New Therapeutic Strategies: Polymerase Inhibitors

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Direct antiviral targets

NS3 Bifunctional protease / helicase

NS5A

NS5B RNA-dependent RNA polymerase
Antiviral Activity of DAAs Vary Among and Within Classes

3-14 day monotherapy in genotype 1 patients

Characteristics of DAAs and HTAs

<table>
<thead>
<tr>
<th></th>
<th>Efficacy</th>
<th>Genotype independency</th>
<th>Barrier to resistance</th>
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</thead>
<tbody>
<tr>
<td><strong>NS3/4A</strong></td>
<td>+++</td>
<td>++</td>
<td>+ - ++</td>
</tr>
<tr>
<td>(protease inhibitors)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>NS5A</strong></td>
<td>+++</td>
<td>+ - ++</td>
<td>+ - ++</td>
</tr>
<tr>
<td><strong>NS5B</strong></td>
<td>+ - +++</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>(nucleosides)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NS5B</strong></td>
<td>+ - ++</td>
<td>+</td>
<td>+</td>
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<tr>
<td>(non-nucleosides)</td>
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<tr>
<td><strong>Cyclophilin</strong></td>
<td>++</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td><strong>Inhibitors</strong></td>
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</table>
Nucleosidic polymerase inhibitors

- RG-7128 (Mericitabine): moderate efficacy, safe
- GS-7977 (Sofosbuvir): high efficacy, safe
- Alios-2200 = VX135: high efficacy, early phase 2
- NM-283 (Valopicitabine): low efficacy, GI toxicity
- R-1626: moderate efficacy, lymphopenia
- INX-189 = BMS-986094: high efficacy, cardiac tox.
- IDX-184: moderate efficacy, on hold
- PSI-938: high efficacy, hepatotoxicity
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PROPEL study: Efficacy and safety of MCB + PR in G1/4 treatment-naive patients

- Mericitabine nucleoside analog polymerase inhibitor
- 5–10% G4
- 9–11% Stage 4 fibrosis
- On-treatment responses enhanced by MCB
- SVR unaffected by MCB
- No new toxicities or resistance

![Graph showing SVR rates]

- SVR not better with MCB, despite better on-treatment responses
- May reflect inadequate duration of therapy, contrasting to JUMP-C study where SVR was increased

Wedemeyer H, et al. EASL 2012, Barcelona, #1213
Relapse rates: MCB 28%; PR 32%
- Non-cirrhotics MCB 19% vs PR 30%; Cirrhotics MCB 50% vs PR 40%

High relapse rates led to suboptimal SVR rates despite increment above control
- With no emergent S282T, high barrier to resistance affirmed
- Results illustrate importance of optimizing potency even if a nucleotide has high resistance barrier

Pockros P, et al. EASL 2012, Barcelona, #1205
DNVr, MCB, RBV + PEG-IFN in G1-infected partial and null responders: Results from the MATTERHORN study

Efficacy of DNVr +PR and QUAD for 24 weeks

Feld JJ, et al. AASLD 2012, Boston. #81
SVR12 by subtype:
Addition of MCB improves SVR12 in G1a by 45%.

- Triple therapy effective in G1b partials, much less so in G1a.
- Mericitabine helps to prevent relapse.
- Very high SVR rates to QUAD in nulls, higher in G1b.

Feld JJ, et al. AASLD 2012, Boston. #81
Once daily Sofosbuvir (GS-7977) plus RBV in patients with HCV G1, 2, and 3: ELECTRON trial

**HCV G2/3**
- n=40 SOF + RBV ± PEG → 100% SVR24
- n=10 SOF → 60% SVR24
- n=10 SOF + reduced-dose RBV (800 mg) → 60% SVR8
- n=25 SOF + RBV → 64% SVR12
- n=25 SOF + RBV (treatment-experienced) → 68% SVR12

**HCV G1**
- n=25 SOF + wt-based RBV (G1 treatment-naive) → 84% SVR12
- n=10 SOF + wt-based RBV (G1 null responders) → 10% SVR12

Add 2nd DAA to increase regimen potency and maintain 12 week duration
GS-5885 (NS5A inhibitor)
- n=25 SOF + GS-5885 + RBV (G1 treatment-naive)
- n=10 SOF + GS-5885 + RBV (G1 null responders)

Gane EJ, et al. AASLD 2012, Boston #229
N=332, treatment naive, non-cirrhotic
G1a= 68–78%
IL28B CC= 25–29%
ATOMIC study: A new plateau for IFN-based therapy

- SVR12 not yet reported for the 24 week groups

Kowdley KV, et al. EASL 2012, Barcelona, #1
ATOMIC: Genotype 4 and 6 results

Patients with HCV RNA < LOD (%)

<table>
<thead>
<tr>
<th>Genotype 4 (n=11) SOF+PR 24 weeks</th>
<th>Genotype 6 (n=5) SOF+PR 24 weeks</th>
</tr>
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<tbody>
<tr>
<td>Week 4 100 100 82 82</td>
<td>Week 4 100 100 100 100</td>
</tr>
<tr>
<td>EOT 100</td>
<td>EOT 100</td>
</tr>
<tr>
<td>SVR4 100</td>
<td>SVR4 100</td>
</tr>
<tr>
<td>SVR12 100</td>
<td>SVR12 100</td>
</tr>
</tbody>
</table>

- Safety
  - No new safety signals
- Resistance
  - No S282T variants identified

Hassanein T, et al. AASLD 2012, Boston #230
Resistance testing in relapsers after treatment with sofosbuvir-containing regimens in Phase 2 studies

- 661 patients in P7977-0221, PROTON, ELECTRON and ATOMIC
  - No breakthroughs, 53 relapses
- All had WT S282 at baseline
- 52/53 treatment failures underwent population and deep sequencing

<table>
<thead>
<tr>
<th>G</th>
<th>Number of patients with relapse samples sequenced</th>
<th>Population sequence change from BL: NS5B</th>
<th>Deep sequencing: S282T ≥1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>n=27 n=25</td>
<td>S79N V/I147I S282T I/T309T T/A/I/V312T</td>
<td>&gt;99% S282T</td>
</tr>
<tr>
<td>1b</td>
<td>n=13 n=13</td>
<td>S79N V/I147I S282S/T I/T309T T/A/I/V312T</td>
<td>27.6% S282T</td>
</tr>
<tr>
<td>2</td>
<td>n=2 n=2</td>
<td>S79N V/I147I I/T309T T/A/I/V312T</td>
<td>&gt;99% WT S282</td>
</tr>
<tr>
<td>3</td>
<td>n=10 n=10</td>
<td></td>
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</tr>
</tbody>
</table>

- Single patient with confirmed S282T mutation

Svarovskaia ES, et al. AASLD 2012, Boston. #753
ALS-2200 demonstrates potent antiviral activity over 7 days in treatment-naive G1 patients

- Novel uridine base nucleotide analog
- Potent, specific inhibition of HCV NS5B
- No cross-resistance to other DAAs
- Pan-genotypic activity in replicon
- Long intracellular T1/2 of triphosphate
- Multiple ascending dose for 7 days in treatment-naive, non-cirrhotic G1

<table>
<thead>
<tr>
<th>HCV RNA after 7 days treatment</th>
<th>PBO (n=8)</th>
<th>15 mg (n=8)</th>
<th>50 mg (n=8)</th>
<th>100 mg (n=8)</th>
<th>200 mg (n=8)</th>
<th>200mg + RBV (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;LLOQ, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (13)</td>
<td>4 (50)</td>
<td>5 (63)</td>
</tr>
<tr>
<td>&lt;LOD, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (13)</td>
<td>0 (0)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Median HCV RNA reduction (min, max)</td>
<td>0.11 (-0.28, 0.66)</td>
<td>-0.97 (-0.17, -1.59)</td>
<td>-3.02 (-2.21, -3.57)</td>
<td>-3.95 (-3.39, -4.51)</td>
<td>-4.54 (-3.81, -5.08)</td>
<td>-4.18 (-3.6, -5.2)</td>
</tr>
</tbody>
</table>

Marcellin P, et al. AASLD 2012, Boston #86
Non-Nucleosidic polymerase inhibitors

- **Thumb I inhibitors** (benzimidazole site)
  - TMC-647055
  - BI-207127
- **Thumb II inhibitors** (thiophene site)
  - PF-868554 (Filibuvir)
  - VX-222
- **Palm I inhibitors** (benzothiadiazine site)
  - ABT-072, ABT-333
  - ANA-598 (Setrobuvir)
- **Palm II inhibitors** (benzofuran site)
  - HCV-796 (Nesbuvir)
  - IDX-375
HCV non-nucleoside inhibitor TMC647055: Change in HCV RNA from BL in individual G1a/1b pts

Leempoels J, et al. AASLD 2011, San Francisco, #350
ABT-072 or ABT-333 combined with PR

Poordad F, et al. EASL 2012, Barcelona, #1206
34% CC; 20% TT; 46% CT
Overall SVR rate 83% Arm C, 90% Arm D
- Quad therapy may still be an option for difficult-to-cure patients

Penney MS, et al. EASL 2012, Barcelona, #1203
Conclusions

• HCV polymerase is an attractive target with two drug classes: nucleosidic (NI) and non-nucleosidic polymerase inhibitors (NNI)
• Potent NIs in combination with P/R achieve high SVR rates; no clinically relevant selection of RAVs
• Less potent NIs show some promising results in quadruple therapies
• NNIs of little importance in the combination with P/R, some interesting data in quadruple therapies; risk of RAVs
• Both, NIs and NNIs play a pivotal role in the clinical development of IFN-free regimen