Hepatitis C Virus Resistance to Protease Inhibitors

David L. Wyles, M.D.
Associate Professor of Medicine
University of California San Diego

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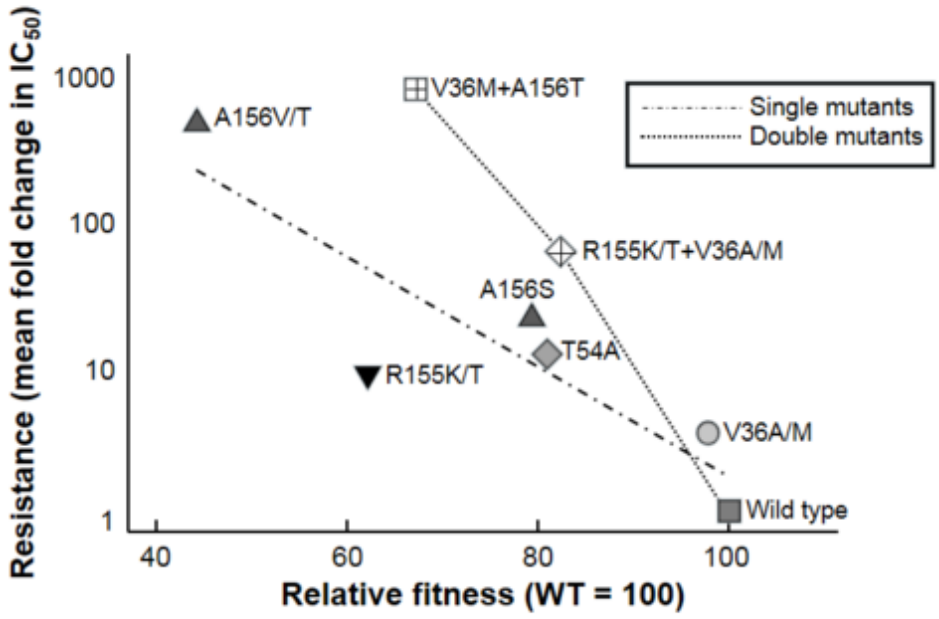
IAS–USA
International AntiViral Society–USA

Key Resistant Variants and Viral Fitness



Sarrazin C. Gastro 2007.

High Rates of Resistance in Treatment Failures

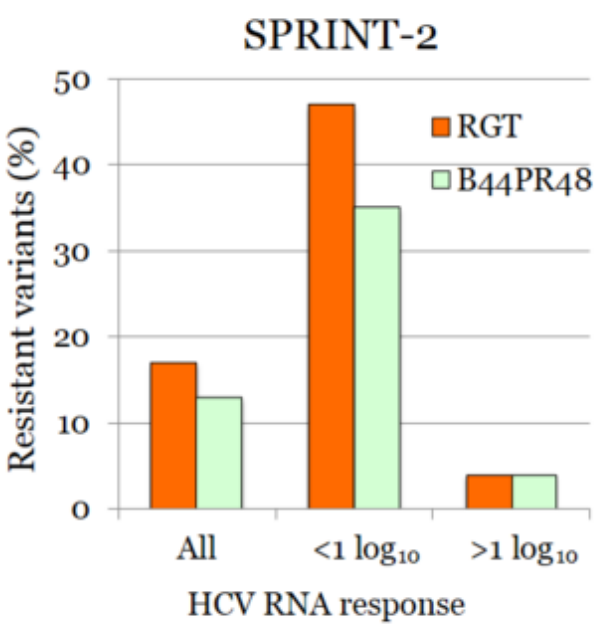
Triple therapy: PI + Peginterferon alfa (PEG) + ribavirin (RBV)

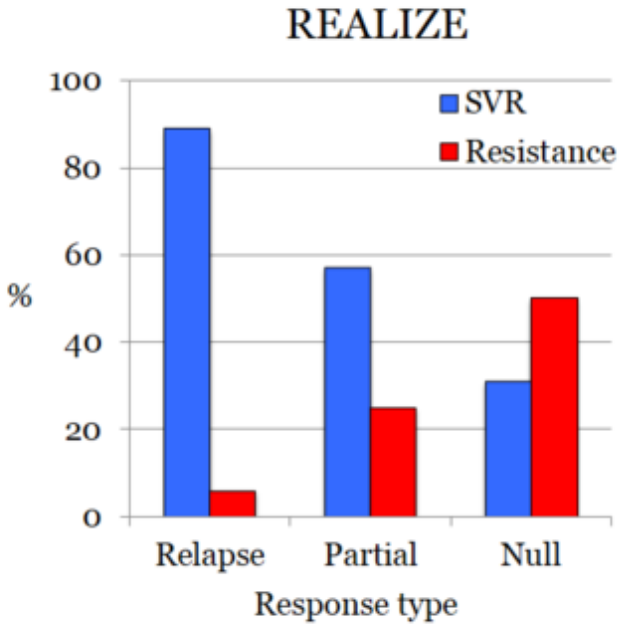
- 50%-80% of all non-SVRs with resistance
  - On treatment virologic failure
    - 90-95% with resistant variants
  - Relapse
    - 30-70% with resistant variants

Poor interferon alfa responsiveness results in increased rates of treatment failure and, thus, resistance

Ogert RA. Antiviral Ther 2013 (epub 13 FEB 2013). Kieffer T. PlosONE 2012; 7(4): e34372.

Interferon Alfa Response and Emergence of Resistance in 2 Studies

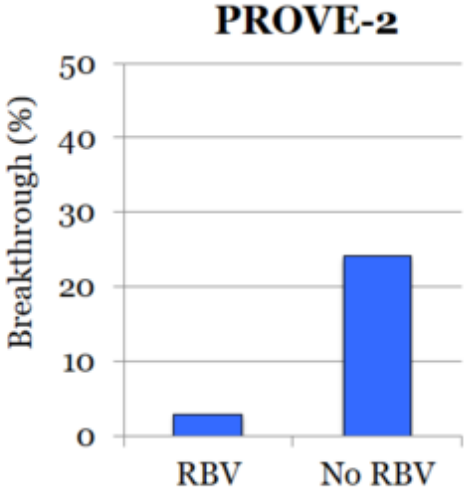


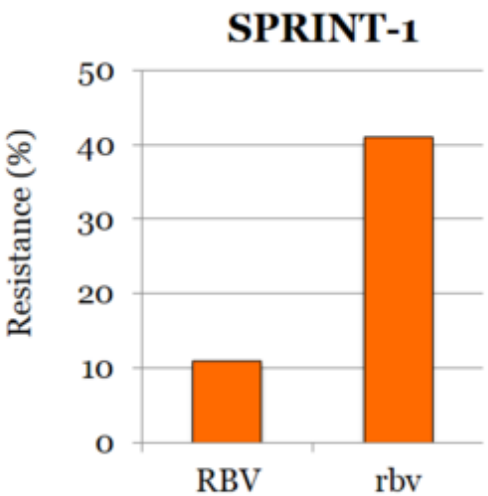


Poordad et al. 2010 Hepatology 52(s4): 402-3A. DeMeyer et al. 2011 J Hepatol 54(s1): S475.

Essential Role of Ribavirin in Preventing Protease Inhibitor Resistance

Ribavirin must be given with HCV PIs and interferon alfa





RBV: 800-1400 mg; rbv: 400-1000 mg

Hézode et al. 2009 NEJM 360:1839-50 . Barnard et al. #954 CROI 2011.

Resistance Testing in Clinical Practice

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Commercial HCV Resistance Assays

- HCV genotyping is clinically available
  - Population sequencing–resistant variants reported
  - Virtual (inferred) phenotype reported
  - LabCorp or Monogram test
    - CPT code: 87902
    - Requires HCV viral load ≥ 2000 IU/mL
      - Genotype 1a or 1b
- The clinical utility of HCV resistance testing is unclear

Key Clinical Questions on Resistance

Does the presence of genotypic resistance predict treatment outcomes?

- If so, under what circumstances…
  - Should baseline resistance testing be performed?

Does resistance testing at the time of virologic failure possess clinical utility?

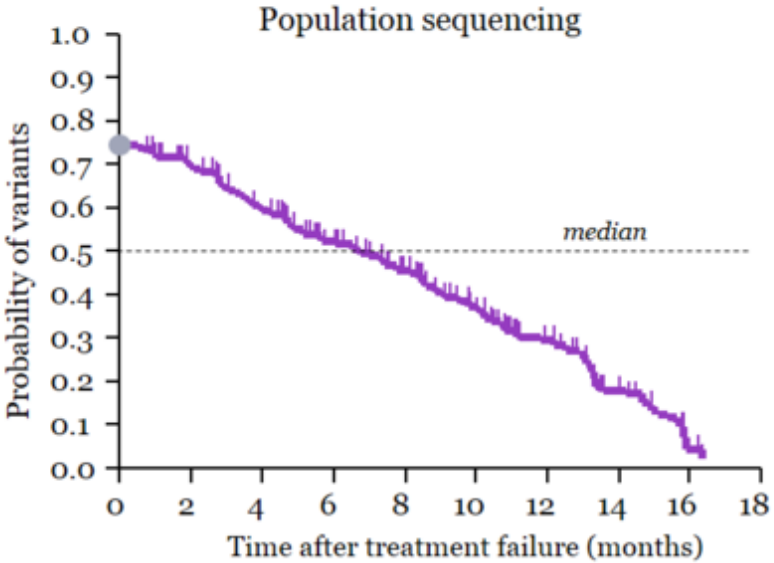
Can patients with genotypic resistance and treatment failure be retreated successfully in the future with regimens containing a cross-resistant drug?

Prevalence of Baseline Variants

- Key resistant variants were detected in <1% of treatment-naive patients (n=3477)
  - V36M: 0.5%; R155K: 0.9% (1a only)
  - A156S/T/V: not observed
    - Population sequencing
- Any variant: 7%-17% prevalence (most frequent V55A/I)
- The presence of baseline variants did not impact treatment outcomes in treatment-naive patients
  - There may be an impact in the small number of experienced patients who have both a poor response to interferon alfa and harbor key baseline variants

Bartels D. J Virol 2013; 87: 1544-53. Ogert RA. Antiviral Ther 2013 (epub 13 FEB 2013). Kieffer T. PlosONE 2012. DeMeyer S. Hepatol 2012; 56:2106-15.

Decay of Resistant Variants Over Time



96% had no detectable variants by 16 months posttreatment

Similar data for variants selected during boceprevir therapy

Sullivan JM et al. J Hepatol. 54: S4, 2011.

Key Clinical Questions on Resistance

Does the presence of genotypic resistance predict treatment outcomes?

- Should baseline resistance testing be performed?
  - No, not for treatment-naive patients
  - Combinations of baseline resistance and poor interferon alfa response are rare enough that routine baseline testing cannot be recommended for interferon-experienced patients

Does resistance testing upon virologic failure possess clinical utility?

- Not with currently available treatment options
  - Lack of significantly potent alternative treatments
    - Regardless of resistance issues

Disclosure Information

Dr Wyles has reported the following financial relationships with commercial firms:

- Consultant: Bristol-Myers Squibb, Merck & Co, Inc, and Janssen Therapeutics, Inc
- Payments to the Regents of the University of California San Diego for the conduct of clinical research: Gilead Sciences, Inc, Vertex Pharmaceuticals, Merck & Co, Inc, and AbbVie

Key Clinical Questions on Resistance

Can patients failing with genotypic resistance be re-treated successfully in the future with regimens containing a cross-resistant drug?

- Lacking adequate data

Potential Impact of Resistance on Future HCV Therapies

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HCV Therapies in Development and Resistance

Drug class	Resistance barrier	Clinical genotypic resistance	Subtype dependence (resistance likelihood)
NS3 PI	++ to +++	frequent	Yes (1a>1b)
NS5A	++ to +++	frequent	Yes (1a> 1b)
NS5B Nucleoside/tide	+++ to ++++	extremely rare	No
NS5B Nonnucleoside	+	frequent	Yes
Cyclophilin inhibitor	+++	rare	No

- Subjects in whom multiclass interferon alfa-free regimens are failing generally have multiclass resistant variants detected
  - Exceptions have been trials containing a nucleotide inhibitor
- The impact of selected resistance mutations on salvage therapies, with or without interferon alfa, is unknown

Resistance Summary

- HCV rapidly becomes resistant under non-curative therapy with most direct acting antivirals; however, it does not have a mechanism for archiving of resistant variants
  - The majority of patients in whom current PI therapy is failing will have detectable resistant variants
- Genotypic resistance testing does not have a well-defined role with current therapy
- Approaches to optimizing treatment outcomes are the key to preventing resistance
  - Medication adherence
    - Dosing schedule
    - Method of administration
  - Avoid deleterious drug-drug interactions
  - Adherence to established treatment stopping rules
- Studies are needed to determine the role of resistance in response to salvage therapy and interferon alfa-free regimens

End

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Outline

1. Resistance concepts and nomenclature
2. HCV virology as it relates to resistance
3. Overview of telaprevir and boceprevir resistance
4. Guidance on the practical management of resistance
5. Drug resistance and the emergence of interferon alfa-free regimens

Antiviral Resistance Concepts 1

- Resistant variant (resistance mutation also used)
  - Amino acid change responsible for the phenotype change (change in susceptibility)
    - Variant preferred indicating these changes preexist and are selected as opposed to an induced change ("mutation")
- Viral fitness
  - The "cost" the mutation imposes on the virus
    - Usually in the form of attenuated replication capacity
    - This is why on removal of drug pressure, resistant variant prevalence tends to decrease in the viral population
- Resistance barrier
  - Numerous-component metric describing the "ease" with which resistant variants arise and propagate
    - Number of nucleotide changes required
    - Fold-change in susceptibility conferred
    - Pharmacokinetics of the antiviral

Antiviral Resistance Concepts 2

- Genotypic resistance
  - Nucleic acid sequencing to identify nucleotide changes
    - Phenotypic resistance inferred
    - Population vs. clonal or ultra-deep sequencing
  - Genotypic tests are clinically available
- Phenotypic resistance
  - Testing of patient virus or genes in vitro to directly measure sensitivity to an antiviral
  - No phenotypic HCV resistance tests are clinically available
- Clinical resistance
  - Failure to achieve the treatment goal in the patient
    - May or may not be associated with genotypic resistance

The HCV Lifecycle Favors Resistance Development…But Not Persistence

Favors Resistance

- High viral turnover rate
  - 10^{12} virions/day
- Error-prone RNA polymerase
  - ~1 error per 10,000 bases
  - Involved twice in replication
- Lack of overlapping reading frames

Lack of Persistence

- No DNA intermediate
  - Cytoplasmic replication
  - Contrast to HIV/HBV
- No long-lived cellular reservoir
  - Hepatocyte turnover
  - Transient replication complex

Resistant variants are predicted to pre-exist in all patients[1]

1. Rong L. Sci Transl Med 2(30), May 5, 2010.

Overview of Resistance to HCV Protease Inhibitors

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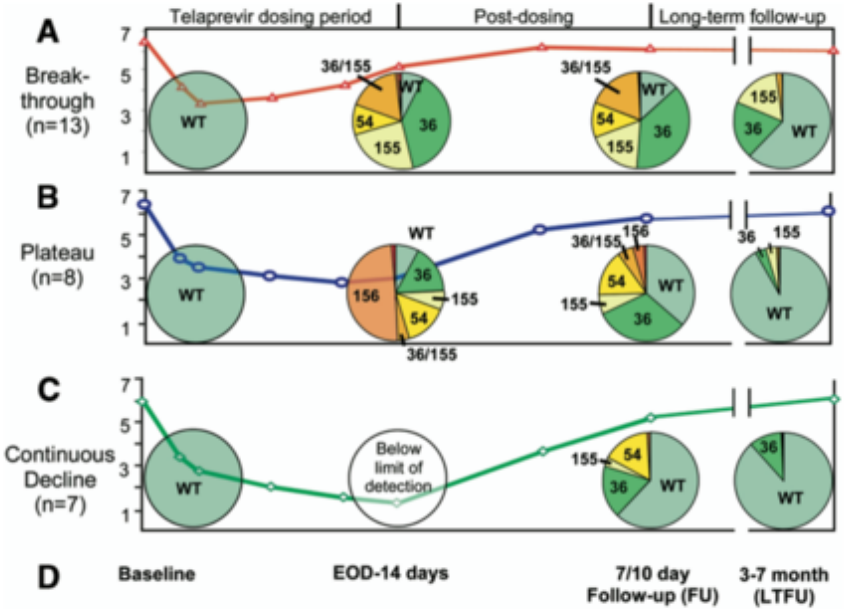
Rapid Resistance Selection With Monotherapy

Resistant variants predominate after 2 weeks



Sarrazin C. Gastro 2007.

Key Resistant Variants and Viral Fitness

- Profiles for telaprevir and boceprevir are overlapping
  - **Complete cross-resistance should be assumed**
  - Variants differ by genotype subtype
  - Genotype 1a
    - Low fold-change:* V36M, T54S, R155K
    - High fold-change:# R155K + V36M
  - Genotype 1b
    - Low fold-change: V36A, T54A/S, V55A, A156S, V170A
    - High fold-change: A156T/V
  - Low fold-change variants predominate during relapse
  - High fold-change variants predominate during breakthrough

* 3-25 fold increase in IC_{50} #>25 fold increase in IC_{50}

Ogert RA. Antiviral Ther 2013 (epub 13 FEB 2013). Kieffer T. PlosONE 2012; 7(4): e34372.