Host Genetic determinants of HCV treatment outcome

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Disclosures

- Advisory board member - Gilead, Abbvie, Bristol-Myers Squibb (BMS), Janssen, Merck, and Roche
- Speaker - Gilead, Janssen, Merck, BMS, Abbvie
- PI - Gilead, Merck, Roche, BMS, Janssen, Achillion, Springbank
- Research / grant support – Gilead, Merck, BMS, Abbvie
- My presentation includes discussion of genetic tests and drugs which are not approved for clinical use

Genome-wide association studies identify an association b/w *IL28B* polymorphism and SVR

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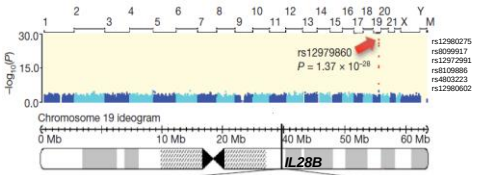
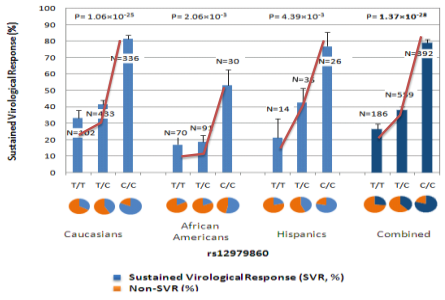
IDEAL study pharmacogenomics cohort, n = 1604



IL28B = IFN-lambda-3

Ge, Fellay*, Thompson* et al, Nature, 2009*

C/C genotype predicts SVR



IDEAL: *IL28B*-type is the strongest pre-treatment predictor of SVR

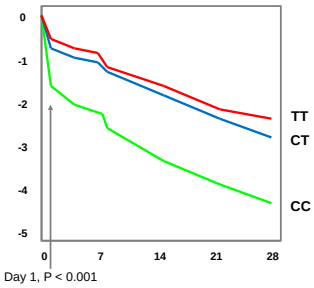
	Odds Ratio	95% Confidence Interval		p-value
CC *IL28B*-type vs non-CC	5.2	4.1	6.7	*<0.0001*
VL ≤ 600,000 IU/mL	3.1	2.3	4.1	*<0.0001*
Caucasian vs AA ethnicity	2.8	2.0	4.0	*<0.0001*
Hispanic vs AA ethnicity	2.1	1.3	3.6	0.004
METAVIR F012	2.7	1.8	4.0	*<0.0001*
Fasting Blood Sugar < 5.6 mmol/L	1.7	1.3	2.2	*<0.0001*

Co-variates - rs12979860 (2-level), ethnicity (4-level), age (≤ 40), gender, BMI (< 30), VL (≤ 600,000), ALT (≤ ULN), fasting glucose (< 5.6), hepatic steatosis (N/Y[>0%]), fibrosis (METAVIR F012), RBV (>13 mg/kg/d)

Thompson, Gastro, 2010

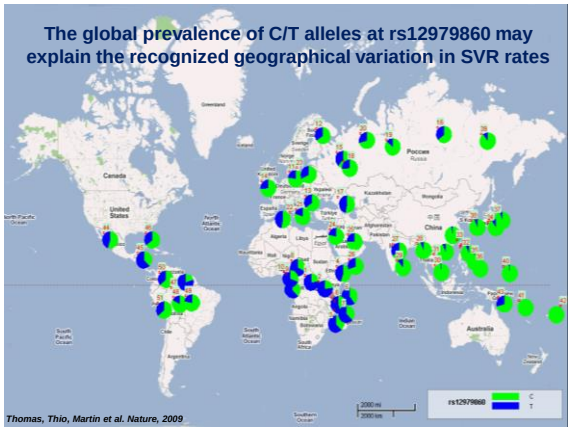
IL28B genotype is associated with phase 1 viral kinetics

- Genotype 1 HCV, *IL28B* rs12979860



Neumann, EASL, 2010

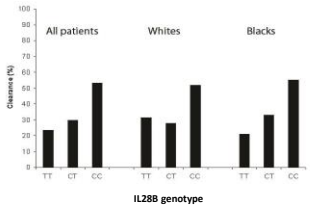
The global prevalence of C/T alleles at rs12979860 may explain the recognized geographical variation in SVR rates



Thomas, Thio, Martin et al. Nature, 2009

IL28B variation is associated with spontaneous clearance of HCV

- Multi-national IDU cohort, n = 388 (cleared) vs 620 (chornic)
- Case-control candidate gene study, SNP = rs12979860
- OR for clearance (CC vs non-CC) = 3.0, P = 10-13



Thomas, Thio, Martin et al. Nature, 2009

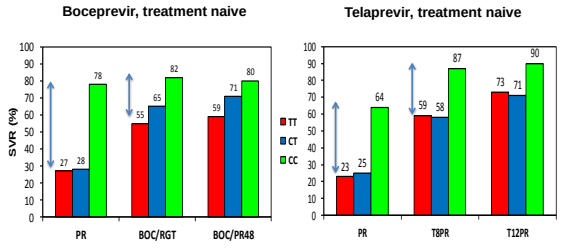
Summary

- In genotype 1(/4) HCV patients, *IL28B* genotype:
  - strongly associated with cure of HCV
    - strongest baseline predictor
  - explains much of the ethnic difference in response rates
  - profoundly influences viral kinetics
- In genotype 2/3/6 HCV, the association between *IL28B* genotype and PR response is attenuated
- *IL28B* polymorphism is also strongly associated with spontaneous clearance of HCV

Direct acting antiviral agents (DAAs)

DAA + peginterferon and ribavirin
PI - Telaprevir, boceprevir, simeprevir
NI - sofosbuvir

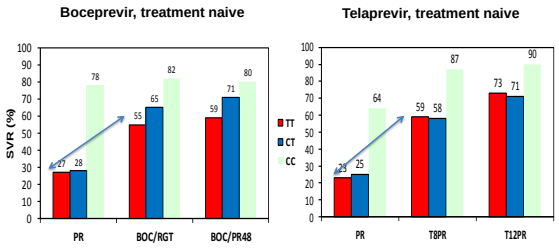
PIs attenuate the association between IL28B genotype and SVR



Poordad, Gastroenterology, 2012

Pol, J Hepatology, 2013

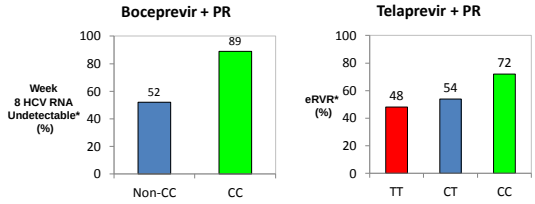
PIs attenuate the association between IL28B genotype and SVR



Poordad, Gastroenterology, 2012

Pol, J Hepatology, 2013

IL28B CC genotype predicts for short duration therapy

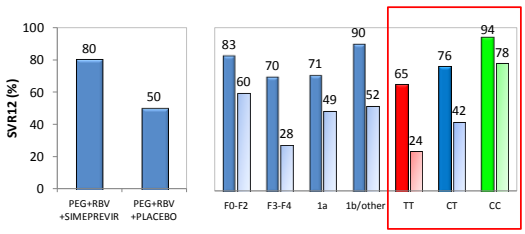


*Decision point for short vs. long treatment duration with RGT

Poordad, Gastro, 2012; Jacobson, EASL, 2011

Simeprevir + PR: *IL28B* genotype predicts SVR
Clinical utility similar to the setting of TVR / BOC + PR

QUEST-1
Simeprevir + PR, Phase 3, n=394

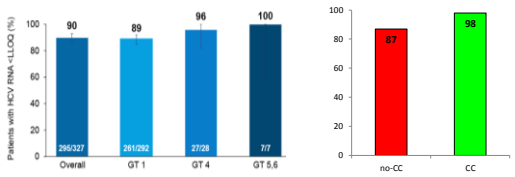


Predicts short duration therapy
(note – 85% of patients overall were eligible)

Jacobson, EASL, 2013

Sofosbuvir + PR: *IL28B* genotype is less relevant

NEUTRINO (n=327)



12 week fixed duration (no RGT)

Lawitz, NEJM, 2013

Summary

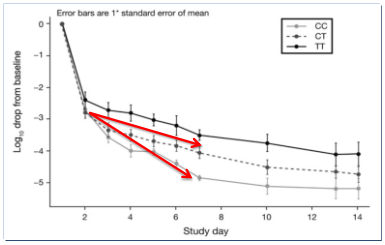
- PI + PR regimens:
  - Naïve patients - association b/w *IL28B* and SVR is attenuated
  - CC patients:
    - small absolute increase in SVR
    - goal = short duration therapy
  - Non-CC patients:
    - 2-fold increase in SVR with DAA
  - PR experienced patients - *IL28B* less useful
- Sofosbuvir + PR:
  - As SVR rates approach 100%, *IL28B* is less clinically useful

Direct acting antiviral agents (DAAs)

IFN-free regimens

IL28B genotype is associated with viral kinetics during IFN-free therapy – 2nd phase more important?

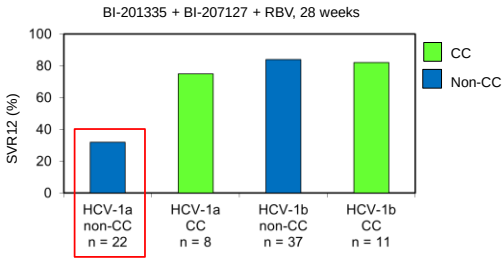
- INFORM-1 : Mericitabine (NS5B NI) + danoprevir (NS3 PI), 14 days



Chu, Gastro , 2012

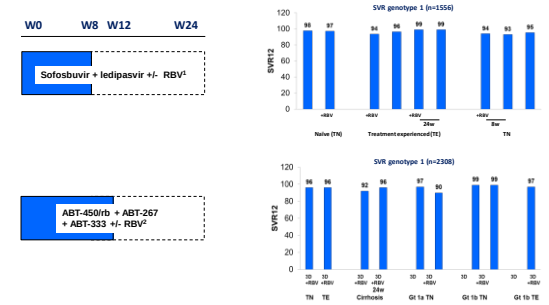
Lessons from SOUND-C2: *IL28B* genotype predicted SVR for HCV-1a

- IL28B genotype is important for HCV-subtype 1a



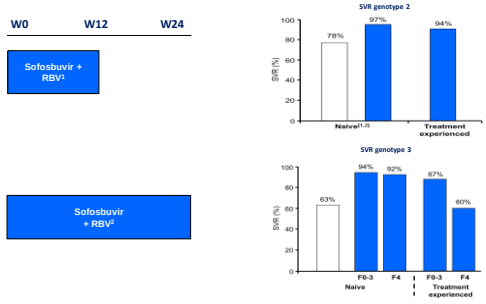
Zeuzem S, EASL, 2012: A101

2014 – IFN-free treatment for Gt 1



1Gilead press release, Dec 18, 2013 2Abbvie press release, Dec 2013

2014 – IFN-free treatment for Gt 2/3

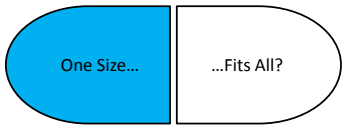


1Jacobson, NEJM, 2013; 2Zeuzem AASLD, 2013

Summary: IFN-free therapy

- *IL28B* genotype was relevant to early IFN-free DAA regimens
  - CC patients were "easy to cure", esp HCV-1a
- As SVR rates increase with more potent combination DAA regimens, *IL28B* no longer predicts for SVR
- There may not be any baseline variables that predict for outcome
  - Cirrhotic null responders?
  - Adherence may remain an issue?

Predictors of response: 2015+

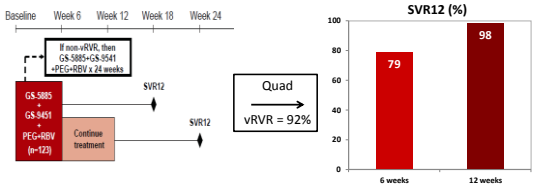


"Perfectovir"

But does everyone need perfectovir?

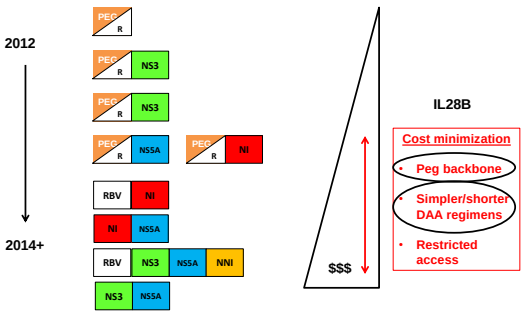
Can *IL28B* genotype individualize treatment: Shorter? Cheaper?

- Ultra-short duration for C/C *IL28B* patients is possible



[1]*Thompson A, et al. EASL, 2013*

The future of HCV therapy



Beyond IL28B…?

We have the technology…

- ITPA polymorphism predicts RBV-associated anemia
  Fellay, Nature, 2010; Thompson, Gastro, 2010; Holmes, Hepatology, 2014
- Fibrosis progression
  - Cirrhosis Risk Score - 7-snp signature (*AZIN1, TLR4, TRPM5, AQP2, Chr 1(rs2290351), Chr 3 (rs4290029)*, and Chr 5 (*rs17740066)*)
    Huang , Hepatology. 2007; Marcolongo, Hepatology, 2009; Trepo, J Hepatol., 2011
  - *RNF7, MERTK* polymorphisms
    Patin, Gastro, 2012
- Hepatic steatosis
  - PNPLA3 on 22q13.31 (rs738409 C>G encoding I148M)
  - Has also been associated with HCV-related fibrosis progression
    Trepo, Hepatology, 2011; Cai, J Hep, 2011; Valenti, Hepatology, 2011; Clark, Dig Dis Sci. 2012
- HCC
  - MICA on 6p21.33 (rs2596542)
    - Recent data suggests this signal may be due to linked variation in HCP5
      Kumar, Nature genetics, 2011; Lange, EASL, 2013 (Late-breaker)
  - DEPDC5 on 22q12 (rs1012068)
    Miki, Nature genetics, 2011

Conclusion

- The discovery of the association between *IL28B* genotype and peginterferon-response was a success story for pharmacogenomics
  - Personalized medicine became reality for HCV
  - *IL28B* genotype informed pre-treatment counselling
- *IL28B* genotype predicts for short duration treatment with first generation protease inhibitors (TVR/BOC)

Conclusion

- The field is now moving away from personalized therapy for HCV
  - Multiple "optimized" treatment regimens from 2015+
  - *IL28B* genotype will not directly predict SVR
  - One size will fit all
- BUT… **not all patients will be able to pay** for perfectovir ($$$)
- *IL28B* genotyping will remain useful to personalize regimens:
  - Cheaper
  - Simpler (less drugs)
  - Shorter