Supportive Care for Patients on Biologic Therapy

RYAN ZWICK, PHARM.D.
VANESSA VESELY, PHARM.D.
PGY-1 PHARMACY RESIDENTS
BRYAN MEDICAL CENTER
LINCOLN, NE

Disclosure

The speakers have no actual or potential conflict of interest in relation to this presentation.

Learning Objectives

- Differentiate the terms “biologic” and “biosimilar”
- Identify preventative measures indicated for patients on biologic therapy
- Discuss treatment of common complications associated with biologic therapy

What are biologics?

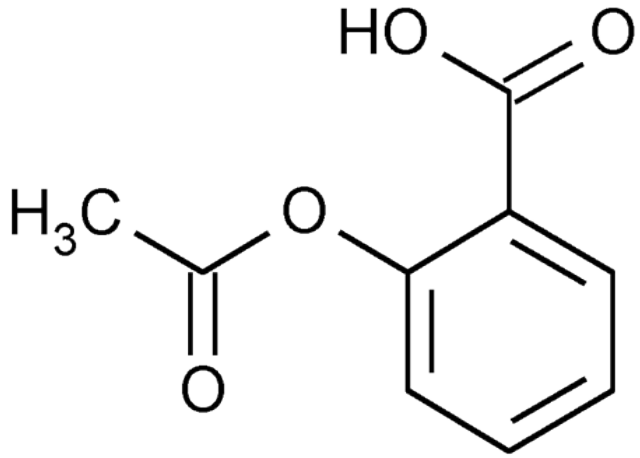
Definition

- **Biological product**
  - Generally large, complex molecules
  - Typically produced from microorganisms
  - Variety of products
    - Therapeutic proteins
    - Monoclonal antibodies
    - Vaccines
  - Indicated to treat variety of conditions including:
    - Rheumatoid Arthritis (RA)
    - Psoriasis
    - Crohn's Disease
    - Malignancies

What are "biologics" questions and answers. 2017.

Small vs. Large Molecule Drugs

Small Molecules (Pharmaceuticals)	
Chemical Structure	Small, well-defined
Form	Homogeneous product • Made by chemistry
Shape	Small and stable
Degradation/ metabolism	Few routes: CYP enzymes



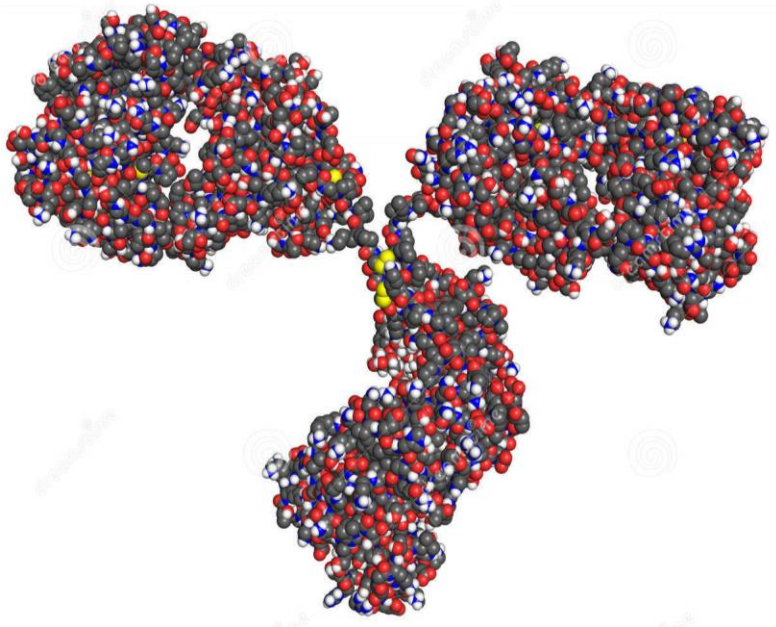
Aspirin

CYP = Cytochrome P450

Lybecker K. 2016.
Image: http://www.uspbpep.com/usp31/v31261/usp31nf26s1_m6240.asp

Small vs. Large Molecule Drugs

Large Molecules (Biologics)	
Chemical Structure	Large, difficult to define
Form	Heterogeneous product • Made by cells
Shape	Large and variable
Degradation/ metabolism	Many routes: Proteases



Trastuzumab (Herceptin®)

Lybecker K. 2016.
Image: https://www.dreamstime.com/royalty-free-stock-images-antibody-structure-image26640389

How do biologics work?

Mechanisms of Biologics

- Tumor Necrosis Factor-alpha (TNF-α) inhibitors
- Interleukin (IL) antagonists
- Co-stimulation blockers (Anti-CD20, CD 80/86)
- Janus Kinase (JAK) inhibitor

When to use biologics?

Pathophysiology of Rheumatoid Arthritis (RA)

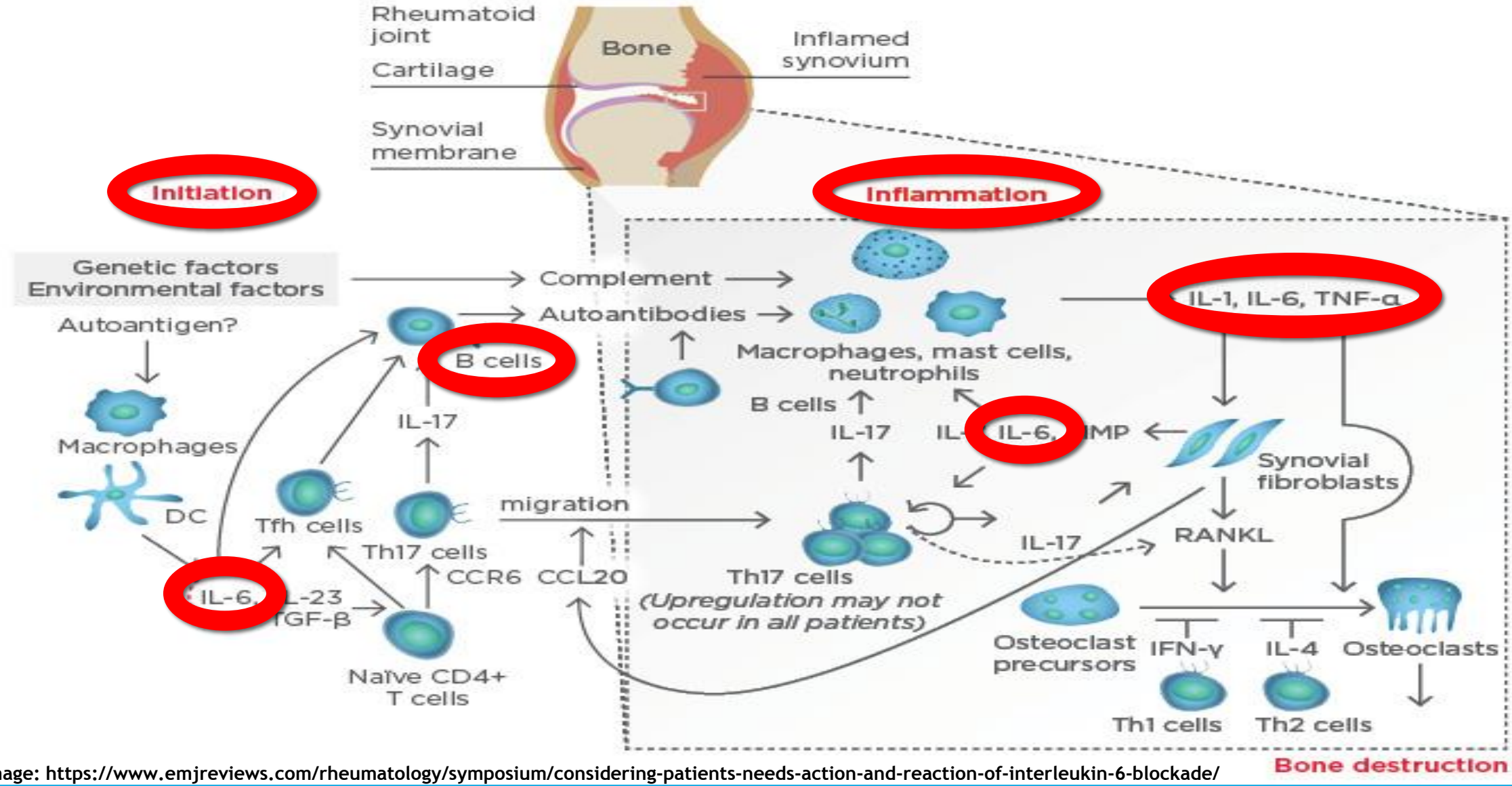


Image: https://www.emjreviews.com/rheumatology/symposium/considering-patients-needs-action-and-reaction-of-interleukin-6-blockade/

Biologics Approved to Treat RA

Generic	Brand	Route	Frequency	Half-life
TNF-α Inhibitors				
Etanercept	Enbrel®	SQ	Weekly	4.2 days
Infliximab	Remicade®	IV	Every 4-8 weeks	7-12 days
Adalimumab	Humira®	SQ	Every 2 weeks	14 days
Certolizumab	Cimzia®	SQ	Every 4 weeks	14 days
Golimumab	Simponi®	SQ	Every 4 weeks	14 days

SQ = subcutaneous
IV = intravenous

Biologics Approved to Treat RA

Generic	Brand	Route	Frequency	Half-life
IL-6 Inhibitors				
Tocilizumab	Actemra®	SQ	Weekly	13 days
Sarilumab	Kevzara®	SQ	Every 2 weeks	8-10 days
IL-1 Inhibitors				
Anakinra	Kineret®	SQ	Daily	4-6 hours (terminal)

SQ = subcutaneous
IV = intravenous

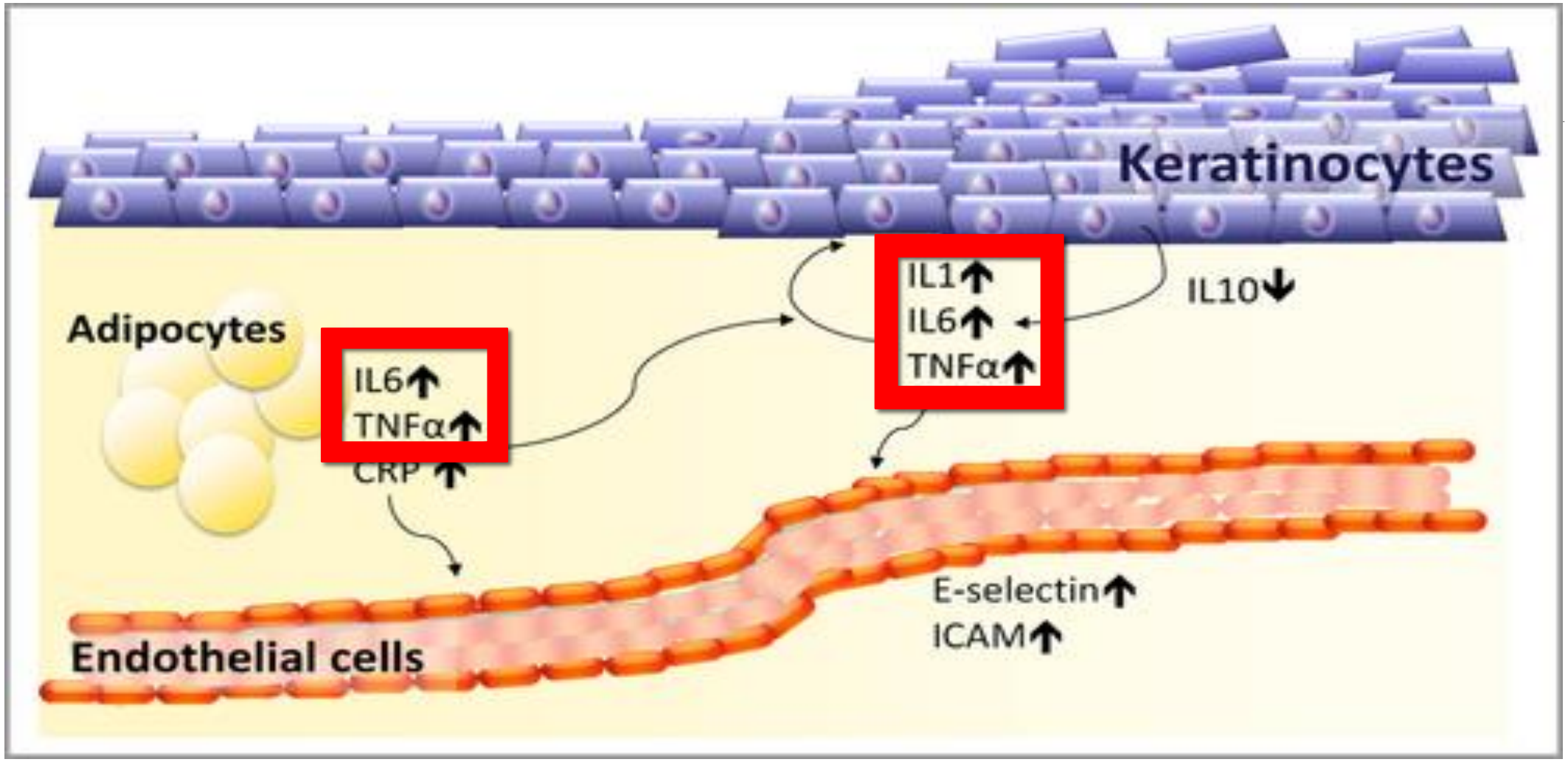
Biologics Approved to Treat RA

Medication	Brand	Route	Frequency	Half-life
Costimulation Blockade (CD 80/86)				
Abatacept	Orencia®	IV	Every 4 weeks	13 days
B-cell Inhibition and Depletion (CD 20				
Rituximab	Rituxan®	IV	Every 24 weeks	18 days
Janus Kinase Inhibitors				
Tofacitinib	Xeljanz®	PO	Daily	3 hours
Baricitinib	Olumiant®	PO	Daily	12 hours

PO = Per Oral

IV = intravenous

Pathophysiology of Psoriasis



Dowlatshahi E. Br J Dermatol. **2013.**

Biologics Approved to Treat Psoriasis

Generic	Brand	Route	Frequency	Half-life
TNF-α Inhibitors				
Etanercept	Enbrel®	SQ	Weekly	4.2 days
Infliximab	Remicade®	IV	Every 2 months	7-12 days
Adalimumab	Humira®	SQ	Every 2 weeks	14 days
Certolizumab	Cimzia®	SQ	Every 2 weeks	14 days
IL-12/23 Inhibitor				
Ustekinumab	Stelara®	SQ	Every 12 weeks	15-46 days

IV = intravenous

Biologics Approved to Treat Psoriasis

Medication	Brand	Route	Frequency	Half-life
IL-17 Inhibitors				
Secukinumab	Cosentyx®	SQ	Every 4 weeks	22-31 days
Ixekizumab	Taltz®	SQ	Every 4 weeks	13 days
Brodalumab	Siliq®	SQ	Every 2 weeks	—
IL-23 Inhibitors				
Guselkumab	Tremfya®	SQ	Every 8 weeks	15-18 days
Tildrakizumab	Illumya®	SQ	Every 12 weeks	23 days

SQ – subcutaneous

Pathophysiology of Crohn's Disease

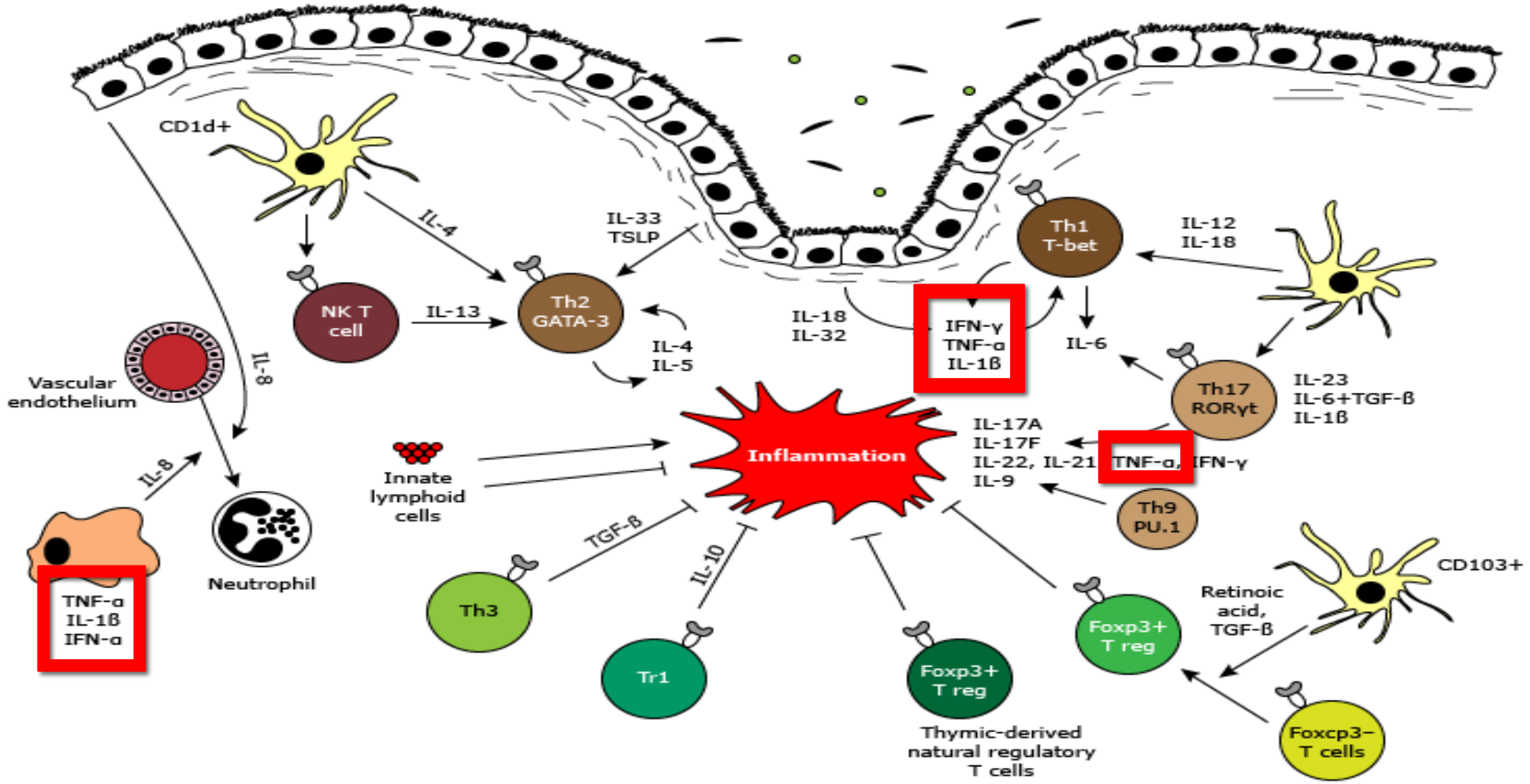


Image: https://www.uptodate.com/contents/image?imageKey=GAST%2F74195&topicKey=GAST%2F4077&search=crohns&source=outline_link

Biologics Approved to Treat Crohn's Disease

Generic	Brand	Route	Frequency	Half-life
TNF-α Inhibitors				
Infliximab	Remicade®	IV	Every 8 weeks	7-12 days
Adalimumab	Humira®	SQ	Every 2 weeks	14 days
Certolizumab	Cimzia®	SQ	Every 4 weeks	14 days
Miscellaneous				
Ustekinumab	Stelara®	SQ	Every 8 weeks	19 days
Vedolizumab	Entyvio®	IV	Every 8 weeks	25 days
Natalizumab	Tysabri®	IV	Every 8 weeks	3-17 days

SQ = subcutaneous

IV = intravenous

Biologics in Common Disease States

Class	Rheumatoid Arthritis	Psoriasis	Crohn's Disease
TNF-α Inhibitor	✓	✓	✓
Interleukin Inhibitors	✓	✓	
Anti-CD 20 Blocker	✓		
JAK Inhibitors	✓		

What about biosimilars?

Definition

- **Biosimilar**
  - Highly similar to a biological product
  - Has no clinically meaningful differences from an existing FDA approved product
  - Minor differences (i.e. stabilizers or buffers added to formulation)
  - Use pharmacokinetic and pharmacodynamics studies to assess for “clinically meaningful differences”

Biosimilars and Interchangeable Products. 2017.

Biosimilar	Generic
Similar to reference product	Bioequivalent and identical to reference product
Cannot automatically substitute for reference product	Interchangeable with reference product
Estimated cost to develop: $75-$250 million	Estimated cost to develop: $1-$5 million
Estimated duration of development process: 8-10 years	Estimated duration of development process: 3-5 years

Lybecker KM. Frazer Institute. 2016.
Biosimilars and Interchangeable Products. 2017.

Definition

- **Interchangeable product**
  - Biologics Price Competition and Innovation Act of 2009
  - Must meet additional requirements for approval than biosimilar
  - Can be substituted without provider notification
  - Currently, no biologic or biosimilar agents meet this criteria

Biosimilars and Interchangeable Products. 2017.

Biologics Price Competition and Innovation Act of 2009

- Expedited process
- Extrapolation approval
- Biosimilar product application must include:
  - Analytical studies with only minor differences (if any) in clinically inactive components
  - Animal studies assessing toxicity
  - Clinical studies to assess pharmacokinetics, pharmacodynamics, safety, potency, and purity
- Additional information required for interchangeable product

Biosimilar Development, Review, and Approval. 2017.

Biologics Price Competition and Innovation Act of 2009

- Goals of extrapolation approval
  - Reduce need for costly clinical trials
  - Accelerate access to new products
  - Provide additional therapeutic options
  - Reduced prices for patients
- Nomenclature
  - Will use same “core” name as reference product with a unique 4-letter suffix
  - Ex: pegfilgrastim-**jmdb**
- First biosimilar approved by FDA in March 2015
  - 17 total biosimilars approved
  - No approved interchangeable products

Biosimilar Development, Review, and Approval. 2017.
Nonpropietary naming of biological products. 2017.

Switching Between Products

- Possible concerns
  - Immunogenicity
  - Safety
  - Efficacy
  - Interval between discontinuation and initiation
- FDA has not approved any biosimilar products as fully interchangeable with reference biologic
- Literature is limited

Cohen HP. Drugs. 2018.
Moots R. Curr Rheumatol Rep. 2017.

Switching Between Products

- Cohen 2018
  - Literature review of 90 studies
    - 54 studies for larger biologics with 8,443 total patients
  - Most evaluated only a single switch
  - 41% of studies evaluated immunogenicity by immunoassays
  - Overall concluded switching from a reference product to biosimilar is not “inherently dangerous”
- Moots 2017
  - Literature review, assessed similar studies as Cohen 2018
  - Inconclusive regarding similar safety and efficacy when switching
  - More pharmacovigilance programs needed

Cohen HP. Drugs. 2018.
Moots R. Curr Rheumatol Rep. 2017.

Preventative Measures

Preventative Measures

- Coordination of care
  - Medication reconciliation
  - Lab Screening
  - Vaccine recommendations

Center for Disease Control Vaccination Schedule

Vaccine	19–21 years	22–26 years	27–49 years	50–64 years	≥65 years
Influenza inactivated (IIV) or **Influenza recombinant** (RIV)	1 dose annually				
or					
Influenza live attenuated (LAIV)	1 dose annually				
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap, then Td booster every 10 yrs				
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born in 1957 or later)				
Varicella (VAR)	2 doses (if born in 1980 or later)				
Zoster recombinant (RZV) *(preferred)*				2 doses	
or				or	
Zoster live (ZVL)				1 dose	
Human papillomavirus (HPV) **Female**	2 or 3 doses depending on age at initial vaccination				
Human papillomavirus (HPV) **Male**	2 or 3 doses depending on age at initial vaccination				
Pneumococcal conjugate (PCV13)	1 dose				
Pneumococcal polysaccharide (PPSV23)	1 or 2 doses depending on indication				1 dose
Hepatitis A (HepA)	2 or 3 doses depending on vaccine				
Hepatitis B (HepB)	2 or 3 doses depending on vaccine				
Meningococcal A, C, W, Y (MenACWY)	1 or 2 doses depending on indication, then booster every 5 yrs if risk remains				
Meningococcal B (MenB)	2 or 3 doses depending on vaccine and indication				
***Haemophilus influenzae* type b** (Hib)	1 or 3 doses depending on indication				

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended vaccination for adults with an additional risk factor or another indication

No recommendation

Image: https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html

Inactivated Vaccination Recommendations

	Pneumococcal (PCV13, PPSV23)	Influenza (Inactivated)	Hepatitis (A, B)	Tetanus, diphtheria, and Pertussis	Recombinant Zoster
Before biologic therapy initiation	Yes	Yes	Yes	Yes	No data
During biologic therapy or if immuno-suppressed	Yes	Yes	Yes	Yes	No data

Rubin LG. Clin Infect Dis. 2013.
Recommended Immunization Schedules. 2019.

Live Vaccine Recommendations

	Human Papilloma Virus	Varicella	Influenza (Live, attenuated)	Measles, Mumps, Rubella	Live Zoster
Before biologic therapy initiation	Yes	Yes[A]	No	Yes[A]	Yes[B]
During biologic therapy or if immuno-suppressed	Yes	Contra-indicated	Contra-indicated	Contra-indicated	Contra-indicated

[A] If no evidence of immunity, administer ≥ 4 weeks prior to immunosuppressive therapy
[B] Administer ≥4 weeks prior to immunosuppression, consider waiting ≥ 2 weeks until starting biologic therapy

Rubin LG. Clin Infect Dis. 2013.
Recommended Immunization Schedules. 2019.

Considerations while on biologics

Other Considerations with Biologic Therapy

- Surgeries
- Adverse Events
  - Infections
  - Gastrointestinal (GI) perforation or bleeding
  - Malignancies

Surgical Considerations

- Holding biologics in perioperative period
  - **2008 American College of Rheumatology Guidelines**
    - Considerations:
      - Half life of individual agent
      - Risk of surgery
    - Recommendations:
      - Stop therapy ≥1 week prior
      - Resume ≥1 week after surgery

Saag KG. Arthr Care Res. 2008.

Surgical Considerations

- Holding biologics in perioperative period
  - **2019 Joint American Academy of Dermatology- National Psoriasis Foundation Guidelines**
    - Case by case risk stratification
      - Stop biologic 3-4 half lives prior to surgery

Adalimumab	Humira®	Subcutaneous	Every 2 weeks	Half-life 14 days

      - Restart 1-2 weeks after surgery

Menter A. J Am Acad Dermatol. 2019.

Surgical Considerations

- Impaired wound healing and surgical site infections
  - Conflicting evidence in studies
  - Other contributing factors
    - Advanced patient age
    - Duration of therapy prior to surgery
  - Risk vs benefit
  - Guideline-issued statements regarding holding and resuming therapy

Krause ML. World J Orthop. 2014.
Momohara S. Mod Rheumatol. 2011.
Tada M. Clin Rheumatol. 2016.

Infectious Considerations

- Monitoring of infectious parameters
  - Fever/febrile neutropenia
- Holding biologic medications

Risk of Infection

- Listing J, 2005
  - Prevalence of infection
- Singh JA, 2015
  - Dose dependent risk

Listing J. et.al. Arthritis Rheum. 2005.
Singh JA. et al. Lancet. 2015.

Infection Treatment

- Medication reconciliation
  - Which biologic agent
  - When last taken
- Considerations
  - Infectious disease consultation
  - Source of infection
  - Duration of therapy
  - Pathogens isolated
    - Opportunistic organisms

Gastrointestinal Perforation or Bleeding

- Rare but serious adverse event
- Lower gastrointestinal (GI) bleed more common than upper GI bleed
- Other possible contributing factors
  - Class of biologic
  - Concomitant use of biologics and non-steroidal anti-inflammatory (NSAID) medications and/or glucocorticoids
  - History of diverticulitis
- Literature findings

Curtis JR. Arthr Care Res. 2012.
Xie F. Arthr Rheumatol. 2016.
Curtis JR. Arthr Rheumatol. 2011.
Jagpal A. Drug Saf. 2018.

Gastrointestinal Perforation or Bleeding

- **Curtis JR, 2012**
  - Retrospective insurance claim analysis, for patients with RA hospitalized with GI perforation
  - Perforation rate: 1.7 per 1,000 person-years
  - Most significant risk factors:
    - Diverticulitis
    - Age
    - Use of glucocorticoids
    - NSAIDs
  - Biologic use without glucocorticoid exposure NOT a risk
  - Focused predominantly on TNF-α inhibitors

Curtis JR. Arthr Care Res. 2012.

Gastrointestinal Perforation or Bleeding

- **Xie F, 2016**
  - Retrospective insurance claim analysis, focused on RA patients hospitalized for GI perforation
  - Stratified perforation rate by biologic agent
    - Higher rates in IL inhibitors vs TNF-α inhibitors (1.55 per 1,000 person years vs 0.84 per 1,000 person years)
  - Other predictors of lower-GI perforation:
    - Older age
    - Diverticulitis
    - Prednisone dose ≥ 7.5 mg/day

Xie F. Arthr Rheumatol. 2016.

Malignancies

- Risk thought to be due to immunosuppression
- **2019 Joint American Academy of Dermatology- National Psoriasis Foundation Guidelines**
  - TNF-α inhibitors
    - Not associated with risk for malignancy
  - IL-12/IL-23 inhibitors and IL-17 inhibitors
    - No definitive evidence
- **Garcia-Doval I, 2018**
  - Meta-analysis including ~60,000 patient years of observations
  - Main outcome: odds ratio of cancer in case vs controls
  - Found risk of first cancer NOT significantly associated with cumulative exposure to biologic therapy
  - Study not powered to detect differences in specific types of cancer

Menter A. J Am Acad Dermatol. 2019.
Wilton KM. Rheumatol Ther. 2017.
Garcia-Doval I. Br J Dermatol. 2018.

Summary

- Biologic vs biosimilar
- Biosimilar vs generic
- Most inactivated vaccines are safe to administer during treatment with biologic therapy
- Complications associated with biologic therapy
  - Perioperative management
  - Infection awareness
  - Gastrointestinal perforation and bleeding
  - Malignancies

References

- Biosimilar development, review, and approval. U.S. Food and Drug Administration. 2017. Web. Accessed 5 Mar 2019. Available from: https//www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580429.htm
- Biosimilar and Interchangeable Products. U.S. Food and Drug Administration. 2017. Web. Accessed 5 Mar 2019. Available from: < https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580419.htm>
- Cohen HP, Blauvelt A, Rifkin RM, Danese S, et al. Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes. Drugs. 2018; 78(4):463-478.
- Curtis JR, Lanas A, John A, Johnson DA, Schulman KL. Factors Associated with Gastrointestinal Perforation in a Cohort of Patients with Rheumatoid Arthritis. Arthr Care Res. 2012;64(12)1819-1828.
- Curtis JR, Xie F, Chen L, Spettell C et al. The Incidence of Gastrointestinal Perforations Among Rheumatoid Arthritis Patients. Arthritis Rheum. 2011; 63(2): 346-351.
- Garcia-Doval I, Descalzo MA, Mason KJ, Cohen AD, et al. Cumulative exposure to biological therapy and risk of cancer in patients with psoriasis: a meta-analysis of Psonet studies from Israel, Italy, Spain, the U.K. and Republic of Ireland. Br Dermatol. 2018;179(4): 863-871.
- Jagpal A, Curtis JR. Gastrointestinal Perforations with Biologics in Patients with Rheumatoid Arthritis: Implications for Clinicians. Drug Saf. 2018;41(6):545-553.
- Krause ML, Matteson EL. Perioperative management of the patient with rheumatoid arthritis. World J Orthop. 2014;5(3): 283-291.
- Listing J, Strangfeld A, Kary S et al. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis & Rheumatism. 2005;52(11):3403-3412. doi:10.1002/art.21386
- Lybecker KM. The Biologics Revolution in the Production of Drugs. Fraser Institute. 2016. Available from: <http://www.fraserinstitute.org>

References

- Menter A, Strober BE, Kaplan DH, Kivelevitch D, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019; doi: 10.1016/j.jaad.2018.11.057.
- Momohara S, Kawakami K, Iwamoto T, Yano K, et al. Prosthetic joint infection after total hip or knee arthroplasty in rheumatoid arthritis patients treated with nonbiologic and biologic disease-modifying antirheumatic drugs. Mod Rheumatol. 2011;21(5): 469-475.
- Moots R, Azvedo V, Coindreau JL, Dorner T et al. Switching Between Reference Biologics and Biosimilars for the Treatment of Rheumatology, Gastroenterology, and Dermatology Inflammatory Conditions: Considerations for the Clinician. *Curr Rheumatol Rep*. 2017; 19(6): 37.
- Nonpropietary naming of biological products. U.S. Food and Drug Administration. 2017. Web. Accessed 5 Mar 2019. Available from: <https://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf>
- Recommended Adult Immunization Schedule by Medical Condition and Other Indications, United States, 2019. Centers For Disease Control and Prevention. 2019. Available from: https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html
- Rubin LG, Levin MJ, Ljungman P, Davies EG et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58(3):e44-e100.
- Saag KG, Ten GG, Patkar NM, Anuyntiyo J et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthr Care Res*. 2008; (59):6: 762-784. https://doi.org/10.1002/art.23721
- Singh J, Saag K, Bridges S et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol*. 2015;68(1):1-26. doi:10.1002/art.39480
- Singh JA, Cameron C, Noorbaloochi S, Cullis T et al. The risk of serious infection with biologics in treating patients with rheumatoid arthritis: A Systematic Review and Meta-analysis. Lancet. 2015; 386 (9990): 258-265.

References

- Tada M, Inui K, Sugioka Y, Mamoto K et al. Delayed wound healing and postoperative surgical site infections in patients with rheumatoid arthritis treated with or without biological disease-modifying antirheumatic drugs. Clin Rheumatol. 2016; 35:1475-1481.
- What are “biologics” questions and answers. U.S. Food and Drug Administration. 2017. Web. Accessed 5 Mar 2019. Available from: < https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cber/ucm133077.htm>
- Wilton KM and Matteson EL. Malignancy incidence, management, and prevention in patients with rheumatoid arthritis. Rheumatol Ther. 2017;4(2):333-347.
- Xie F, Yun H, Bernatsy S, Curtis JR. Risk for Gastrointestinal Perforation among Rheumatoid Arthritis Patients receiving Tofacitinib, Tocilizumab, or other Biologics. Arthr Rheumatol. 2016; 68(11): 2612-2617.
- **Images:**
- Dowlatshahi E, Van der Voort E, Arends L. Markers Of Systemic Inflammation In Psoriasis: Asystematic Review And Meta-Analysis. Br J Dermatol; 2013:1-17.
- https://www.dreamstime.com/royalty-free-stock-images-antibody-structure-image26640389
- https://www.emjreviews.com/rheumatology/symposium/considering-patients-needs-action-and-reaction-of-interleukin-6-blockade/
- https://www.uptodate.com/contents/image?imageKey=GAST%2F74195&topicKey=GAST%2F4077&search=crohns&source=outline_link
- http://www.uspbpep.com/usp31/v31261/usp31nf26s1_m6240.asp
- https://onlinelibrary-wiley-com.cuhsl.creighton.edu/doi/full/10.1111/bjd.12355

A Special Thank You

University of Nebraska Medical Center Hiram R. Walker, MD, Lectureship in Family Medicine

Supportive Care for Patients on Biologic Therapy

VANESSA VESELY, PHARM.D.

RYAN ZWICK, PHARM.D.