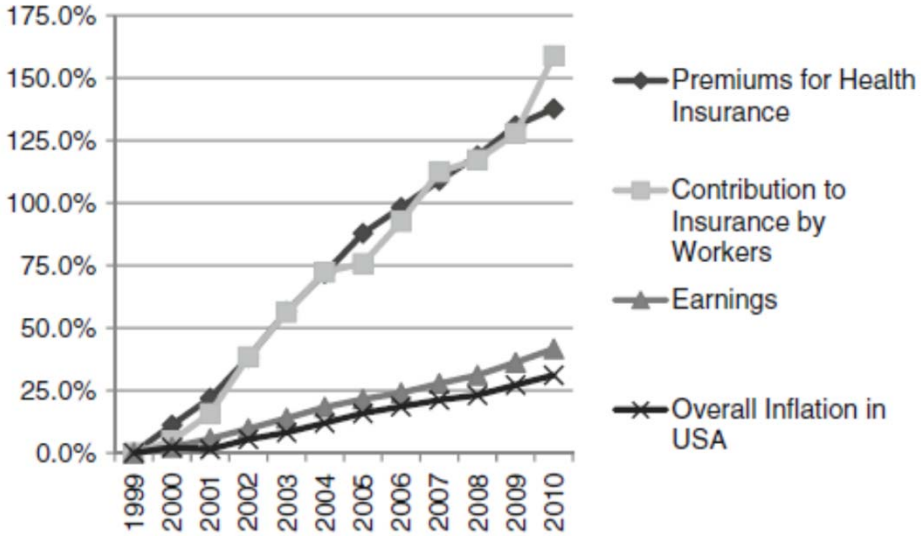
Evaluation de la CEESP

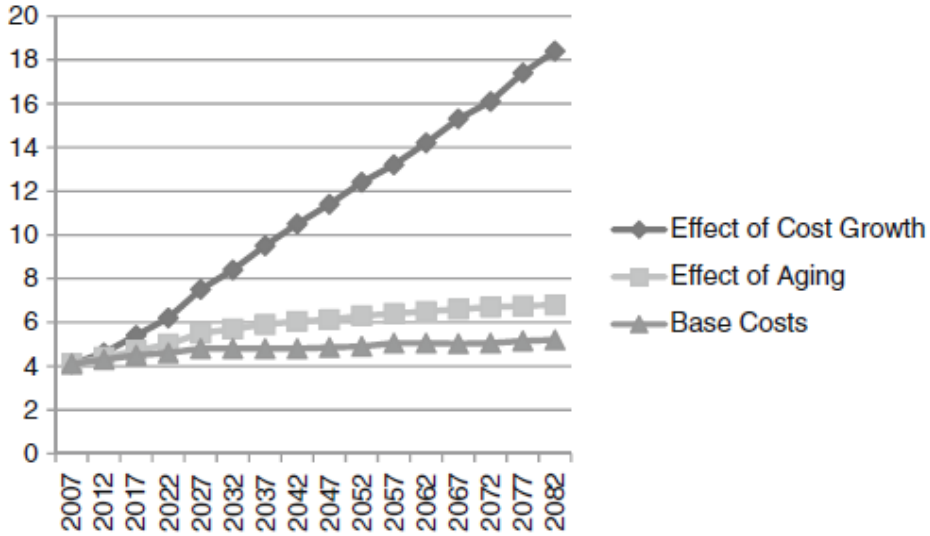
		ADEMPAS	KADCYLA	SOVALDI	TIVICAY
INDICATION FOR ASSESSMENT		Pulmonary Hypertension	HER2 positive locally advanced cancer	Chronic Hepatitis C	Human Immunodeficiency Virus (HIV)
TRANSPARENCY COMMISSION	SMR	MOD.	IMP.	IMP.	IMP.
	ASMR*	IV	II	II	IV
# OF CEESP RESERVES	MINOR	6	2	8	10
	IMPORTANT	4	0	8	1
	MAJOR	4	0	1	0

Lévy P, personal communication

Tendance inflationniste

- **Innovation thérapeutique : forcément inflationniste**





Cornes P, Targ Oncol 2012

Une nouvelle « haie »

Lévy P, personal communication

Quelles sont les marges?

Cut the drug

Or

Cut the dose

Or

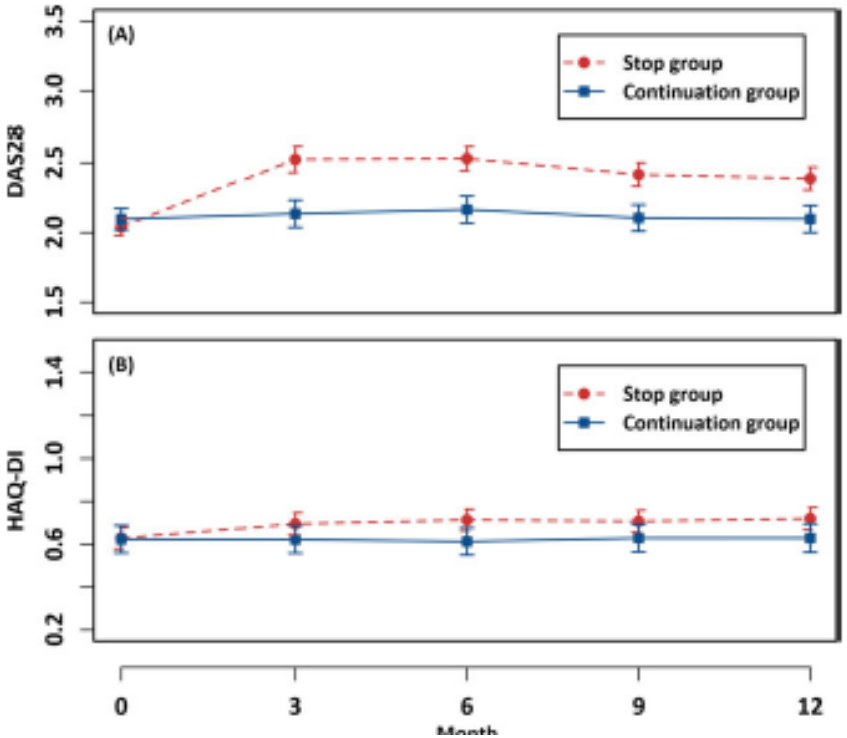
Cut the price

“Cut the dose” : Vacances thérapeutiques

	Molécule	Caractéristiques Patients	Rémission À 1 an
Nice *(Brocq, Rheumatology 2009)*	**Anti-TNF**	**21 RA** **DAS28 < 2.6 ; > 6 mo**	**25 %**
RRR *(Tanaka, ARD 2010)*	**IFX**	**114 RA** **DAS28 < 3.2 ; > 6 mo**	**49 %**
HONOR *(Tanaka, ACR 2012)*	**ADA**	**197 RA** **DAS28 < 2.6 ; > 6 mo**	**38 %** **(LDA 19%)**
ADMIRE *(Chatzidionysiou, ACR 2012)*	**ADA**	**31 RA** **DAS28 < 2.6 ; > 3 mo**	**40 %** (6 mo)
ORION (LTE) *(Takeuchi, ACR 2012)*	**ABA**	**34 RA** **DAS28 < 2.6 ; > 6 mo**	**41 %**
DREAM (LTE) *(Nashimoto, EULAR 2010)*	**TCZ**	**187 RA** **DAS28 < 3.2 ; > 6 mo**	**13 %**
OPTION (LTE) *(Vargas-Serafin, ACR 2012)*	**TCA**	**45 RA** **DAS28 < 2.6 ; > 6 mo**	**40 %**

Cut the drug

- **Essai POET: Arrêt étanercept**
  - Impact clinique



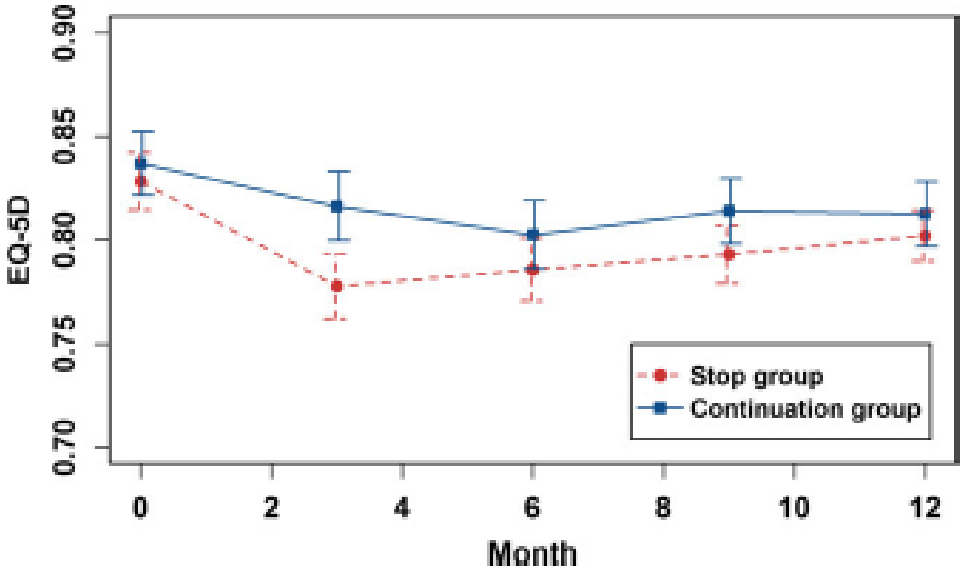
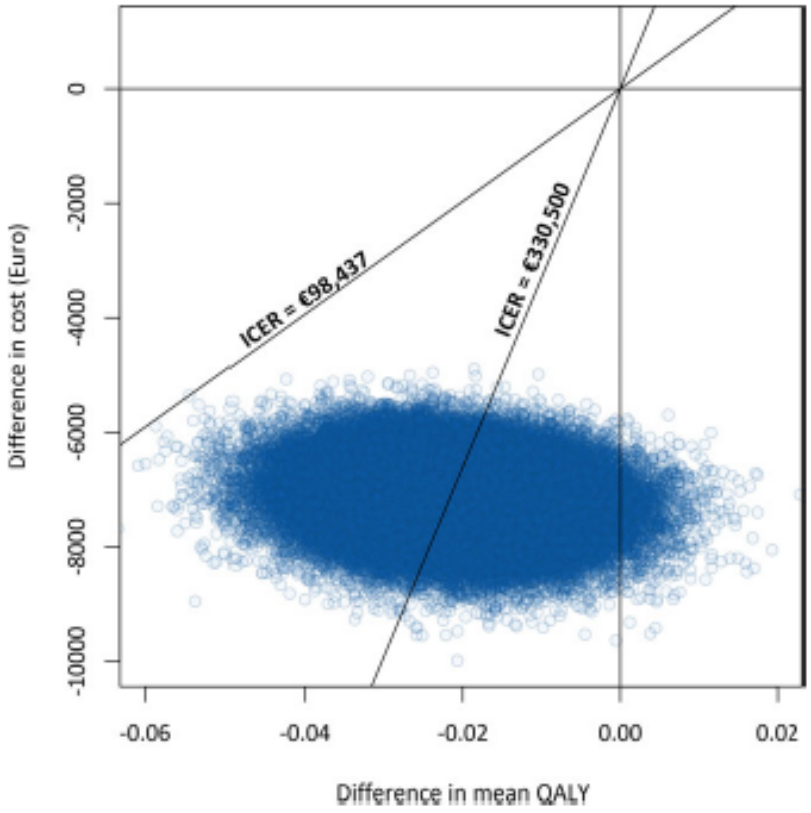


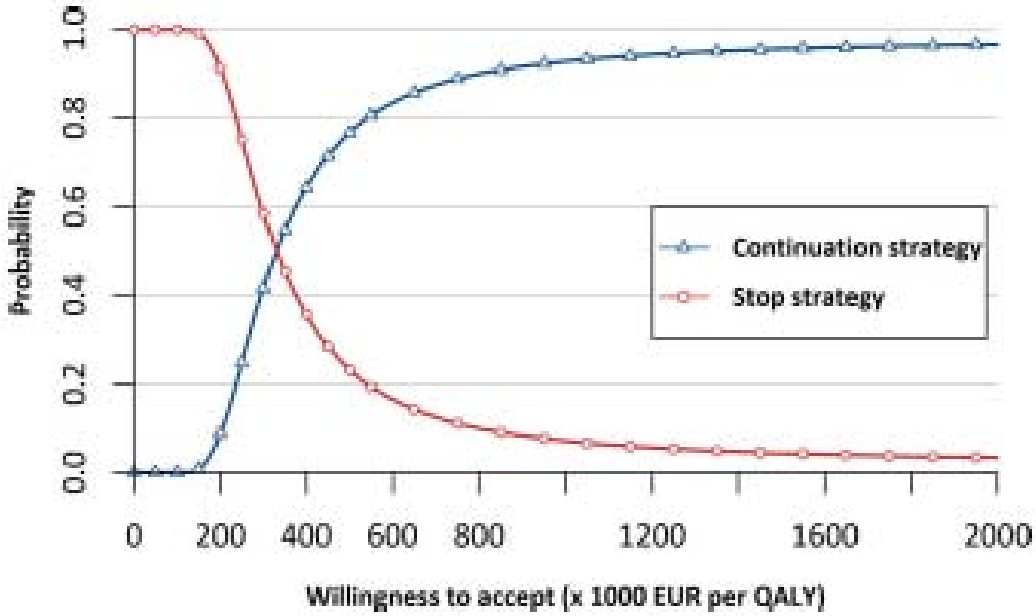
Figure 2. Mean EuroQol 5-domain (EQ-5D) 3-level measure scores at different points in time during the 1-year follow-up in the 2 treatment groups. Vertical bars represent 95% confidence intervals.

Tran-Duy A et al. Arthritis Rheumatol, 2018 70;10:1557-64

Cut the drug

- **Essai POET : évaluation économique**



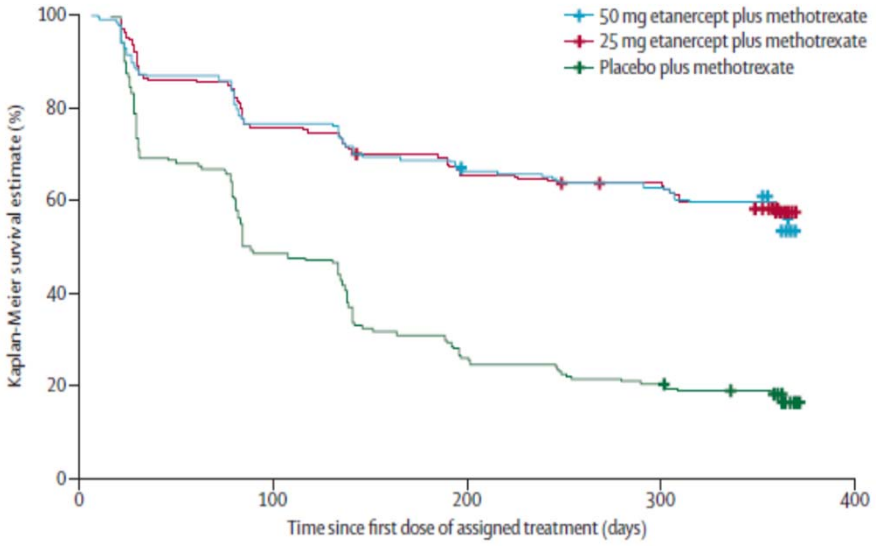


Tran-Duy A et al. Arthritis Rheumatol, 2018 70;10:1557-64

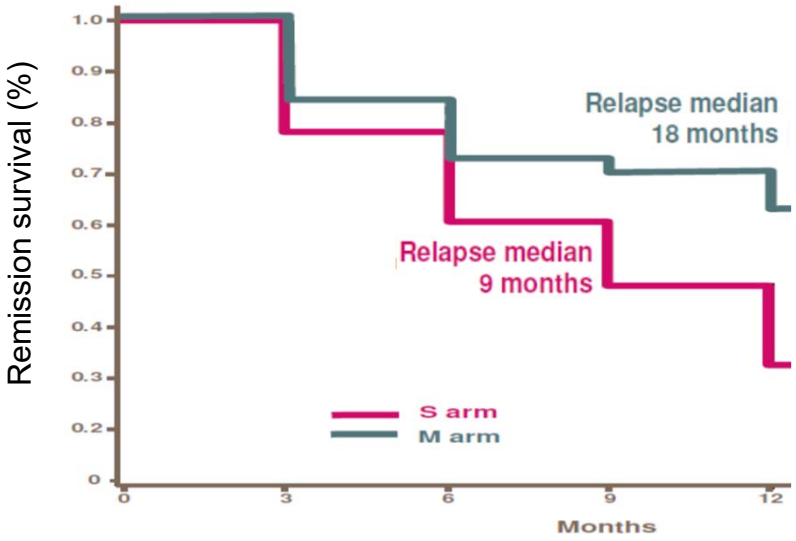
“Cut the dose”: stratégie de décroissance

- **Plusieurs essais : PRESERVE, DOSERA, DRESS, STRASS, RETRO**

PRESERVE trial: 604 RA patients with DAS28 ≤ 3.2
FLARE (DAS28 > 3,2 and Δ DAS28 > 0,6)



STRASS trial: 138 RA patients with DAS28 ≤ 2.6
FLARE (DAS28 > 2.6 and ΔDAS28 > 0.6)



Smolen JS, et al. Lancet 2013
Fautrel B et al. EULAR 2013

Cut the dose

- **Essai STRASS: faisabilité de l'espacement**

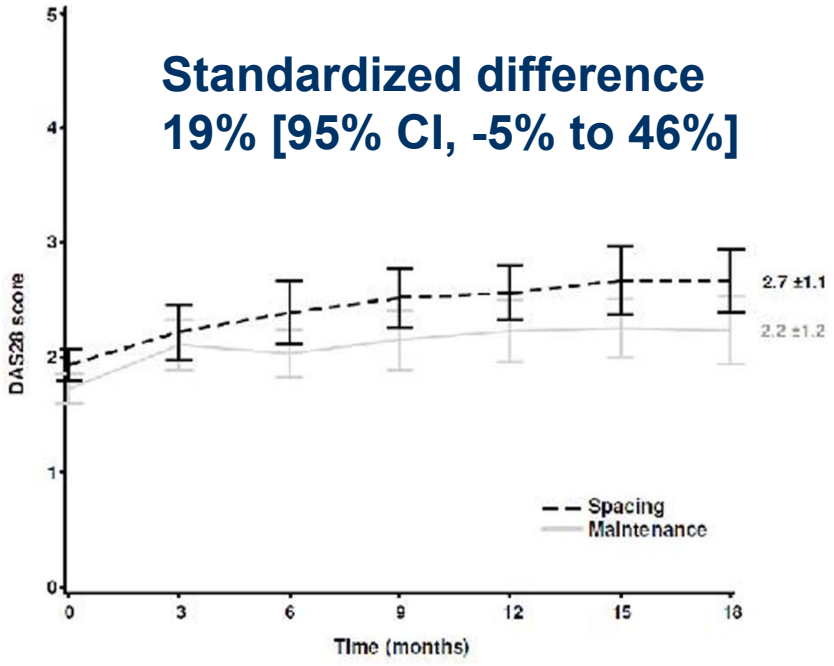
	Arm S N = 64	Arm M N = 73
Anti-TNF regimen	**N (%)**	
Step 0 (ETA /7d – ADA / 14d)	**13 (20.3 %)**	**65 (89.5 %)**
Step 1 (ETA / 10d – ADA / 21d)	**6 (9.4 %)**	**-**
Step 2 (ETA / 14d – ADA / 28d)	**7 (10.9 %)**	**-**
Step 3 (ETA / 21d – ADA / 42d)	**10 (15.6 %)**	**-**
Step 4 (full stop)	**25 (39.1 %)**	**-**
Withdrawal	**6 (9.4 %)**	**7 (9.5 %)**
switch for another bDMARD	***1 (1.6 %)***	***1 (1.4 %)***

Fautrel B et al. Ann Rheum Dis 2015

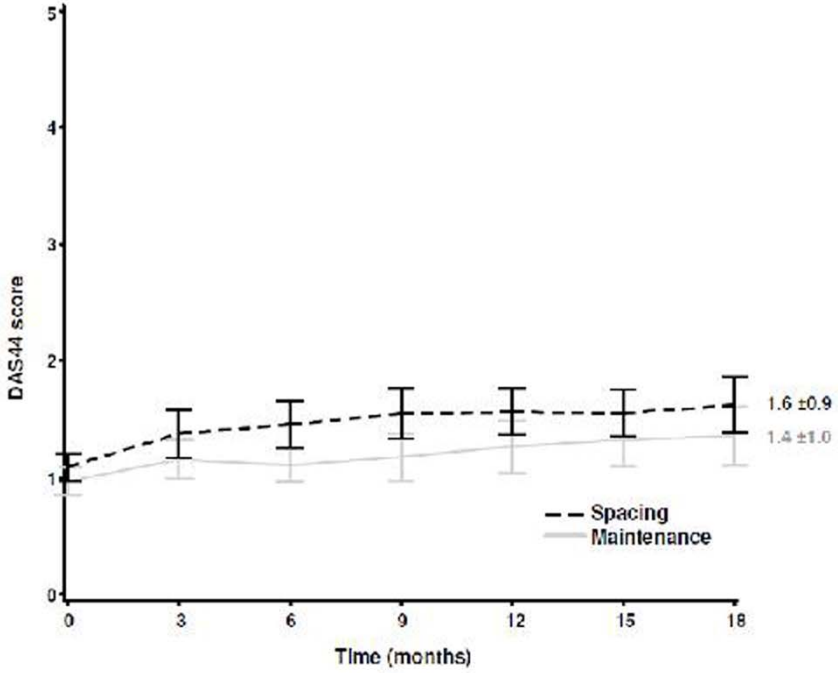
Cut the dose

- **Essai STRASS: impact clinique**

a: DAS28



b: DAS44



- **Failed to demonstrate non inferiority**

Fautrel B et al. Ann Rheum Dis 2015

Cut the dose

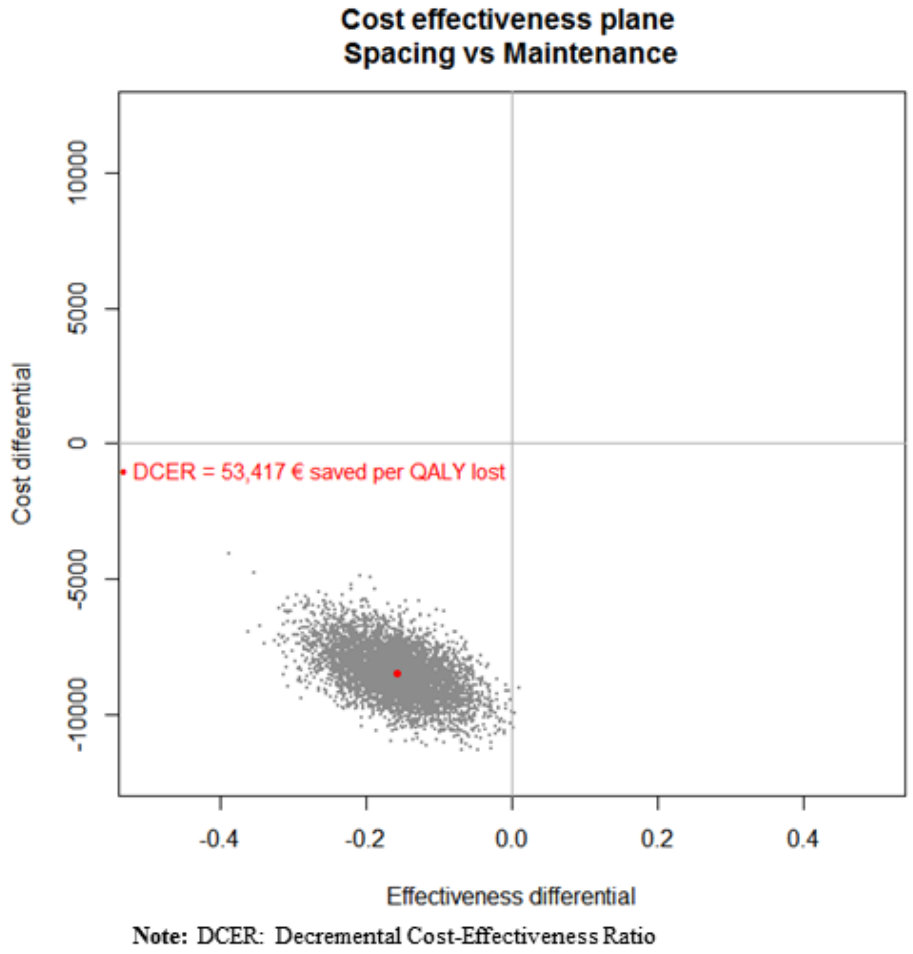
- **Essai STRASS: impact économique**

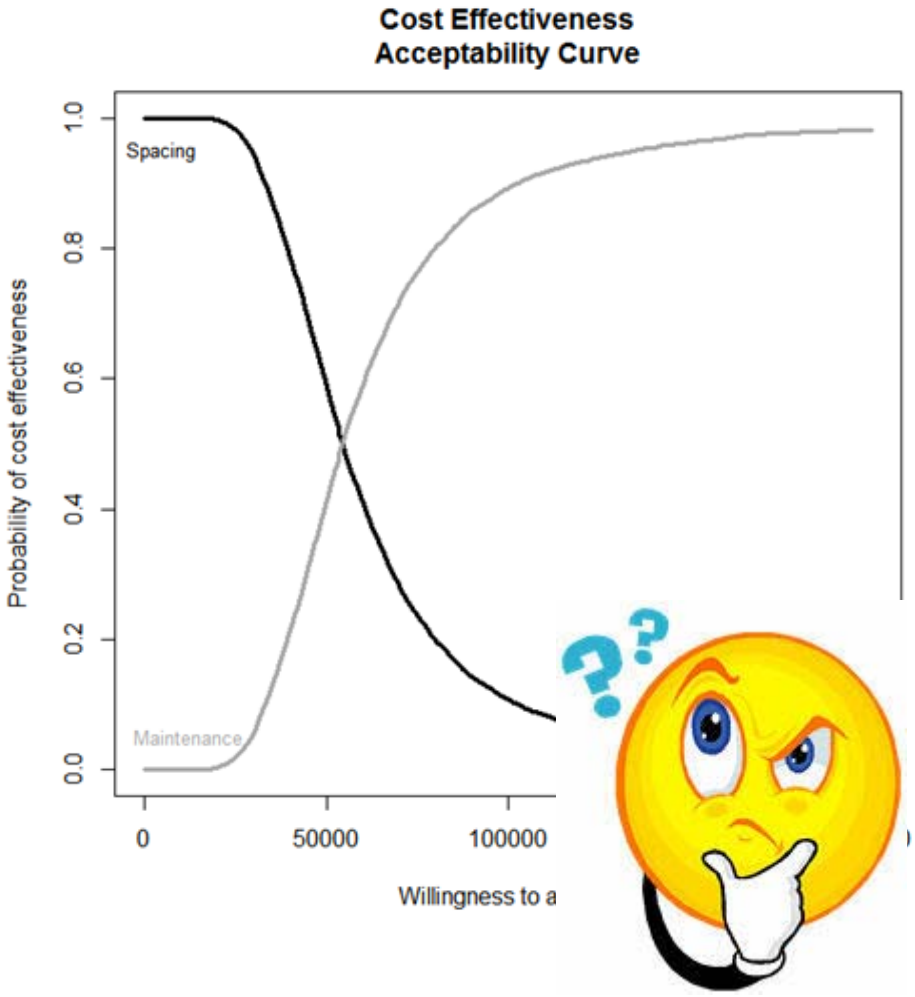
Sensitivity analysis	Mean total costs over 18 months (€)	Mean QALYs gained over 18 months	DCER (€/QALY)
	Difference	Difference	
Main analysis, Utilities scores derives from EQ-5D-3L French norms	-8,440	-0.158	53,417
Utilities scores from EQ-5D-3L UK norms	-8,440	-0.153	55,163
Utilities scores from SF-6D UK norms	-8,440	-0.059	143,051

Vanier et al, Value in Health, 2017 ;20(4):577-585

Cut the dose

- **Essai STRASS: évaluation économique**





Vanier et al, Value in Health, 2017 ;20(4):577-585

Cut the drug / dose : impact économique

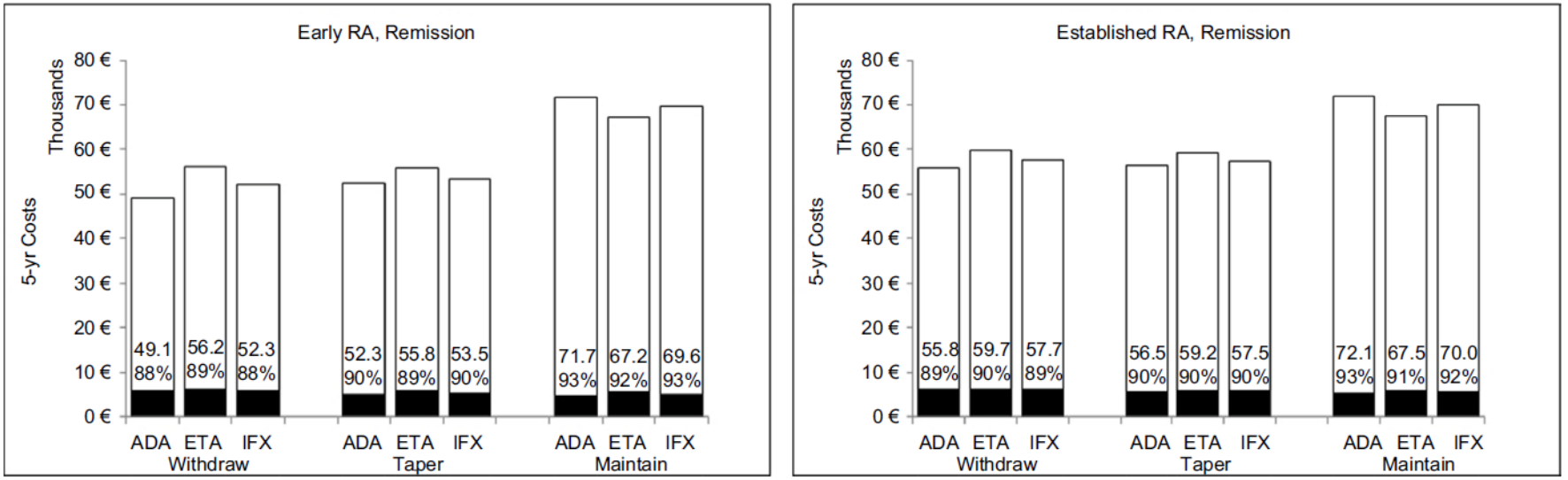


Figure 3 Total 5-year direct costs of withdrawal, tapering, and maintenance after a period of sustained remission or LDA.
Notes: Black and white portions of bars indicate mean medical and anti-TNF costs, respectively (left axis). Values within each bar indicate total costs (top, in thousands of Euros) and the proportion of costs due to anti-TNFs (bottom, in %).

“Cut the price”

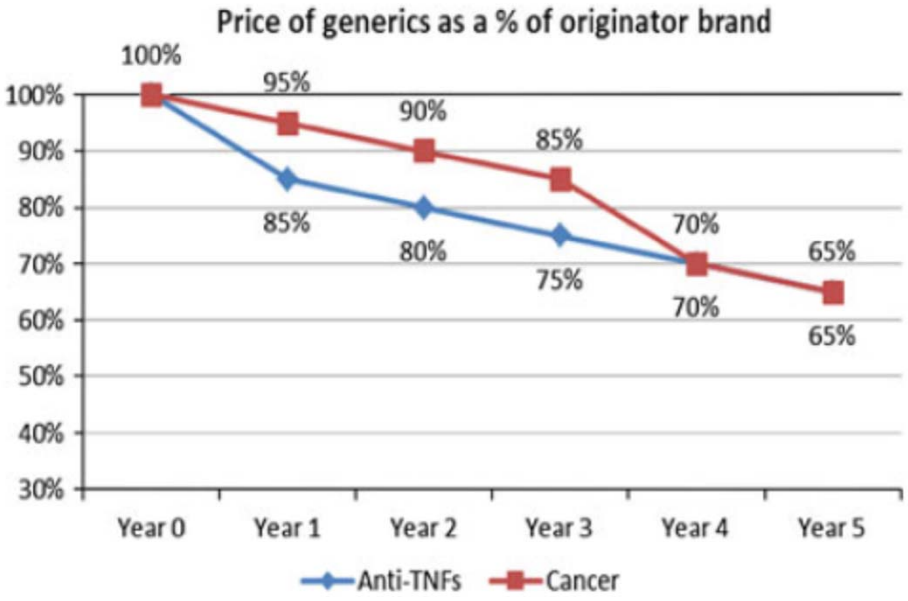
- **Plusieurs options**
  - Accord prix – volumes
  - 10 à 40% discount

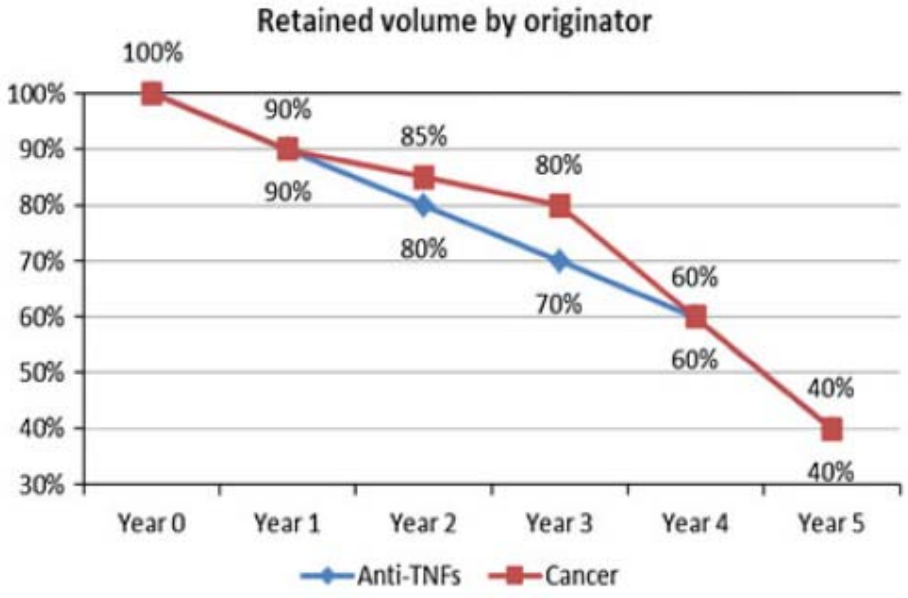
- **Partage de risque**
  - 1ers mois à la charge de la firme
  - Reversement du traitement par la firme si arrêt dans les 3 mois après prescription initiale (échecs primaires)

- **Biosimilaires**
  - Développement clinique allégé
  - Discount 10 à 40% (70% pour les génériques)

Estimation du NHS (UK)

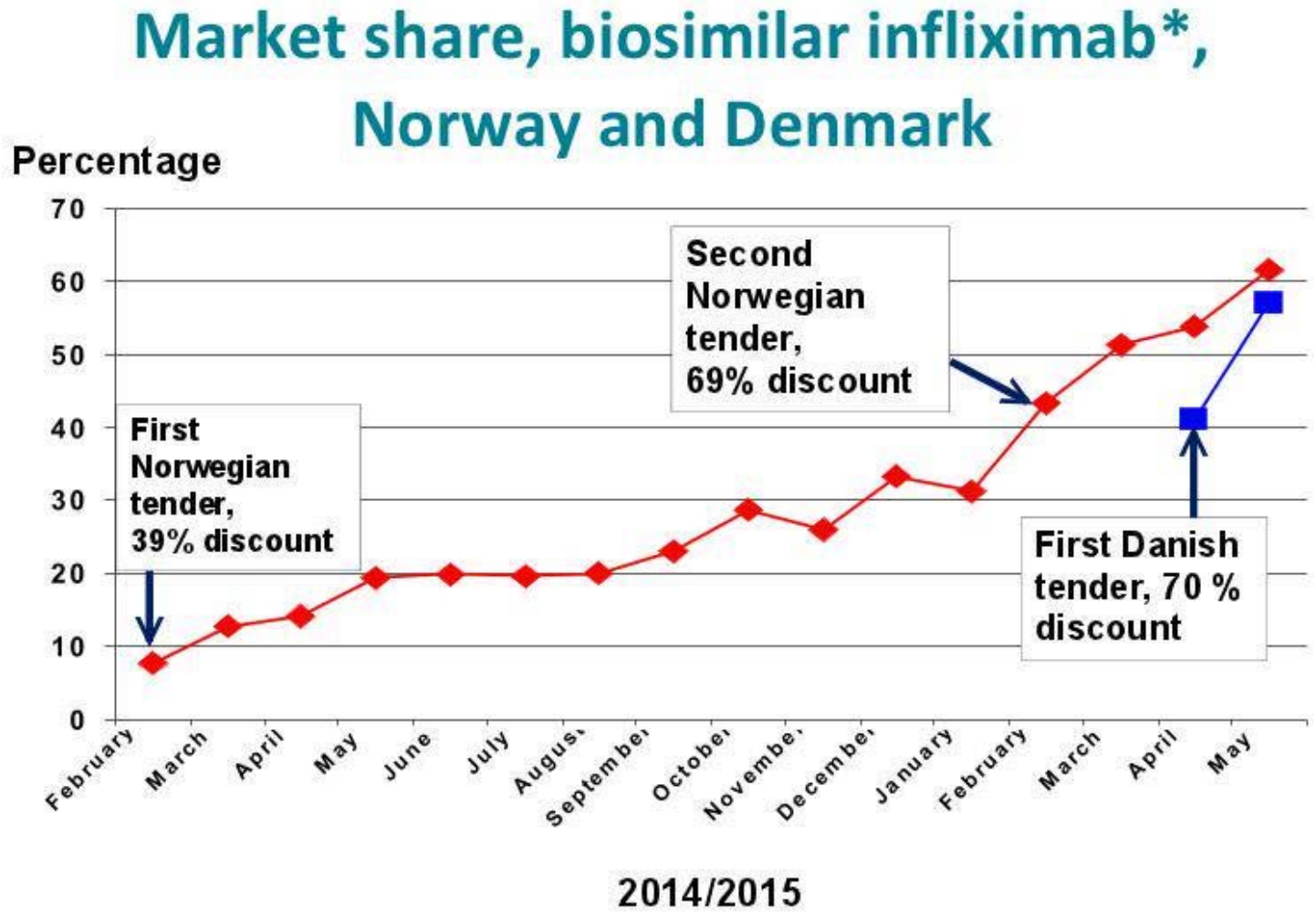
- **Evolution des prix des bDMARDs**
  - Biosimilaires et princeps





O'Neill P, PharmacoEconomics 2013

Pénétration du marché par Infliximab-bs

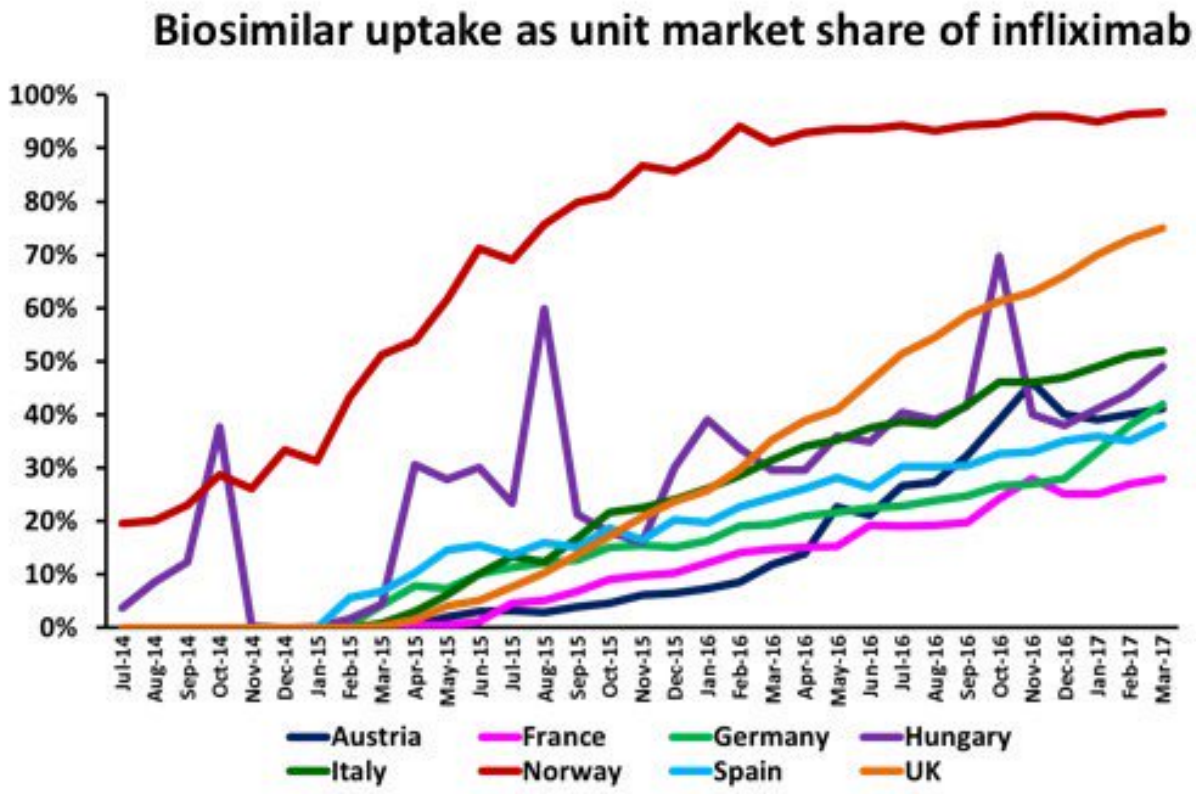


*Based on vials sold

Farmastat

Pénétration du marché par Infliximab-bs

- **Vision européenne**



Created from IMS MIDAS Unit Sales data by month (March 2017)

Dernière alternative : « cut the system »

- **Accepter l'inflation sur l'innovation**
- **Réduire les coûts ailleurs**
  - Réduire le poids des hospitalisations -> Virage ambulatoire
  - Réguler certaines prescriptions d'examens complémentaires
  - Limiter les conséquences du handicap, favoriser le retour au W
  - …
- **Tensions en perspective dans le secteur de la santé…**

« Where To From Here » ??

Complexe… mais pas désespéré !

- **Laisser faire**
  - Evolution à l'anglaise si l'autorité publique prend la main
  - Evolution à l'américaine si les acteurs privés sont leaders

- **Attitude proactive pour une pérennité du système**

Merci

Historical Vignette

The Salpêtrière Hospital in Paris and Its Role in the Beginnings of Modern Rheumatology

IRVING KUSHNER, MD, Professor Emeritus of Medicine, Department of Medicine, Division of Rheumatology, Case Western Reserve University at MetroHealth Medical Center, Cleveland, Ohio, USA. Address correspondence to Dr. I. Kushner, MetroHealth Medical Center, Cleveland OH 44109; E-mail: ixk2@case.edu. J Rheumatol 2011;38:1990–3; doi:10.3899/jrheum.101320

The Journal of Rheumatology

The Journal of Rheumatology Volume 38, no. 9

In the early hours of the morning of August 31, 1997, Diana, Princess of Wales, was a passenger in a Mercedes-Benz being driven at high speed through the fashionable 8th Arrondissement of Paris. Passing through a tunnel along the Seine River, the vehicle ran into a wall. An ambulance took her to the decidedly unfashionable 13th Arrondissement, where she was pronounced dead about 2 hours later at La Salpêtrière Hospital.

La Salpêtrière, or saltpeter works (intriguing name for a hospital!), the largest hospital in Paris, has a fascinating history. About 400 years ago, an arsenal for the manufacture of munitions was relocated to the present Salpêtrière site from across the river. Since gunpowder is largely a mixture of sulfur and saltpeter (KNO_3), the site was referred to as the saltpeter works. This appellation has been applied to the successive institutions that have stood on this site, and persists to this day.

Under Louis XIV, who reigned from 1643 to 1715, a large proportion — estimated as high as 10% — of the Paris popu-

Figure 1. La Salpêtrière toward the end of the 17th century. From Goudon de Genouillac. Paris a travers les siecles. Paris; 1882. Courtesy Musée de la civilisation, bibliotheque du Séminaire de Quèbec, fonds ancien.