Infectious and Other Complications of Immunobiologic Agents Used by Individuals With HIV Infection

Peter Chin-Hong, MD
Professor of Medicine
University of California San Francisco
San Francisco, California

Learning Objectives

After attending this presentation, learners will be able to:

▪ List the types of conditions for which biologic agents may be prescribed for people with HIV infection
▪ Explain the mechanism of action in general of these agents to a patient in your practice so that he or she may understand why certain opportunistic infections and other complications may arise
▪ Describe the array of infectious and other complications that may arise with these agents
▪ Design strategies that you can use in clinic to prevent infectious and other complications in your patients

HIV-infected patients living longer

HIV-infected patients living longer

Autoimmunity
Malignancy

Life expectancy in US declines for 2 years in row

Autoimmune disease and cancer increase with age

Rheumatoid arthritis
Vasculitis
Crohn disease
Ulcerative colitis
Psoriasis
Lymphoma
Melanoma
Prostate cancer
Lung cancer
Leukemia
Immunobiologics treat autoimmune disease and cancer

- Rheumatoid arthritis
- Vasculitis
- Crohn disease
- Ulcerative colitis
- Psoriasis
- Lymphoma
- Melanoma
- Prostate cancer
- Lung cancer
- Leukemia

TNF-α inhibitors
- Infliximab
- Adalimumab
- Etanercept

Anti-CD20
- Rituximab

Checkpoint block
- Ipilimumab

CAR-T cells

What is a “biologic”?

- Any biologically derived product
- Binds or interferes with a specific molecular target
  - Monoclonal antibodies
  - Receptor analogues
  - Chimeric small molecules
- Abbreviations placed at the ends of the names of therapeutic agents convey specific information relating to their structure:
  - "cept" refers to fusion of a receptor to the Fc part of human IgG1
  - "mab" indicates a monoclonal antibody (mAb)
  - "ximab" indicates a chimeric mAb
  - "zumab" indicates a humanized mAb

Who is the most immune suppressed?

- Bone malignancy/stem cell transplant
- Organ transplant
- Autoimmune disease treatment
- Solid tumor treatment
- Congenital/acquired immune deficiency
- Hyposplenism
Who is the most immune suppressed?

- Heme malignancy/stem cell transplant
- Organ transplant
- Autoimmune disease treatment
- Solid tumor treatment
- Congenital/acquired immune deficiency
- Hyposplenism

Type of immune defect related to drugs used

<table>
<thead>
<tr>
<th>Humoral immunity</th>
</tr>
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<tbody>
<tr>
<td>- Rituximab (anti-CD20)</td>
</tr>
<tr>
<td>- Hyposplenism</td>
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<tr>
<td>- CVID (low IgG)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Cell-mediated immunity</th>
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<tbody>
<tr>
<td>- Solid organ transplant</td>
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<tr>
<td>- Stem cell transplant</td>
</tr>
<tr>
<td>- TNF-α inhibitors</td>
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<tr>
<td>- Steroids</td>
</tr>
<tr>
<td>- Other biologics</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Innate (PMNs) immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Cancer chemoRx</td>
</tr>
<tr>
<td>- Chronic gran dz (CGD)</td>
</tr>
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</table>

How is this different from HIV immunosuppressed patients?

<table>
<thead>
<tr>
<th></th>
<th>HIV</th>
<th>Non-HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune defect</td>
<td>Death of CD4+ T-cells</td>
<td>Heterogeneous</td>
</tr>
<tr>
<td>OI risk stratification</td>
<td>CD4+ count</td>
<td>No reliable tests available</td>
</tr>
</tbody>
</table>
Case

- 56 year-old woman with HIV (CD4 360, VL <50) with Crohn disease managed with infliximab and 6-MP
- Presents to ED complaining of shortness of breath x 3 weeks
- What else do you want to know?

Case courtesy Dr. Camille Kotton, MGH/Harvard

Case

- 56 year-old woman with HIV (CD4 360, VL <50) with Crohn disease managed with infliximab and 6-MP
- Presents to ED complaining of shortness of breath x 3 weeks
- PPD negative prior. Lives in New York. Came back 4 weeks ago from a trip to Puerto Rico where she visited family and helped with property clean up

Case courtesy Dr. Camille Kotton, MGH/Harvard

Case

- 56 year-old woman with HIV (CD4 360, VL <50) with Crohn disease managed with infliximab and 6-MP
- Presents to ED complaining of shortness of breath x 3 weeks
- What do you check next?

Case courtesy Dr. Camille Kotton, MGH/Harvard
Case

- 56 year-old woman with HIV (CD4 360, VL <50) with Crohn disease managed with infliximab and 6-MP
- Presents to ED complaining of shortness of breath x 3 weeks
- Urinary histoplasma antigen positive. Chest CT: symmetric nodules

Diagnosis: Acute histoplasmosis

Case courtesy Dr. Camille Kotton, MGH/Harvard

TNF-α inhibitors: tuberculosis

- Post-marketing survey of TB cases following release of infliximab (1998-2001)
- 70 cases of TB
- Median time to diagnosis: 12 weeks (range 1-52)
- TB characteristics
  - Extrapulmonary disease: 57%
  - Disseminated disease: 24%

CXR showing disseminated TB in patient on infliximab

Keane J. NEJM. 2001

TNF-α inhibitors: mycobacteria and fungi

- Survey of serious infection on TNF-α inhibitors in the US
  - Non-tuberculous mycobacteria: 32
  - TB: 17
  - Histoplasmosis: 56

- FDA alert 2008: 256 cases of histoplasmosis in patients on TNF-α inhibitors

Winthrop KL. CID. 2008

Endemic mycoses in the US
Case

- 42 year-old male with Crohn disease x 3 years, started on infliximab after persistent diarrhea 5 months prior
- Admitted with 3 weeks shortness of breath, low grade temps, dry cough. No help with amoxicillin x 1 week
- What is your differential diagnosis?

Case

- Sputum AFB negative x 3
- Sputum AFB Cx negative
- Respiratory virus PCR negative
- Chest CT: ground glass opacities
- BAL DFA+ P. jiroveci
- HIV Ab positive
- Diagnosis: Pneumocystis pneumonia
- Treated with clindamycin and primaquine (TMP/SMX allergic)
- Started ART

What is your differential diagnosis?

What diagnostic tests do you send?

- Sputum AFB negative x 3
- Sputum AFB Cx negative
- Respiratory virus PCR negative
- Chest CT: ground glass opacities
- BAL DFA+ P. jiroveci
- HIV Ab positive
- Diagnosis: Pneumocystis pneumonia
- Treated with clindamycin and primaquine (TMP/SMX allergic)
- Started ART

Case courtesy Dr. Ivan Hung, University of Hong Kong
Case
- 74 year-old HIV-negative man with interstitial lung disease and chronic lymphocytic leukemia on idelalisib
- Admitted with progressive shortness of breath on exertion and dry cough for 1 month
- Diagnosis: Pneumocystis pneumonia

Case courtesy Dr. Jen Mulliken, UCSF

Biologics and PCP
- Retrospective analysis of 2198 patients (across 8 studies) with relapsed CLL or NHL
- Patients on idelalisib +/- co-therapy (ritux or ritux/benda)
- PCP RR: 12.5
- Median time to PCP: 141 days
- No standard PCP prophylaxis guidance

Sehn LH, Blood, 2016 Furman, NEJM, 2014

Case
- 69 year-old HIV-negative woman with low grade lymphoma, treated only with rituximab (anti-CD20)
- Months after treatment, develops slowly progressive mental status changes
- CSF PCR positive for JC virus and MRI consistent with PML
- Diagnosis: Progressive Multifocal Leukoencephalopathy (PML)

Case courtesy Dr. Camille Kotton, MGH/Harvard
Biologics and viral infections

- **Hepatitis B** reactivation
  Reactivation with TNF-α inhibitors reported
  Rituximab – common

- **JC virus** (progressive multifocal leukoencephalopathy)
  Natalizumab – must check JCV IgG
  Rituximab – reports, less common

- **Varicella zoster virus**

Cancer immunotherapy in the beginning

- [Image]

How Jimmy Carter beat cancer

- [Image]

New immunotherapy drug behind Jimmy Carter’s cancer cure

- [Image]
Checkpoint blockade: a billion dollar industry

- Block the inhibitory receptor with monoclonal antibodies (CTLA-4, PD1)
- Target the immune system – not the cancer
- May lead to autoimmune disease & immune-related adverse events
- Infection risk may increase as immune suppression used to treat complications of therapy

Del Castillo M et al, CID, 2016

Case

- 52 year-old male with HIV (CD4 450, VL <50 on abacavir + dolutegravir + lamivudine) with skin squamous cell cancer. Enrolled in AMC-095 trial. On nivolumab x 1 year. Presents with fecal incontinence and diarrhea
- Diagnosis: Checkpoint inhibitor associated colitis
- Treated with prednisone high dose and infliximab. Nivolumab stopped
- Skin cancer in partial remission

Case courtesy Dr. Jackie Wang, UCSF
Gene therapy was a boy’s last chance to stop leukemia. And it worked.

**PBS** March 4, 2018

“CAR” Adoptive T cell therapy: CAR T cells

- **Chimeric Antigen Receptor (CAR) T cells** are genetically modified T cells
- T cells respond when tumor cell surface antigen recognized
- Substantial immune-related adverse events (cytokine release syndrome)
- Infection risk may increase as immune suppression used to treat complications of therapy

Lee DW et al, Lancet, 2015

KQED, March 4, 2018

Evaluation prior to TNF-α inhibitor use

- **HIV**
  - Is patient adequately immune reconstituted? CD4>200. Any drug interactions?
- **TB risk**
  - Check PPD or IGRA, CXR, take TB history
- **Endemic mycoses/fungi**
  - Take travel history, symptom check
- **Hepatitis B**
- **Vaccines**
  - Check hepatitis B surface antigen and core antibody

National Harbor, Maryland, December 9-11, 2018
Evaluation during biologic use

- HIV
  Is patient maintaining good immune function? CD4?

- Infection vs “Infection”
  Is patient experiencing any known adverse effect associated with the biologic?

- Vaccines
  Live vaccines usually contraindicated

- Be vigilant
  Your patient may have a new complication not previously reported

Anti-TNF inhibitors in patients with CD4<500

Fink DL et al, Int J STD&AIDS, 2017

HIV-infected patients started on biologics

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients (n)</th>
<th>Age (years)</th>
<th>ART at time of biologic agent</th>
<th>VmD suppression at time of biologic agent</th>
<th>Baseline CD4 cell count prior to biologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatology</td>
<td>32</td>
<td>53 (21)</td>
<td>4/9</td>
<td>4/9</td>
<td>444</td>
</tr>
<tr>
<td>Parapsoriasis vulgaris (I)</td>
<td>32</td>
<td>54 (21)</td>
<td>4/9</td>
<td>4/9</td>
<td>444</td>
</tr>
<tr>
<td>Psoriasis (I)</td>
<td>36</td>
<td>52 (21)</td>
<td>4/9</td>
<td>4/9</td>
<td>444</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>36</td>
<td>53 (21)</td>
<td>4/9</td>
<td>4/9</td>
<td>444</td>
</tr>
<tr>
<td>Chronic diarrhea (J)</td>
<td>32</td>
<td>53 (21)</td>
<td>4/9</td>
<td>4/9</td>
<td>444</td>
</tr>
<tr>
<td>Uveitis (I)</td>
<td>60</td>
<td>52 (21)</td>
<td>4/9</td>
<td>4/9</td>
<td>444</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>36</td>
<td>52 (21)</td>
<td>4/9</td>
<td>4/9</td>
<td>444</td>
</tr>
<tr>
<td>Psoriatic arthropathy (B)</td>
<td>36</td>
<td>52 (21)</td>
<td>4/9</td>
<td>4/9</td>
<td>444</td>
</tr>
<tr>
<td>Rheumatoid arthritis (M)</td>
<td>45</td>
<td>53 (21)</td>
<td>4/9</td>
<td>4/9</td>
<td>444</td>
</tr>
<tr>
<td>Reactive arthritis (A)</td>
<td>36</td>
<td>52 (21)</td>
<td>4/9</td>
<td>4/9</td>
<td>444</td>
</tr>
<tr>
<td>Arthritis of unknown origin (I)</td>
<td>33</td>
<td>53 (21)</td>
<td>4/9</td>
<td>4/9</td>
<td>444</td>
</tr>
<tr>
<td>ANCA-associated vasculitis (I)</td>
<td>31</td>
<td>53 (21)</td>
<td>4/9</td>
<td>4/9</td>
<td>444</td>
</tr>
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Fink DL et al, Int J STD&AIDS, 2017

1Age displayed is age of individual patient. Where study reported two or more patients, the median age is displayed.

2Range of CD4 cell counts. If studied reported two or more, range is displayed.
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Thanks Michelle Hermiston, Ivan Hung, Camille Kotton, Jen Mulliken, Brian Schwartz, Paul Volberding, Jackie Wang

Question-and-Answer
SUGGESTED READINGS


