Antiviral Therapy

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Challenges to the Development of Effective Antiviral Agents

- Myriad number of agents
- Need knowledge of replication at molecular level to define targets
  - Viruses as intracellular parasites make targeting more difficult to avoid host toxicity
- Lack of culture systems for some agents hinders development
- High through-put screening plus ‘rational’ drug design are both labor intensive and expensive

Diagnosis of Viral Infections

- Clinical suspicion
  - Is syndrome diagnostic of a specific entity?
  - Is viral disease in the differential diagnosis of a presenting syndrome?
- Knowledge of appropriate specimen(s) to send
  - Blood
  - Body fluids
  - Lesion scraping
  - Tissue
  - Proper transport is essential

Herpes Zoster

Progress in Antiviral Therapy

<table>
<thead>
<tr>
<th>Virus Family</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpesviruses (HSV, VZV, CMV)</td>
<td>Acyclovir, famciclovir, valacyclovir, ganciclovir, cidofovir, fomivirsen, valganciclovir</td>
</tr>
<tr>
<td>HIV-1</td>
<td>25 approved agents</td>
</tr>
<tr>
<td>Influenza</td>
<td>Amantadine, rimantadine, oseltamivir, zanamivir</td>
</tr>
<tr>
<td>Resp. syncytial virus</td>
<td>Ribavirin</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>3TC, FTC, adefovir, tenofovir, entecavir, telbivudine</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>pegIFN-ribavir</td>
</tr>
<tr>
<td>Papillomaviruses</td>
<td>IFN, ?cidofovir</td>
</tr>
<tr>
<td>Poxviruses</td>
<td>?cidofovir</td>
</tr>
<tr>
<td>JC virus</td>
<td>?cidofovir</td>
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</table>
Non-HIV Antiviral Therapy: Targets

- Herpesviruses
- Respiratory viruses
- Hepatitis viruses
- Others

Anti-Herpesvirus Agents

- Acyclovir
- Valacyclovir
- Famciclovir
- Ganciclovir
- Valganciclovir
- Foscarnet
- Cidofovir
- Formivirsen
- Trifluridine
- Idoxuridine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
<th>Active Moiety</th>
<th>Target Agents</th>
<th>Route of Admin</th>
<th>Toxicities</th>
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<tr>
<td>Acyclovir</td>
<td>Acyclic nucleoside</td>
<td>Tri-phosphate</td>
<td>HSV, VZV</td>
<td>Oral, intravenous, topical</td>
<td>Renal, Neuro</td>
</tr>
<tr>
<td>Val-ACV</td>
<td>Ester prodrug of acyclovir</td>
<td>Tri-phosphate</td>
<td>HSV, VZV</td>
<td>Oral</td>
<td>Renal, Neuro</td>
</tr>
<tr>
<td>Penciclovir</td>
<td>Acyclic nucleoside</td>
<td>Tri-phosphate</td>
<td>HSV</td>
<td>Topical</td>
<td>Local irritation</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>Ester prodrug of penciclovir</td>
<td>Tri-phosphate</td>
<td>HSV, VZV</td>
<td>Oral</td>
<td>Headache, nausea</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Acyclic nucleoside</td>
<td>Tri-phosphate</td>
<td>CMV, HSV, VZV</td>
<td>Intravenous, oral, intracocular</td>
<td>Hematologic</td>
</tr>
<tr>
<td>Val-GCV</td>
<td>Ester prodrug of ganciclovir</td>
<td>Tri-phosphate</td>
<td>CMV</td>
<td>Oral</td>
<td>Hematologic</td>
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<tr>
<td>Foscarnet</td>
<td>Pyrophosphate analog</td>
<td>Parent drug active</td>
<td>CMV, HSV</td>
<td>Intravenous</td>
<td>Renal, metabolic</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>Nucleotide analog</td>
<td>Diphosphate</td>
<td>CMV, HSV, HPV, pos</td>
<td>Intravenous</td>
<td>Renal, ocular</td>
</tr>
<tr>
<td>Formivirsen</td>
<td>Antisense oligo-NT binds to CMV mRNA</td>
<td>Parent drug active</td>
<td>CMV</td>
<td>Intracocular</td>
<td>Ocular</td>
</tr>
<tr>
<td>Trifluridine</td>
<td>Nucleoside analog</td>
<td>Tri-phosphate</td>
<td>HSV keratitis</td>
<td>Topical</td>
<td>Ocular</td>
</tr>
<tr>
<td>Idoxuridine</td>
<td>Nucleoside analog</td>
<td>Tri-phosphate</td>
<td>HSV keratitis</td>
<td>Topical</td>
<td>Ocular</td>
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Acyclovir I

- Development represents a watershed in the field of antiviral chemotherapy
- Acyclic guanosine analog
- Active vs. HSV, VZV and modestly CMV
- Mechanism of action
  - Preferentially taken up by virally infected cells
  - Monophosphorylated by virally encoded thymidine kinases
  - Bi- and triphosphorylation completed by cellular kinases
  - ACV-TP is the active moiety
    - Competitive inhibitor of viral DNA polymerase
      - Cellular DNA polymerases much less susceptible to inhibition
    - Leads to viral DNA chain termination

Acyclovir: Mechanism of Action

- Orally bioavailable 15-30%
- T1/2 3 hrs
- Primarily renally excreted

Toxicities
- Headache, nausea
- Renal
- Neurologic

Resistance
- Mediated by mutations in viral thymidine kinase and/or viral DNA polymerase genes
  - TK-deficient and TK altered virus can be produced
  - Clinically significant infections can be caused by drug resistant HSV and VZV

Acyclovir II

- Pharmacology
  - Administered by oral, intravenous and topical routes
  - Oral bioavailability 15-30%
  - T1/2 3 hrs
  - Primarily renally excreted

- Toxicities
  - Headache, nausea
  - Renal
  - Neurologic

- Resistance
  - Mediated by mutations in viral thymidine kinase and/or viral DNA polymerase genes

Anti-Respiratory Virus Agents

- Amantadine
- Rimantadine
- Zanamivir
- Oseltamivir
- Ribavirin

Amantadine and Rimantadine

- Tricyclic amines
- Active vs. influenza A only at clinically achievable concentrations
- Mechanism of action
  - Interference with function of viral M2 protein
    - M2 protein acts as an ion channel facilitating the hydrogen ion mediated dissociation of the matrix protein from the nucleocapsid
- Pharmacology:
  - Orally bioavailable
  - Amantadine: renal excretion
  - Rimantadine: hepatic metabolism and renal excretion
- Major toxicity
  - Neurotoxicity: amantadine > rimantadine
- Useful for treatment and prophylaxis of influenza A infections
  - Should not be used when amantadine resistant strains are in circulation
- Resistance mediated by mutations in M2 coding region

Amantadine and Rimantadine

- Chemical structures of amantadine and rimantadine.
Influenza Virus Replication Cycle

Mechanism of Action of Neuraminidase Inhibitors

Uncoating of Influenza Virus

Zanamivir and Oseltamivir II

- Pharmacology
  - Zanamivir
    - Oral inhalation
  - Oseltamivir
    - Orally bioavailable
    - Converted from ester prodrug to active form
    - Renally excreted
- Toxicities
  - Exacerbation of reactive airway disease by zanamivir
  - Nausea and vomiting for oseltamivir

Zanamivir and Oseltamivir I

- Active vs. influenza A and B
- Mechanism of action
  - Viral neuraminidase catalyzes cleavage of terminal sialic acid residues attached to glycoproteins and glycolipids, a process necessary for release of virus from host cell surfaces
  - Neuraminidase inhibitors thus prevent release of virions from infected cell

Zanamivir and Oseltamivir III

Zanamivir and Oseltamivir IV

- **Indications**
  - Treatment of influenza A and B within 24-48 hrs of symptom onset
  - Prophylaxis
  - N.B.: Neither drug interferes with antibody response to influenza vaccination

- **Resistance**
  - Incidence appears to be increasing
  - Ongoing surveillance necessary

Ribavirin I

- **Synthetic nucleoside analog**
- **Active vs. broad range of RNA and DNA viruses**
  - Flavi-, paramyxov-, bunyav-, arena-, retro-, herpes-, adenov-, and poxviruses
- **Mechanism of action complex**
  - Triphosphorylated by host cell enzymes
    - For influenza
      - Ribavarin-TP interferes with capping and elongation of mRNA and may inhibit viral RNA polymerase
    - For other agents
      - Ribavarin-MP inhibits inosine-5'-monophosphate dehydrogenase depleting intracellular nucleotide pools, particularly GTP

Ribavirin II

- **Pharmacology**
  - Aerosol and oral administration
  - Hepatically metabolized and renally excreted
- **Major toxicity**
  - Anemia
- **Indications**
  - Aerosol treatment of RSV in children
    - Effectiveness debated
  - Oral treatment of HCV (in combination with pegylated IFN-alpha)

Anti-Hepatitis B Virus Agents

- Interferon-alpha (pegylated)
- Lamivudine (3TC)
  - Nucleoside analog first developed for HIV
  - Lower dose used for HBV (100 mg/day)
- Emtricitabine (FTC)
  - Anti-HBV nucleoside analog with strong anti-HBV activity
- Adefovir dipivoxil
  - Nucleoside analog first developed for HIV but nephrotoxic at higher doses
  - Approved for HBV at lower dose (10 mg/day)
- Entecavir
  - Nucleoside analog with activity originally thought limited to HBV but recent reports indicate entecavir also has anti-HBV-1 activity and can induce resistance in HIV-1
  - Approved for use at dose of 0.5-1.0 mg/day
- Telbivudine
  - Nucleoside (thymidine) analog with activity vs. HBV but not HIV
  - Recently approved at a dose of 600 mg/day

Anti-Hepatitis C Virus Agents

- Approved
  - Interferon-alpha (pegylated)
  - Ribavirin
- In development
  - Protease inhibitors
  - Polymerase inhibitors

Interferons I

- Part of cytokine repertoire
- Possess antiviral, immunomodulatory and antiproliferative effects

- **Types**
  - Alpha/Beta (leukocyte/fibroblast)
    - Coding genes located on chromosome 9
    - At least 24 subtypes of alpha, 1 of beta
  - Gamma
    - Coding gene located on chromosome 12
    - 1 subtype
**Interferons II: Mechanism of Action**

- Act by inducing an antiviral state within cells
- Bind to specific receptors on cell surface
- Receptor associated tyrosine kinases activated
  - Tyk2 and JAK 1 for alpha and beta
  - JAK1 and JAK2 for gamma
- Cytoplasmic proteins [signal transducers and activators of transcription (STAT)] phosphorylated
  - Move to nucleus and bind to cis-acting elements in promoter regions of IFN inducible genes

**Interferons III: Mechanisms of Action**

- Synthesis of 2'-5' oligoadenylate synthetase
  - Activated by dsRNA
  - Convert ATP into a series of 2'-5' oligo(A)s
- These activate RNase L, which cleaves single stranded mRNAs
- Synthesis of dsRNA-dependent protein kinase (PKR, eIF-2 kinase)
  - PKR activated by dsRNA and autophosphorylated
  - PKR activated by dsRNA and autophosphorylated
- In turn, phosphorylates alpha subunit of eukaryotic initiation factor 2
- Protein synthesis inhibited
- Induction of a phosphodiesterase with inhibition of peptide chain elongation
- Synthesis of MxA protein which can bind to cytoskeletal proteins and inhibit viral transcriptases
- Induction of nitric oxide by gamma IFN in macrophages

**Interferons IV**

- Pharmacology
  - Injected IM or SC
  - Renal excretion and inactivation in body fluids/tissues
- Toxicities
  - Flu-like symptoms
  - Hematologic effects
  - Leukopenia and thrombocytopenia
  - Neuropsychiatric effects
- Antiviral indications
  - IFN-alpha (pegylated) SC for HCV (in combination with ribavirin)
  - Intraliesional for condyloma acuminate
- Resistance can develop
  - Mutations in NS5A gene of HCV described

**Passive Immunization for Viral Infections I**

- Human immune globulin
  - Prevention of hepatitis A
  - Prophylaxis and treatment of enterovirus infections in neonates and in children with antibody deficiency
  - Treatment of B19 parvovirus infection in immunodeficient individuals
- CMV immune globulin
  - Prophylaxis of CMV in solid organ transplant recipients
  - Treatment of CMV pneumonia in combination with ganciclovir
- Hepatitis B immune globulin
  - Prophylaxis of hepatitis B infection
- Rabies immune globulin
  - Post-exposure prophylaxis for rabies (in combination with rabies vaccine)

**Passive Immunization for Viral Infections II**

- Respiratory syncytial virus immune globulin
  - Prevention of complications of RSV infection in young children
- Palivizumab
  - Humanized RSV monoclonal antibody
  - Prevention of complications of RSV infection in young children
- Varicella-zoster immune globulin
  - Prevention of varicella infection in immunocompromised children and adults within 96 hours of exposure
- Vaccinia immune globulin
  - Available from CDC for complications of smallpox (vaccinia) vaccination
Conclusions

• Field of antiviral therapy has matured dramatically in past 30+ years
• Greatest progress made for
  – Herpesviruses
  – HIV
  – Respiratory viruses
  – Hepatitis viruses
• Preventive vaccination remains the key to global control of viral infections