

Hépatite C

Problème de santé publique

- 170 M dans Monde
- 3% population mondiale
- 1 M nouveaux cas/an
- 3 M aux US / 300 000 France
-

Evolution

- Cirrhose
- Hépatocarcinome
-

Traitement

- Interféron α pégylé (pegIFN)
- Ribavirine
- 48 semaines: Génotype HCV 1 et 4
- 24 semaines: Génotype HCV 2 et 3

Coût

- Effets indésirables:
- Troubles dépressifs
 - Thrombopénie, anémie
 -

Génotype 2
Génotype 3
70 – 90 %

Génotype 1 (++ pays industrialisés)
Génotype 4
< 50 %

Variabilité Interindividuelle +++

- Age
- Sexe
- Origine ethnique
- Facteurs de co-morbidité
- Fibrose hépatique
- Charge virale initiale
- Evolution charge virale (cours TRT)
- Statut génétique des patients ++++
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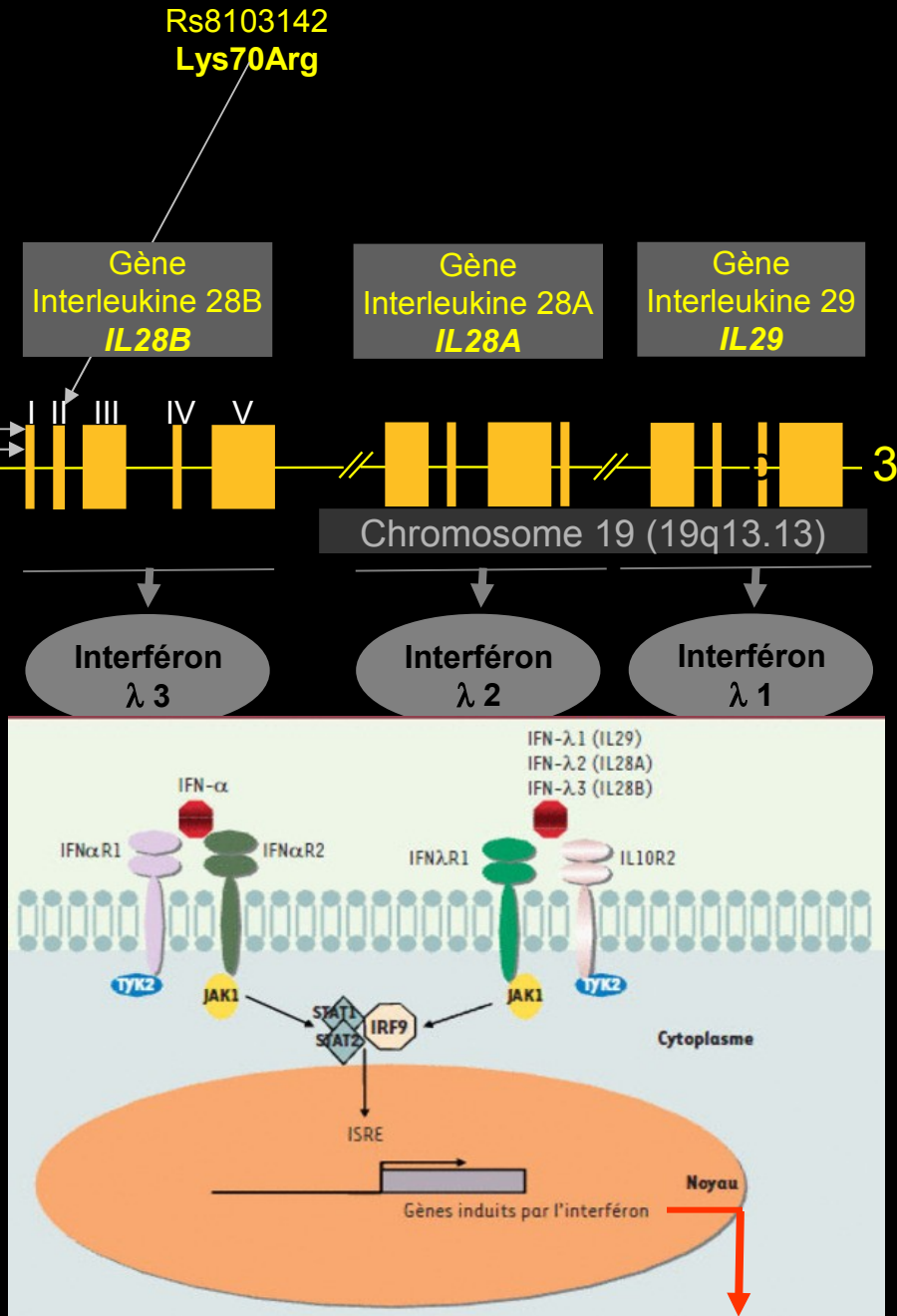
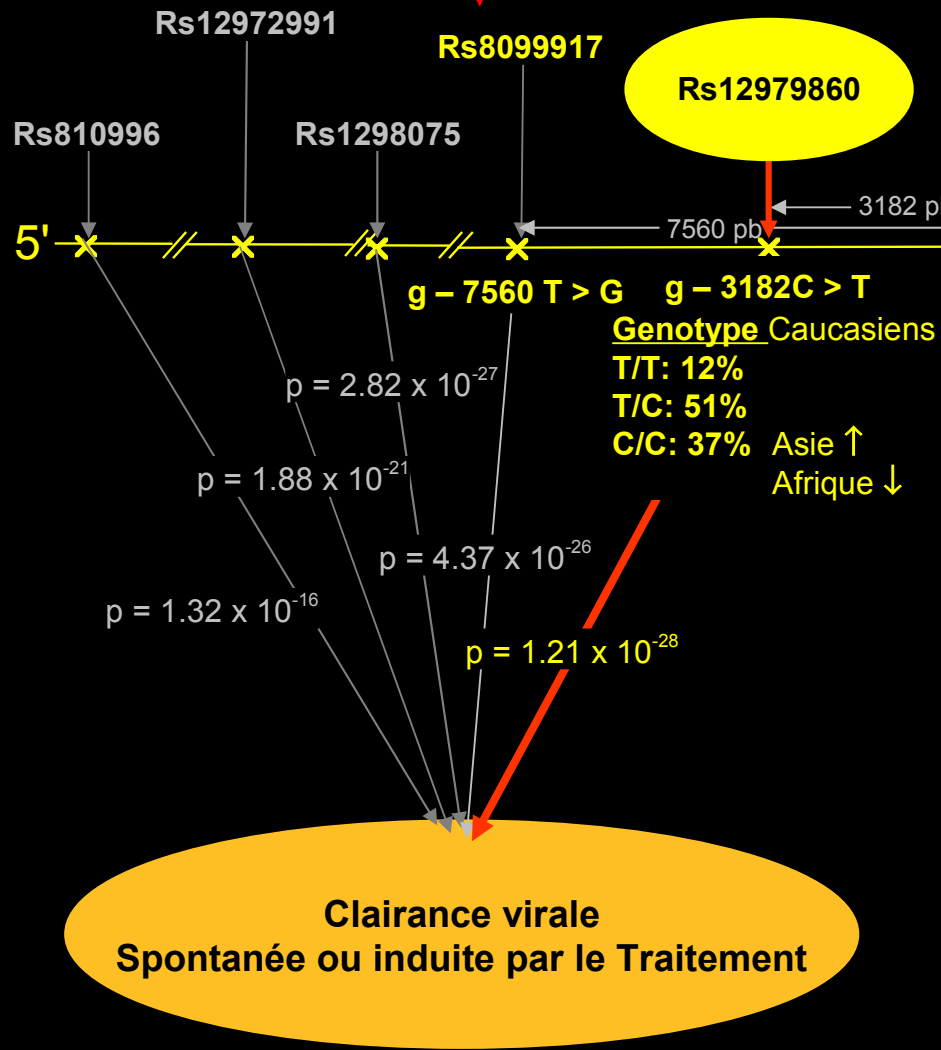
RVS

Réponse Virale Soutenue

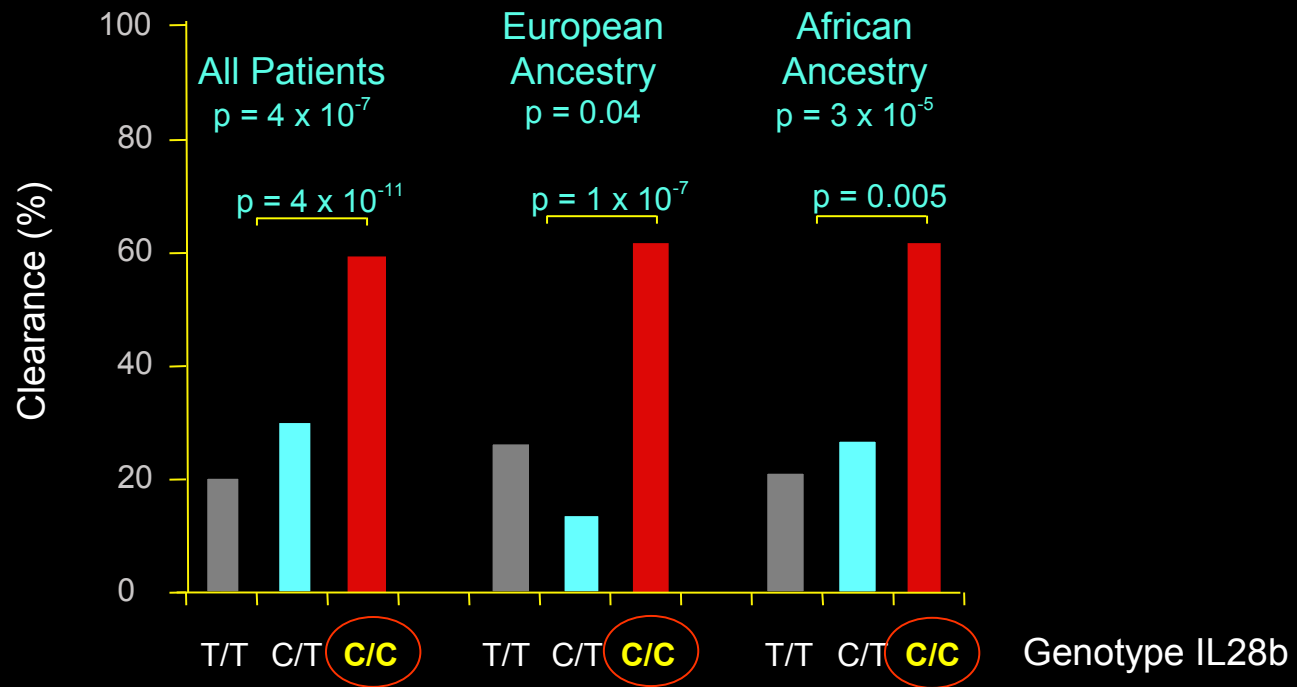
Genome Wide Association Studies (GWAS)

- 1 - Ge D et al., Nature 2009; 461 : 391–401.
- 2 - Tanaka Y et al., Nat Genet 2009; 41 : 1105–9.
- 3 - Suppiah V et al., Nat Genet 2009; 41 : 1100–4.
- 4 - Rauch A et al., Gastroenterology. 2010; 138 : 1338-45.

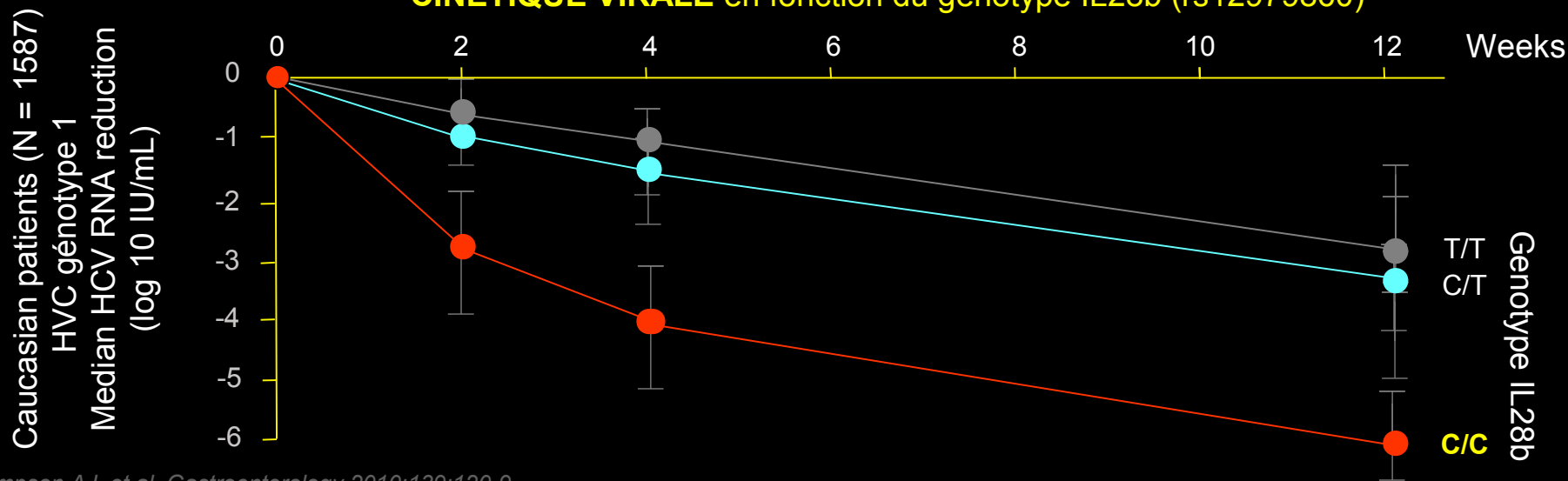
Caucasian, African-American, Hispanic, Japanese
HCV genotype 1



Influence du génotype IL28b (rs12979860) sur la CLAIRANCE SPONTANEE du VHC

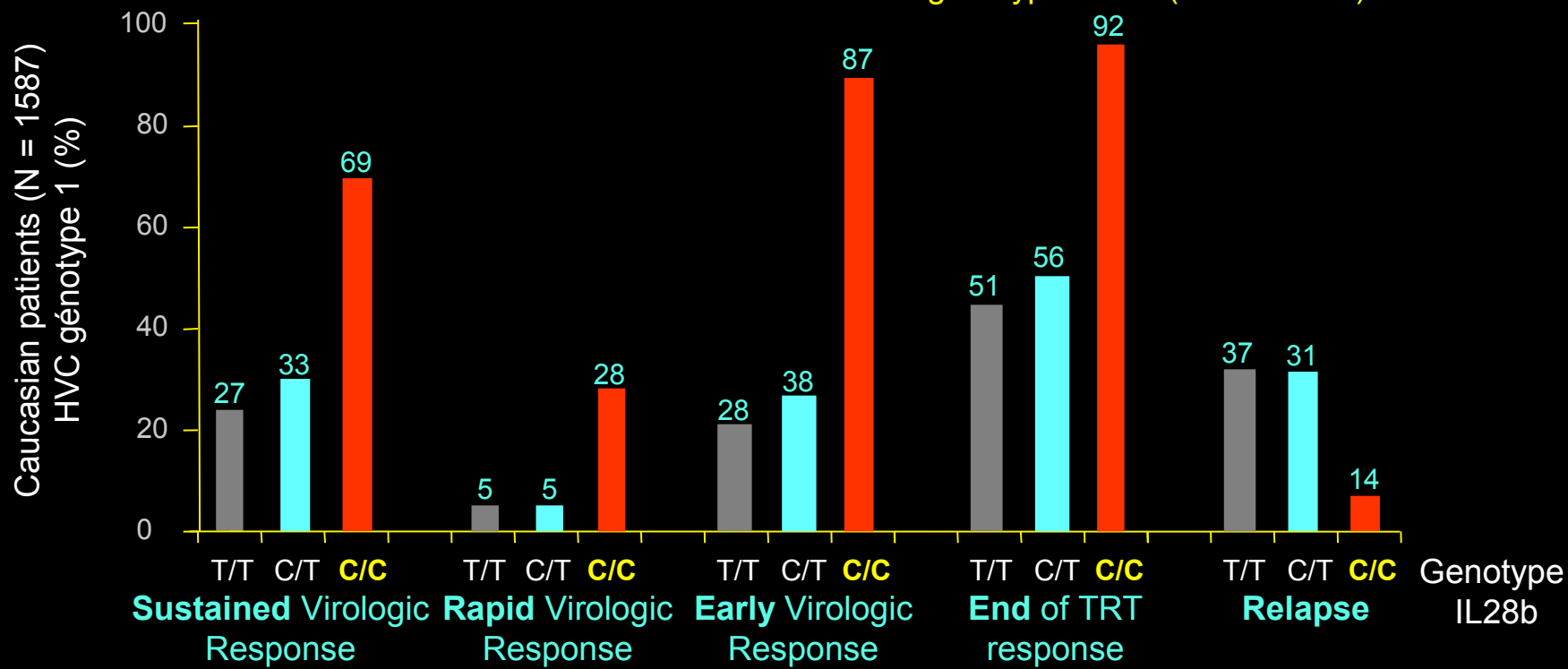


CINETIQUE VIRALE en fonction du génotype IL28b (rs12979860)



Thompson AJ, et al. *Gastroenterology* 2010;139:120-9

REPONSE VIROLOGIQUE en fonction du génotype IL28b (rs12979860)



Le génotype IL28b est le meilleur facteur prédictif préthérapeutique de RVS chez les patients ayant une hépatite C de génotype 1

FACTEURS PRETHERAPEUTIQUES associés à la RVS (analyse multivariée)

	Odds Ratio	IC 95%	P
Genotype C/C vs non-C/C (rs12979860)	5.2	4.1 – 6.7	< 0.0001
Charge viral < vs > 600 000 UI/ml	3.1	2.3 - 4.1	< 0.0001
Caucasiens vs afro-américains	2.8	2.0 – 4.0	< 0.0001
Hispaniques vs afro-américains	2.1	1.3 – 3.6	0.004
METAVIR F012 vs F3F4	2.7	1.8 – 4.0	< 0.0001
Glycémie à jeun < vs > 5.6 mmol/l	1.7	1.3 – 2.2	< 0.0001

Des études prospectives sont encore nécessaires pour qu'il soit inclus définitivement aux recommandations thérapeutiques

Influence du génotype IL28B dans les nouvelles stratégies thérapeutiques DAA (Directly acting antiviral agent)

Arrivée des DAA

A ajouter à la bithérapie standard pour limiter l'apparition de résistance

Inhibiteurs des protéases NS3-4A du HCV (telaprevir et boceprevir)

Inhibiteurs de la polymérase NS5B du HCV

Inhibiteurs NS5A du HCV

Inhibiteur de la cyclophilin A Debio-025 (alisporivir)

.....

Ajout d'un inhibiteur de protéase n'est pas sans problèmes additionnels

Coût supplémentaire

Effets indésirables Fatigue, fièvre, maux de tête, nausée, anémie,
mauvais dysgueusie, rash cutané...

Virus résistance

**Sustained Viral Responses by *IL28B* genotype (rs12979860)
SPRINT-2 and RESPOND-2 phase 3 trials of BOCEPREVIR**

Trial cohort SPRINT – 2

Treatment - naïve patients

HCV Genotype 1 infection
N = 1097

Sustained Virological Response (SVR)
Undetectable virus level 24 weeks after the end of treatment_
Overall C/C C/T T/T

<u>Control</u> pegIFN/ribavirin (48 weeks)	38%	78%	28%	27%
pegIFN/ribavirin + Boceprevir Response Guided Therapy (stop 28 weeks)	63%	82%	65%	55%
pegIFN/ribavirin (4 weeks) followed by pegIFN/ribavirin/Boceprevir (44 weeks)	66%	80%	71%	59%

Trial cohort RESPOND - 2

Prior therapy failed with pegIFN/ribavirin

HCV Genotype 1 infection
N = 403

Sustained Virological Response (SVR)
Undetectable virus level 24 weeks after the end of treatment_
Overall C/C C/T T/T

<u>Control</u> pegIFN/ribavirin (48 weeks)	21%	46%	17%	50%
pegIFN/ribavirin + Boceprevir Response Guided Therapy (stop 36 weeks)	59%	79%	61%	55%
pegIFN/ribavirin (4 weeks) followed by pegIFN/ribavirin/Boceprevir (44 weeks)	66%	77%	73%	72%

**Sustained Viral Responses by *IL28B* genotype (rs12979860)
ADVANCE and REALIZE phase 3 trials of TELAPREVIR**

Trial cohort ADVANCE

Treatment - naïve patients

HCV Genotype 1 infection N = 454	Sustained Virological Response (SVR) Undetectable virus level 24 weeks after the end of treatment_			
	Overall	C/C	C/T	T/T
Control pegIFN/ribavirin (48 weeks)	38%	64%	25%	23%
Telaprevir + pegIFN/ribavirin Response Guided Treatment (stop 24 weeks)	78%	90%	71%	73%
Telaprevir + pegIFN/ribavirin (8 weeks) Followed by pegIFN/ribavirin (40 weeks)	67%	87%	58%	59%

Trial cohort REALIZE

Prior therapy failed with pegIFN/ribavirin

HCV Genotype 1 infection N = 527	Sustained Virological Response (SVR) Undetectable virus level 24 weeks after the end of treatment_			
	Overall	C/C	C/T	T/T
Control pegIFN/ribavirin (48 weeks)	-	29%	16%	13%
Telaprevir + pegIFN/ribavirin (12 weeks) Followed by pegIFN/ribavirin (36 weeks)	-	79%	60%	61%

Influence du génotype IL28b sur d'autres DAA

Inhibiteur de protéase TMC 435 + pegIFN/ribavirin → Influence ± 0
Inhibiteur de polymérase PSI-7977 + pegIFN/ribavirin → Influence ± 0
Inhibiteur de polymérase ANA598 + pegIFN/ribavirin → Influence +++



Influence variable
selon le DAA

TREATMENT ALGORITHM

HCV Genotype 1 (and 4) infection

IL28b variations are strongly associated with SVR

IL28b Rs12979860
C/C

Naïve Patients

IL28b Rs12979860
C/T or T/T

- pegIFN/ribavirin
24 - 48 weeks (individualized duration)

Benefit and Response-guided approach
during triple-therapy is unclear

- Postponement of therapy
- pegIFN/ribavirin + telaprevir / boceprevir
24 weeks if extended RVR (eRVR)
48 weeks if no eRVR
- pegIFN/ribavirin (48-72 weeks)
If contraindication to triple therapy

Prior null responders to standard therapy

Quadruple therapy or DAA agents with a higher genetic barrier
to resistance (pegIFN/ribavirin + NS5B/cyclophilin inhibitor)

HCV Genotype 2 & 3 infection

IL28b variations are only weakly associated with SVR

IL28b Rs12979860
C/C

IL28b Rs12979860
C/T or T/T

- Whether a good response genotype may be an argument of shortened TRT duration (eg 12 weeks) is unclear

- A poor response IL28b genotype might indicate a need for prolonged therapy of 48 wks in patients who do not attain an RVR

Ajout d'un inhibiteur d'un DAA n'est pas sans:

Coût supplémentaire

Effets indésirables Fatigue, fièvre, maux de tête, nausée, anémie,
mauvais dysgeusie, rash cutané...

Virus résistance risquant de compromettre les options thérapeutiques futures

Autres facteurs:

Facteurs individuels (âge, ethnie...)

Facteurs de co-morbidité

Degré de fibrose hépatique

Facteurs viraux (charge virale initiale, évolution de la charge virale au cours du Trt...)

Nouveaux facteurs prédictif : Déficit en vitamine D,

Taux sérique d'Interferon gamma-inducible protein-10 (IP-10),

Resistance à la stéatose/insuline....

Autres facteurs génétiques: Natural killer (NK) cell receptor KIR2DL3 et de son ligand

Human leukocyte antigen C group 1 (HLA-C1)

ITPA, UGT1A1, CYP27B1...

Programme de prédiction prenant en considération de nombreux facteurs de variabilité: <http://ideasydesarrollo.com/fundacion/prometheusindex.php?lang=ing>

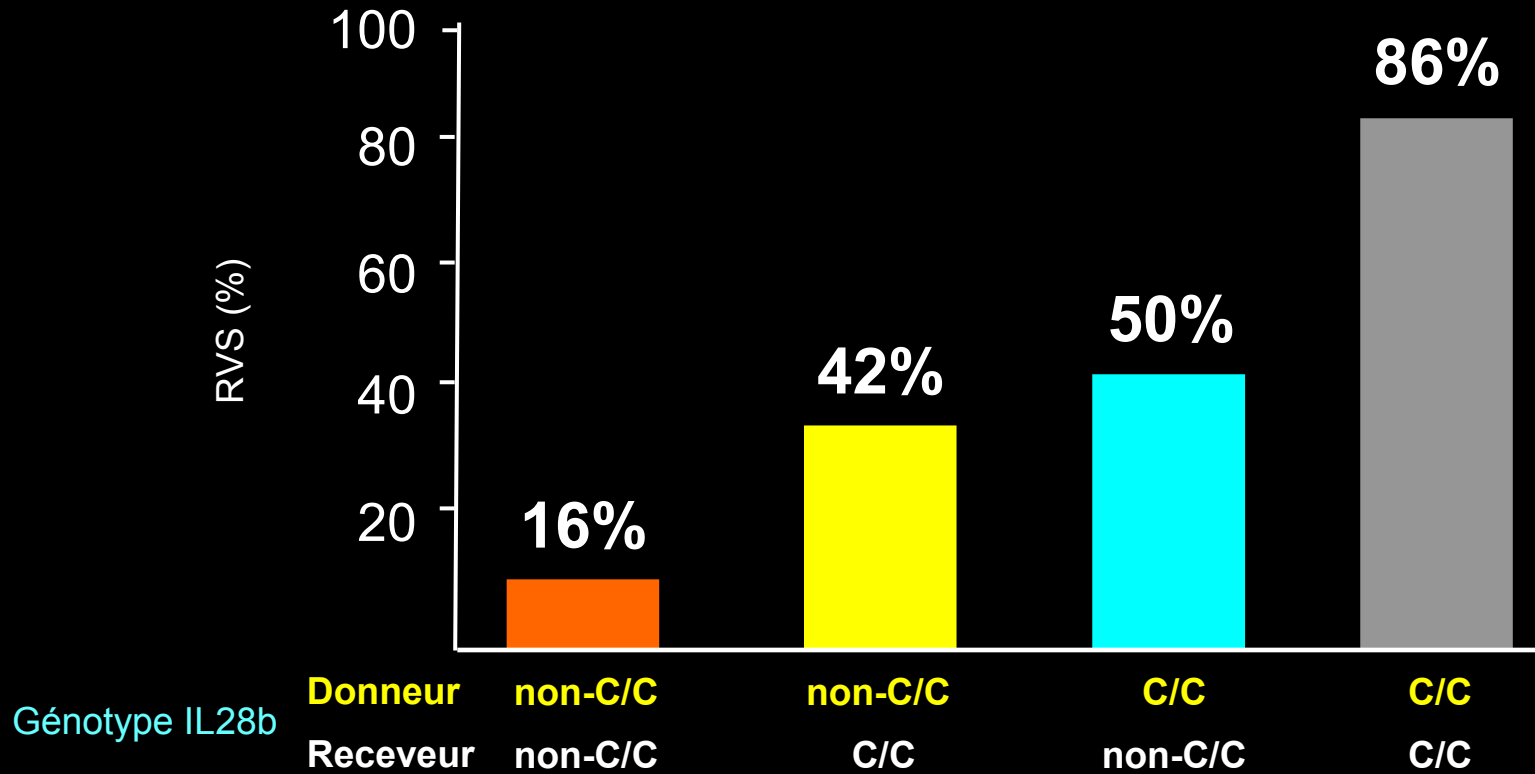
Autres:

Patient demand for shorter duration, less toxic regimen

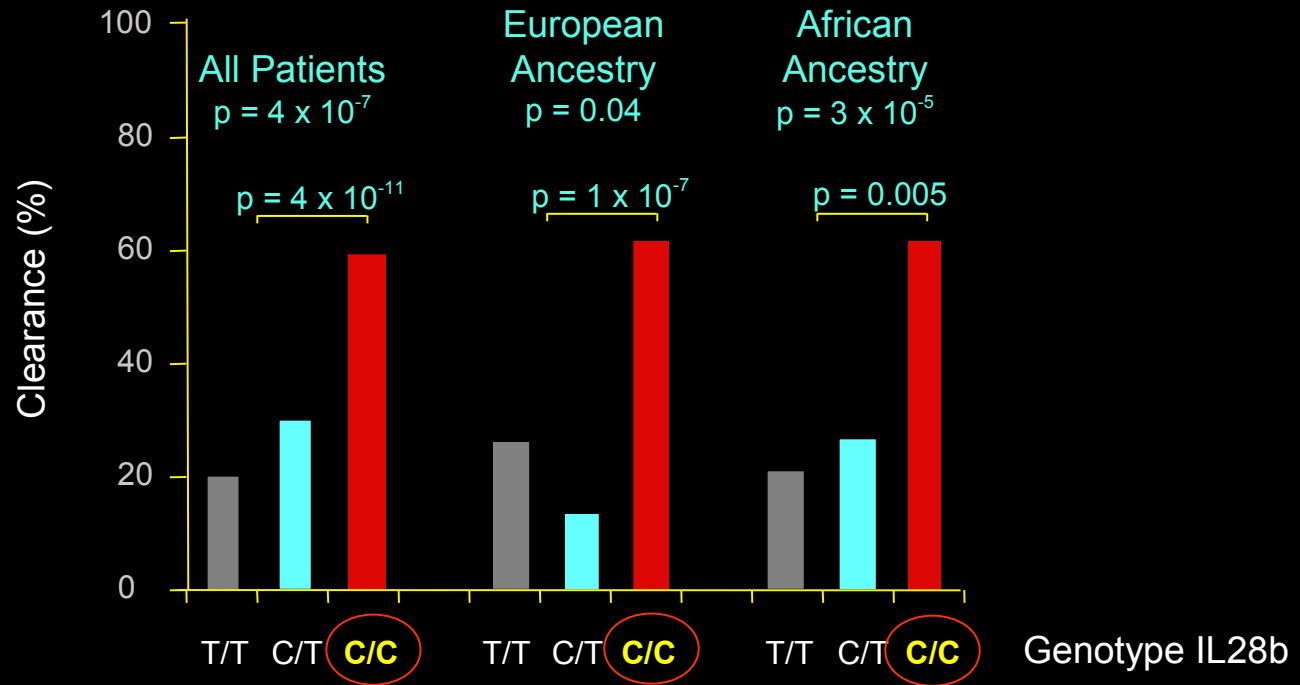
Public health equity

Impact du polymorphisme de L'IL28B sur réponse au traitement après transplantation chez les patients infectés par le VHC

RVS après transplantation



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48 weeks if no eRVR

IL28b Rs12979860
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Characteristics of four pivotal GWAS on treatment-induced HCV clearance

	Ge D et al. <i>Nature</i> 2009; 461 : 391–401	Tanaka Y et al. <i>Nat Genet</i> 2009; 41 : 1105–9.	Suppiah V et al. <i>Nat Genet</i> 2009; 41 : 1100–4.	Rauch A et al. <i>Gastroenterology</i> 2010;138 : 1338-45.
Primary endpoint /	SVR vs non response	NVR vs VR (Non Virological Response, defined as less than 2 log ₁₀ IU/ml decrease in HCV RNA at week 12)	SVR vs non response	SVR vs non response
Genotype	HCV 1	HCV 1	HCV 1	HCV 1, 2, 3, 4
Adherence control	Non-SVR patient excluded if <80% adherent	All patients excluded if < 80% adherent during the first 12 weeks	No specific adherence criteria	>80% adherent
Top SNP	rs12979860 OR (CC genotype, SVR): 2.0 (1.8-2.3) p = 1.06 x 10 ⁻²⁵	rs8099917 OR (G allele, NVR) 27.1 (CI 14.6-50.3) P = 2.68 x 10 ⁻³² (rs12979860 not genotyped)	rs8099917 OR (T allele, SVR) 1.98 (CI 1.6-2.5) p = 9.25 x 10 ⁻⁹ (rs12979860 not genotyped)	rs8099917 OR (G allele, no SVR): 5.19; 95% (CI, 2.90 – 9.30) p = 3.11 x 10 ⁻⁸ (Data for rs12979860 not presented)
Alleles	C / T CC = Good response CT, TT = Poor response	T / G TT = Good response GT, GG = Poor response	T / G TT = Good response GT, GG = Poor response	T / G TT = Good response GT, GG = Poor response
SVR According To IL28B genotype	SVR rates (Caucasians) (Afro Amer) CC = 82% CC = 53% CT = 42% CT, TT = 18% TT = 33%	SVR rates TT = 64% (125/194) GT = 13% (15/113), GG = 0% (0/5)	SVR rates 56 % vs 36% (T/T vs T/G, G/G)	SVR rates 74 % vs 50% (T/T vs T/G, G/G)
Cohort	n = 1137 North America (Caucasian, african-American, Hispanic)	Discovery phase n = 154 Validation phase n = 172 Japanese	Discovery phase n = 293 Validation phase n = 555 Australia / Northern Europe (Caucasian)	N = 465 Northern Europe (Caucasian)