

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

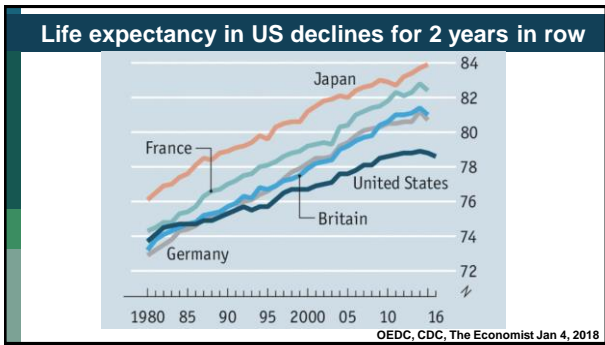
HIV patients: **74 years**

General population: **80 years**

↑ Autoimmunity

↑ Malignancy










Lohse N et al, 2016, Ann Intern Med;165(10):749; ART cohort collab, 2017, Lancet ID, 4(8):e349



Autoimmune disease and cancer increase with age

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

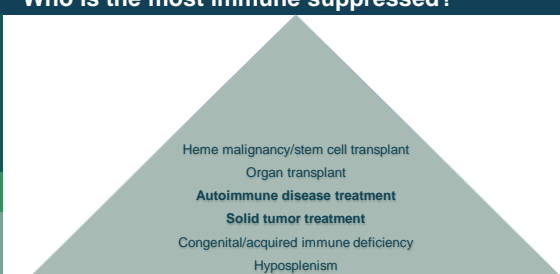
Immunobiologics treat autoimmune disease and cancer

 Rheumatoid arthritis	 Vasculitis	 Crohn disease Ulcerative colitis	 Psoriasis	TNF-α inhibitors Infliximab Adalimumab Etanercept
 Lymphoma				
 Melanoma	 Prostate cancer	 Lung cancer	 Leukemia	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?



Heme malignancy/stem cell transplant

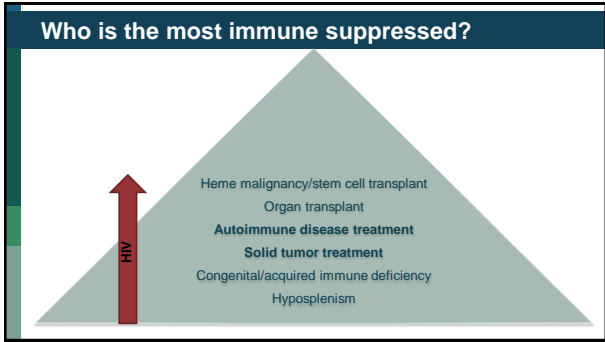
Organ transplant

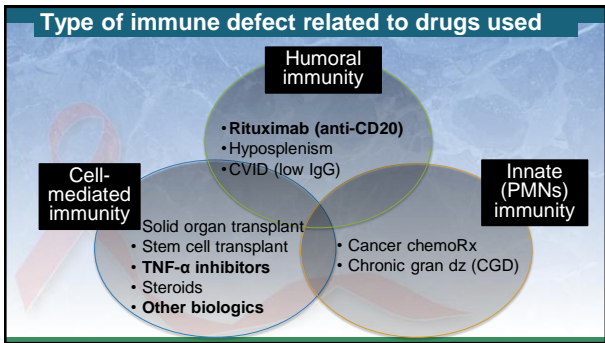
Autoimmune disease treatment

Solid tumor treatment

Congenital/acquired immune deficiency

Hyposplenism





How is this different from HIV immunosuppressed patients?

	HIV	Non-HIV
Immune defect	Death of CD4 ⁺ T-cells	Heterogeneous
OI risk stratification	CD4 ⁺ count	No reliable tests available

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

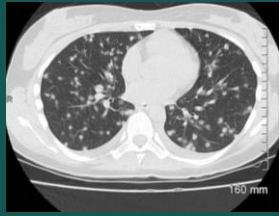
- 56 year-old woman with HIV (CD4 360, VL <50) with Crohn disease managed with infliximab and 6-MP
- Presents to ED complaining of shortness of breath x 3 weeks
- What do you check next?



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

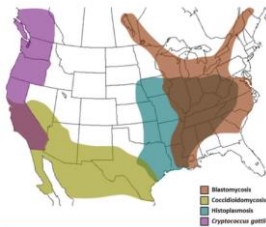
- Post-marketing survey of TB cases following release of **infliximab** (1998-2001)
- 70 cases of TB
- Median time to diagnosis: **12 weeks** (range 1-52)
- TB characteristics
 - Extrapulmonary disease: 57%
 - Disseminated disease: 24%



Keane J. NEJM. 2001 CXR showing disseminated TB in patient on infliximab

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 courtesy Dr. Ivan Hung, University of Hong Kong

Case

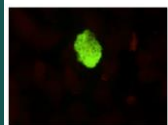
- 42 year-old male with Crohn disease x 3 years, started on infliximab after persistent diarrhea 5 months prior
- Admitted with 3 weeks shortness of breath, low grade temps, dry cough. No help with amoxicillin x 1 week
- What diagnostic tests do you send?



Case courtesy Dr. Ivan Hung, University of Hong Kong

Case

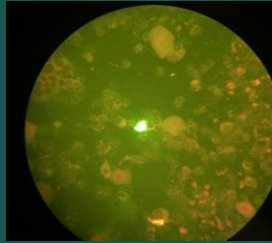
- Sputum AFB negative x 3
- Sputum AFB Cx negative
- Respiratory virus PCR negative
- Chest CT: ground glass opacities
- BAL DFA+ P. jiroveci
- HIV Ab positive
- Diagnosis: Pneumocystis pneumonia
- Treated with clindamycin and primaquine (TMP/SMX allergic)
- Started ART



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

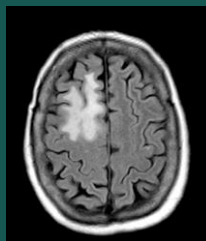
Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia

Event	Median time to event (95% CI)		Pneumonia Myocardial Infarction (MI)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Delusional ideation	44 (35)	NA	37 (25)	NA
Depression	7 (5)	NA	18 (8)	NA
Fatigue	7 (5)	NA	3 (2)	NA
Headache	3 (2)	NA	4 (2)	NA
Stomach pain	4 (3)	NA	3 (2)	NA
Pruritus	4 (3)	NA	3 (2)	NA
Diarrhea	3 (2)	NA	3 (2)	NA
Headache	3 (2)	NA	3 (2)	NA
Abnormal electrocardiogram	3 (2)	NA	3 (2)	NA
Myocardial infarction	3 (2)	NA	3 (2)	NA
Myocardial ischemia	3 (2)	NA	3 (2)	NA
Stroke	3 (2)	NA	3 (2)	NA
Cardiac death	3 (2)	NA	3 (2)	NA

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

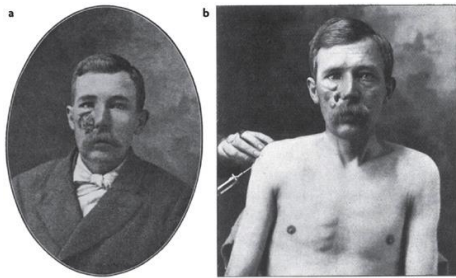
Biologics and viral infections

- **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**



Langer-Gould A. NEJM, 2005

Cancer immunotherapy in the beginning



Slide courtesy Dr. Gabe Mannis, UCSF

How Jimmy Carter beat cancer

TIME
January 20, 2017

New immunotherapy drug behind Jimmy Carter's cancer cure

The Guardian
December 6, 2015



ORIGINAL ARTICLE

**Pembrolizumab plus Chemotherapy
in Metastatic Non–Small-Cell Lung Cancer**

L. Gandhi, D. Rodriguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Dumine, F. Cingari, M.J. Hochhaus, S.P. Powell, S.Y.-S. Cheng, H.G. Bishoff, N. Petrelli, F. Grossi, R.R. Jenness, M. Reck, R. Hui, E.B. Garon, M. Noye, R. Rubin-Vignone, S. Novello, T. Kurata, J.E. Gray, J. Viza, Z. Wei, J. Yang, H. Rafailopoulos, M.C. Piantanida, and M.C. Garassino, for the KEYNOTE-189 Investigators*

ABSTRACT

BACKGROUND

First-line therapy for advanced non–small-cell lung cancer (NSCLC) that lacks targetable mutations is platinum-based chemotherapy. Among patients with a tumor-proportion score for programmed death ligand 1 (PD-L1) of 50% or greater, pembrolizumab has replaced systemic chemotherapy as the first-line treatment of choice. The addition of pembrolizumab to chemotherapy resulted in significantly higher rates of response and longer progression-free survival than chemotherapy alone in a phase 2 trial.

DESIGN

In this double-blind, phase 3 trial, we randomly assigned (in a 2:1 ratio) 616 patients with metastatic nonsquamous NSCLC without sensitizing EGFR or ALK mutations who had received no previous treatment for metastatic disease to receive pemetrexed

The authors' full names, academic degrees, and affiliations are listed in the article. Address reprint requests to Dr. Gandhi at New York University Langone Health, Laura and Isaac Perlmutter Cancer Center, 161E St, Box 20, New York, NY 10016, or at teresa.gandhi@nyu.edu.

An expedited list of investigators in the KEYNOTE189 trial is provided in the Supplementary Appendix, available at NEJM.org.

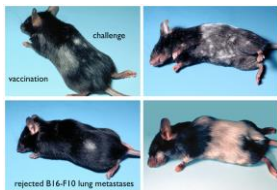
This article was published on April 16, 2018, at NEJM.org.

Gandhi L et al. NEJM, April 16, 2018



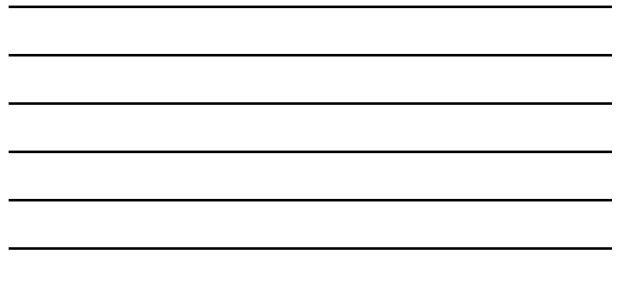
Checkpoint blockade: a billion dollar industry

- 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



Skin and hair depigmentation after treating melanoma with anti-CTLA-4

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



Severe colitis

Case courtesy Dr. Jackie Wang, UCSF



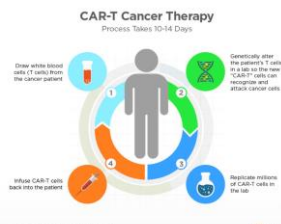
Gene therapy was a boy's last chance to stop leukemia. And it worked.

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

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

Subject: anti-TNF inhibitors in HIV patients with CD4<500

Hi Peter,
I know you are preparing a talk on questions like this, and thought of you when I got this question on e-referral at ZSFG. Is there any data on safety of anti-TNF therapy among patients with lowish CD4?

30yo MSM with Hiv of HIV with last CD4 237 and VL <40 copies back in 09/2018 who is on Genovoy who is currently being work up for abd pain with soft stools s/a colo which is looking more consistent with new Dx of Crohns per GI. The GI fellow contacted me with a question that I am not sure what the answer is so I am asking for your input. They are looking for thoughts/recommendations regarding starting anti-TNF therapy like Remicade or Humira to treat his Crohns. However, they are hesitant 2/2 to his low CD4 count. Im currently working on getting updated labs to reassess current state. GIs other thought is to use vedolizumab which is an integrin inhibitor that is more targeted on gut and is likely less immune suppressive

HIV-infected patients started on biologics

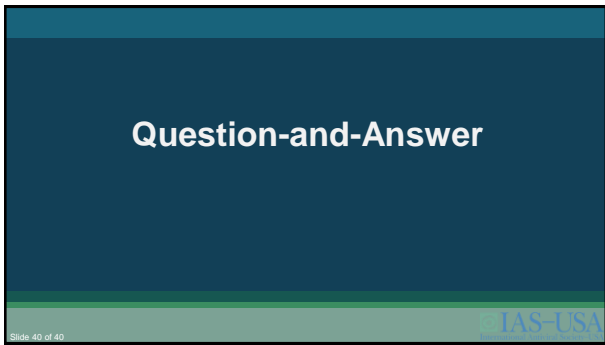
Diagnosis (number of patients)	Age (years) ^a	Male	ART at time of biologic agent	Viral suppression at time of biologic agent	Baseline CD4 cell count prior to biologic ^b
Dermatology					
Pemphigus vulgaris (1)	54	1/1	1/1	1/1	444
Psoriasis (4)	44	4/4	2/4	2/4	432
Gastroenterology					
Crohn disease (2)	39	0/2	2/2	2/2	603
Ulcerative colitis (1)	69	1/1	1/1	1/1	357
Rheumatology					
Psoriatic arthropathy (8)	45	7/8	5/8	4/8	324 (50-750)
Rheumatoid arthritis (4)	45	3/4	3/4	4/4	666 (530-974)
Reactive arthritis (2)	36	2/2	2/2	2/2	752
Ankylosing spondylitis (1)	34	1/1	1/1	1/1	634
Undifferentiated spondyloarthopathy (1)	50	0/1	1/1	1/1	779
ANCA-associated vasculitis (1)	51	0/1	1/1	1/1	400

^aAge displayed is age of individual patient. Where study reported two or more patients, the median age is displayed.
^bRange of CD4 cell counts, if study reported two, or more, patients.

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



Thanks Michelle Hermiston, Ivan Hung, Camille Kotton, Jen Mulliken, Brian Schwartz, Paul Volberding, Jackie Wang



Question-and-Answer

Slide 40 of 40

IAS-USA
