

HCV Drug Pipeline

NASTAD

**National Viral Hepatitis
Technical Assistance Meeting**

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TAG

Treatment Action Group

- **New Treatment: Desirable Elements**
What we want/need
- **Drug Development Process**
How we get there
- **HCV Drug Development: Milestones & Populations**
What are terms of engagement, and issues
- **Candidates**
Some of the players
- **Implications for Care and Treatment, Programs and Policy**
What to keep in mind

Future HCV Therapies: Desirable Elements

Less toxic and more effective

Additional therapies should not increase toxicity of current SOC

- High genetic barrier to avoid resistance
- Potent

Better first-line therapy

For HIV/HCV coinfecting persons, African Americans, people with HCV genotype 1 &/or high viral load, people with advanced liver disease, transplant candidates and recipients

Better second-line therapies for relapsers/non-responders

- Agents to reverse or halt fibrosis progression and decrease liver inflammation

More convenient treatment

- Oral therapies

Affordable!!!!!!

Clinical Trials

Pre-Approval

PHASE I Safety & Activity

- Dose-finding
- Pharmacokinetics (how much drug gets in & how long it lasts)
- Small & short-term
- Healthy volunteers before people with HCV

PHASE II: Safety & Efficacy

- 12- 48 weeks of treatment plus follow up (for now)
- Larger (>100 people)
- Randomized
- SVR is primary endpoint; RVR, EVR, SVR-12 can be co-primary endpoints

Clinical Trials

Pre-Approval

PHASE III: Safety, Efficacy (capacity to produce a certain effect) & **Effectiveness**

(a measure of the accuracy or success of a diagnostic or therapeutic technique when carried out in an average clinical environment)

- Randomized
- Surrogate (or clinical) endpoints
- Large (can be 1000's of people)

Clinical Trials

Post-Approval

PHASE IV

Recommended by FDA--but no teeth

- Diverse populations
- Long-term effectiveness & toxicities
- Treatment strategies

We aren't getting answers to questions that haven't been asked

Milestones

RVR: **rapid virological response** undetectable HCV RNA @ W4

- Of note, people with HCV genotype 1 who have an RVR, particularly if they have a low baseline viral load, only need 24 weeks of HCV treatment; SVR ranges from 78% 84%

EVR: **early virological response** \geq a 2-log drop in HCV RNA, or undetectable HCV RNA @ W12

pEVR: **partial early virological response** \geq a 2-log drop in HCV RNA @ W12

cEVR: **complete early virological response** HCV RNA is undetectable @ W12

SVR-12: used to report research data; according to retrospective data analysis, relapse is most likely within 12 weeks after completing HCV TX

Populations

Treatment Naïve VS. “Treatment Failures”

(Age, race, condition of the liver, condition of the liver, US versus non-US, HCV genotype (1a versus 1b))

~650,000 people in the US have been unsuccessfully treated for HCV

Treatment-experienced: More than one type of experience: null responder, non-responder, partial responder, breakthrough, relapse

What was original treatment regimen, duration, dose, & how were side effects managed?

HCV TX: The Future

- Oral antiviral agents, designed specifically to treat HCV TX
- Target different steps of the HCV lifecycle
- Must be used in with SOC for now--but new drugs may abbreviate treatment duration & improve outcomes
- Hopefully all oral regimens will be possible in the future
- Drug resistance may be present at baseline and can develop rapidly

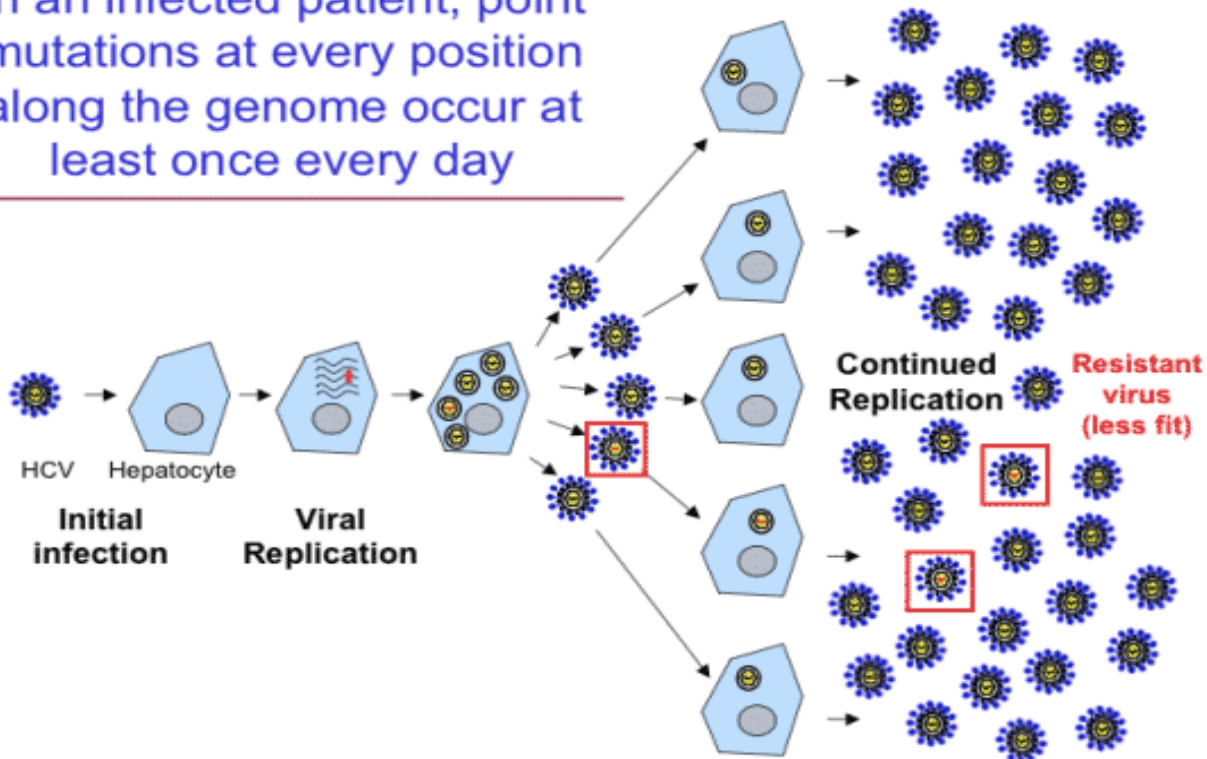


HCV Drug Resistance

the ability to grow in the presence of a chemical (drug) that would normally kill it or limit its growth

In an infected patient, point mutations at every position along the genome occur at least once every day

In an infected patient, point mutations at every position along the genome occur at least once every day



2007 and 2008: Ups & Downs

Stuck with SOC as the backbone

- No one is sure how ribavirin works, but it is a very important component of HCV treatment, even with new HCV-specific antivirals on board
- Two HCV protease inhibitors have entered phase III trials
 - No studies in HIV/HCV coinfecting people underway
- Development of several candidates halted, due to concerns about toxicity, efficacy, & financial issues
 - (NM283, HCV-796 ACH-806, AVI-4065, Actilon, VGX 410, MAXY-alpha, XTL 2125 and XTL 6865)
- Many more candidates are in preclinical development

What's in the Clinic

Oral antivirals

- ▀ protease inhibitors
- ▀ polymerase inhibitors
- ▀ NS5a inhibitor
- ▀ cyclophilin B inhibitor
- ▀ alpha glucosidase inhibitor

Other agents

- ▀ nitazoxanide
- ▀ taribivirin

Novel interferon formulations (injection)

Immunomodulators(infusion)

Anti-fibrotics (oral)

HCV Protease Inhibitors

- Resistance develops quickly-within days
- Activity may be genotype-specific
- Anemia is class-wide side effect
- May have additional toxicities
- 2 candidates in Phase 3
 - Boceprevir (Schering-Plough)
 - Telaprevir (Vertex/Tibotec)

TMC435350 Tibotec/Medavir Phase 2A

ITMN 191 Roche/Intermune Phase 1 (has also been studied with Roche's polymerase inhibitor candidates in vitro)

Other candidates from Abbott, Idenix, Merck, Phenomix, & Vertex

Telaprevir: Phase 2

Telaprevir: good results in treatment experienced people,
and shorter-course treatment for some treatment naïve people;
toxicity may be a problem

PROVE 1 USA

61% SVR 24 week TVR/PEG RBV

67% SVR 48 week TVR/PEG RBV

41% SVR in the control arm

TX Naïve: PROVE 2 EUROPE

62% SVR 12 week TVR/PEG RBV

68% SVR 24 week TVR/PEG/RBV

48% SVR-12 in the control arm

TX Experienced (SVR-12 data)

41% SVR 24 week TVR/ PEG RBV in prior non-responders

44% SVR 24 week TVR/PEG RBV

73% relapsers SVR 24 weeks TVR/PEG RBV

Boceprevir: Phase 2

Studied in treatment naïve & treatment experienced
People

In treatment naïve, lead-in did not make a difference (tx
shortened for people with RVR) but treatment duration
did

55% SVR 28 weeks BOC PEG RBV no lead-in

56% SVR 28 weeks with PEG RBV lead-in

66% SVR 48 weeks BOC PEG RBV no lead-in

74% SVR 48 weeks PEG RBV lead in

38% SVR 48 weeks control

HCV Polymerase Inhibitors

Nucleoside/nucleotide: Active against all HCV genotypes, high genetic barrier/ resistance less likely

R1626 Roche Phase 2

R7128 Pharmasset/Roche Phase 2

IDX 184 (nucleotide) Phase 1

MK 0608 Phase 1

Non-nucleosides: Genotype-specific, resistance-prone

GS 9190 Gilead (development resuming) Phase 2

PF-868,554 Pfizer Phase 2

AA-837093 Abbott Phase 1

ANA 598 Anadys Phase 1

GSK625433 GlaxoSmithKline Phase 1

VCH 759, 916 Virochem Phase 1

We Need.....

- **Research** on optimal HCV treatment strategies; the treatment paradigm will continue to shift as new agents become available
- **Treatment Guidelines** to avert therapeutic chaos as SOC evolves
- **Infrastructure** to deliver HCV care and treatment
 - HCV treatment may improve, but people will still need supportive services--treatment is only as effective as the system that delivers it!
 - Capacity to deliver HCV treatment to multiply-diagnosed people must be scaled-up to meet increased demand

Current & Future Acce\$\$ Issues

Currently, SOC costs ~\$32,000/year*

This does not include:

- Clinician/ nursing staff time
- HCV RNA testing (at multiple time points)
- Lab work, monitoring
- Side effects management: white and red blood cell growth factors cost ~\$8000 per month
- Psychiatric assessment, periodic screening for depression, mental health care, medication
- Longer treatment duration (may extend beyond 48 weeks)

In the future, we will need to factor in additional costs for resistance testing (and possibly other lab work), adherence support programs/staff, new drugs

*According to DrugStore.com, accessed 9/08