Biologic Agents in Clinical Practice: Risks and Benefits of Use

ELIZABETH VANDEWAA, PHD
COLLEGE OF NURSING, UNIVERSITY OF SOUTH ALABAMA

Disclosures

- Dr. VandeWaa has no financial or other conflicts of interest
- Any unlabeled/unapproved uses of drugs or products referenced will be disclosed

Objectives

1. Describe the rise of biologic drugs in the pharmaceutical industry, considering cost and benefit.
2. Discuss the regulation of biologics and how they come to market.
3. Describe common biologic drugs with regard to their uses, including the side effects and adverse effects of biologic drugs.

What is a Blockbuster Drug?

- A drug that generates sales of at least $1 billion annually
- The top-selling drug in the US?
  - ADALIMUMAB (HUMIRA)
- But the number-one prescribed drug is Atorvastatin…also a blockbuster!
- There is only ONE biologic that is a top-25 prescribed drug in the US

Top Prescribed vs. Top Money Makers

- The top prescribed drugs in the US are not always the top money makers—new drugs tend to be the most expensive
  - New technologies and medication formulations cost more
  - Generics and wide use may drive down cost
- There is SOME overlap, but competition is steep—especially for the development of generics
  - Patents "protect" drugs for 7 years
  - Extension of a patent may allow for another 7 years
  - Application for Orphan Drug status gives the drug additional price-setting opportunities

Top Selling Drugs by Profit Worldwide

- 1. **Adalimumab (Humira):** Sales of $20.39 bn. Used for rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, hidradenitis suppurativa, ulcerative colitis, plaque psoriasis
- 2. **Pembrolizumab (Keytruda):** Sales of $14.38 bn. Used for melanoma, non-small cell lung cancer, small cell lung cancer, head and neck cancer, Hodgkin lymphoma, large B-cell lymphoma, bladder cancer, colorectal cancer, stomach cancer, esophageal cancer, cervical cancer, liver cancer, Merkel cell carcinoma, kidney cancer (in combination with Inlyta), endometrial cancer (in combination with Lenvima)

Top Selling Drugs by Profit Worldwide

- 3. **Lenalidomide (Revlamid):** Sales of $12.15 bn. Used for multiple myeloma, myelodysplastic syndromes, mantle cell lymphoma, follicular lymphoma and marginal zone lymphoma
- 4. Apixaban (Eliquis): Sales of $9.17 bn. Used for nonvalvular atrial fibrillation
- 5. Ibrutinib (Imbruvica): Sales of $8.43 bn. Used for mantle cell lymphoma, chronic lymphocytic leukemia, Waldenstrom's macroglobulinemia, marginal zone lymphoma, chronic graft vs. host disease
- 6. **Aflibercept (Eyelea):** Sales of $8.36 bn. Used for wet age-related macular degeneration, diabetic macular edema, diabetic retinopathy, macular edema

Top Selling Drugs by Profit Worldwide

- 7. **Ustekinumab (Stelara):** Sales of $7.94 bn. Used for plaque psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis
- 8. **Nivolumab (Opdivo):** Sales of $7.92 bn. Used for melanoma, non-small cell lung cancer, small cell lung cancer, kidney cancer, Hodgkin Lymphoma, head and neck cancer, bladder cancer, colorectal cancer, liver cancer
- 9. Bictegravir, emtricitabine, tenofovir (Biktarvy): Sales of $7.26 bn. Used for HIV
- 10. Rivaroxaban (Xarelto): Sales of $6.93 bn. Used for clots and clot prevention

Top Selling Drugs by Profit Worldwide

- 11. **Etanercept (Enbrel):** Sales of $6.37 bn. Used for rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis
- 12. **Prevnar-13:** Sales of $5.95 bn. Used for pneumococcal disease
- 13. Palbociclib (Ibrance): Sales of $5.39 bn. Used for HR-positive, HER2-negative breast cancer
- 14. **Bevacizumab (Avastin):** Sales of $5.32 bn. Used for cervical cancer; colorectal cancer; epithelial ovarian, fallopian tube, or primary peritoneal cancer; glioblastoma; kidney cancer; liver cancer; non-small cell lung cancer

Top Selling Drugs by Profit Worldwide

- 15. **Dulaglutide (Trulicity):** Sales of $5.07 bn. Used for T2DM; reduce risk of CV events in T2DM patients
- 16. **Ocrelizumab (Ocrevus):** Sales of $4.61 bn. Used for MS
- 17. **Rituxumab (Rituxan):** Sales of $4.52 bn. Used for chronic lymphocytic leukemia, granulomatosis with polyangiitis and microscopic polyangiitis, non-Hodgkin's lymphoma, pemphigus vulgaris, rheumatoid arthritis
- 18. Enzalutamide (Xtandi): Sales of $4.39 bn. Used for metastatic, castration-resistant prostate cancer; non-metastatic, castration-resistant prostate cancer; metastatic castration-sensitive prostate cancer

Top Selling Drugs by Profit Worldwide

- 19. Osimertinib (Tagrisso): Sales of $4.33 bn. Used for non-small cell lung cancer
- 20. **Infliximab (Remicade):** Sales of $4.195 bn. Used for Chron's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis
- Of the 20 top-selling drugs, 13 of them are biologics! And 10 of them….
- Many biologics get expanded use, new patent protection and Orphan Drug status from emerging data or off-label use

Among the Top 20 Drugs by Profits…

- 1. Adalimumab (Humira)
- 2. Pembrolizumab (Keytruda)
- 7. Ustekinumab (Stelara)
- 8. Nivolumab (Opdivo)
- 11. Etanercept (Enbrel)
- 12. Prevnar-13
- 14. Bevacizumab (Avastin)
- 16. Ocrelizumab (Ocrevus)
- 17. Rituxumab (Rituxan)
- 20. Infliximab (Remicade)

QUESTION

- Question: What are biologic drugs?
- A. Chemical agents manufactured in a laboratory
- B. Drugs that are useful against autoimmune diseases only
- C. Chemicals that break down easily and may cause infection
- D. Drugs that are typically monoclonal antibodies

Major Classifications of Biologics

- Monoclonal Antibodies
- Interferon
- Erythropoietin
- Insulins, other drugs for diabetes
- Vaccines
- Onabotulinumtoxin a
- Tyrosine kinase inhibitors
- Proteasome inhibitors
- ***In the first half of 2021, 42% of new drug approvals were biologics***

What Are Biologic Drugs?

- A biologic drug is a product that is produced from living organisms or contains components of living organisms.
- Biologic drugs include a wide variety of products derived from human or animal cells, or microorganisms by using biotechnology.
- Types of biologic drugs include vaccines, blood, blood components, cells, allergens, genes, tissues, and recombinant proteins.

Biologics—General Mechanism of Action

- Biologic products may contain proteins that control the action of other proteins and cellular processes, genes that control production of vital proteins, modified human hormones, or cells that produce substances that suppress or activate components of the immune system.
- *Biologic drugs are sometimes referred to as biologic response modifiers because they change the manner of operation of natural biologic intracellular and cellular actions.*
- General mechanism of action includes lymphocyte modulators, interleukin inhibitors, tumor necrosis factor-alpha inhibitors.

Targets for Biologics

- Inflammatory mediators play a role in both chronic and acute illness
  - **Interleukins:** A group of more than 40 proteins that modulate B and T cells, cytokine release, activation of eosinophils and mast cells
  - **Tumor necrosis factor alpha**: inflammatory cytokine produced by macrophages/monocytes during acute inflammation; responsible for a range of signaling events within cells, leading to **necrosis** or apoptosis. The protein is important for resistance to infection and cancers.
  - **Leukotrienes**: cause bronchospasm and production of excess mucus and fluid. These chemicals play a key **role** in allergies, allergic rhinitis, and asthma

What are Biologics Used For?

- **Biologics have broad use as therapeutic agents**
  - Cancers: Have revolutionized treatment of breast ca, lung ca, etc.
  - Rheumatoid arthritis, ankylosing spondylitis
  - Crohn's disease, UC
  - Autoimmune diseases: SLE, Eczema, Psoriasis
  - Diabetes
  - Asthma, CF
  - Hep B and C
  - Migraine
  - Angioedema
  - Bleeding disorders
  - MS
  - Cardiovascular risk (HoFH)

QUESTION

- A difference between monoclonal-antibody-derived drugs and chemical drugs is:
- 1. 'Mabs tend to cost less
- 2. 'Mabs have few side effects and drug-drug interactions
- 3. Chemical drugs work inside of cells; 'mabs work extracellularly
- 4. Chemical drugs activate the host immune response; 'mabs inhibit it

Nomenclature: 'Mabs, 'Mibs and 'Nibs

- 'Mabs are monoclonal antibodies derived from human (or rodent) cell lines
  - The host is injected with an antigen. Cells making the Abs are fused with tumor cells (or rapidly growing cell populations) to produce drugs
  - Mabs work on cell membranes or against other protein antigens; mabs also activate the host immune response
- 'Nibs are tyrosine kinase inhibitors—these interrupt cell growth signals and are especially useful in cancer treatment
- 'Mibs are proteasome inhibitors that work intracellularly to break down cell proteins—they are useful for cancer treatment

Uses and Characteristics of 'Nibs

- 'Nibs are created synthetically, but some are considered biologics; they are given PO; Ex: Ibrutinib
- Many of the 'nibs target EGFR
  - **Epidermal Growth Factor Receptor is expressed aberrantly on cancer cells, allowing for faster growth
  - Degree of toxicity often correlates with therapeutic response
- EGFR is also expressed in the skin and the GI tract, so motility dysfunction, excess chloride secretion, skin necrosis and inflammation may be seen
  - Treatment is supportive, loperamide and rehydration; possible antibiotics

Uses and Characteristics of 'Mibs

- 'Mibs cause unwanted proteins to build up in the cell, promoting cell death; they are given PO or IV Ex: Imatinib
  - Because they are substrates for CYP450, DDIs are common
- Common SE include cardiovascular (HF, dysrhythmias), GI (NVD, constipation)
  - Increased age, concurrent chemo or radiation, GI pathology increase risks of ADRs

Uses and Characteristics of 'Mabs

- 'Mabs are used to treat asthma and COPD, C. difficile infection, rheumatoid arthritis, psoriasis, eczema, cancers, hypercholesterolemia, and to prevent migraine headache….and other conditions
- 'Mabs are given parenterally and work outside of cells to accomplish their outcomes
- Common adverse reactions include: immunogenicity, anaphylaxis, cytokine release syndrome, nonacute reactions, dermatologic reactions, gastrointestinal toxicity and hepatotoxicity

How do Biologics Come to Market?

- Center for Drug Evaluation and Research assesses the market readiness of most monoclonal antibody drugs
- *The Center for Biologic Evaluation and Research regulates some biologic products for human use*
  - *Safety, purity, potency, effectiveness of vaccines, probiotics, blood products, cell and gene therapies*
  - *Biologics License Application (BLA) is a request for permission to introduce a biologic product into interstate commerce*
- More than 350 biologics are currently on the market
  - They account for 32.3% of all pharmaceutical sales and are the biggest contributor to increased drug prices in the US
  - **Biologics are granted TWELVE YEARS of market exclusivity from the time they are licensed by the FDA**

Nomenclature of Biologics

- **Reference product**: The original biologic that obtained CDER/CBER approval
- **Biosimilar product**: A biological product that is highly similar to the reference product, possibly with minor differences in clinically inactive components, but no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product.
  - *May be made by the same company as the reference product*

Nomenclature of Biologics

- **Interchangeable product**: A product that has been shown to be biosimilar to the reference product and can be expected to produce the same clinical result as the reference product in any given patient. In addition, for a biological product that is administered more than once to an individual to be determined to be interchangeable, it must be shown that the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.
  - *Often made by a competitor to the reference product*

QUESTION

- Which of the following is true of biosimilar drugs?
- A. Biosimilars have driven down the cost of tradename biologics
- B. Biosimilars do not have the same efficacy as tradename biologics
- C. Tradename biologic manufacturers see biosimilar drugs as a financial threat
- D. All of the above are true

Biosimilar Medications

- Must have high structural similarity to the Biologic drug
- Same safety and efficacy profile as tested by the CDER/CBER
  - "interchangeable"
- Some aspects of the FDA process are abbreviated, but may take longer due to more extensive testing
  - 7-8 years of development/testing
- Cost may be as high as $100-250 million
- Extrapolation of use (indication) is done once the drug tests safe

Examples of Biosimilars

- Adalimumab-bwwd (Hadlima)
- Rituximab-pvvr (Ruxience)
- Trastuzumab-pkrb (Herzuma)
  - Most biosimilars are used outside of the US, currently
- What do the letters signify?
  - Identifiers that are unique to manufacturer; promotes tracking and tracing to ensure patient safety
  - Make sure these identifiers are included in all patient charting!

The "Mab" Market

- Even though most biologics are injectables, they hold the market share; oral biologics and biosimilars are on the rise
- In February 2019, out of the total 17 approved biosimilars only 7 biosimilars including 4 originating biologics could enter the US commercial market.
- **Thus far, biosimilars have NOT driven down the price of biologics, though many more are expected on the market in the next year**

Top Ten Biologics and Their Indications

- **Adalimumab** (Humira): RA, PP, Crohn's, UC, AS, PA, PJIA
- **Rituxumab** (Rituxan): Non-Hodgkins lymphoma, CLL, RA
- **Etanercept** (Enbrel): RA, psoriasis, psoriatic arthritis
- **Trastuzumab** (Herceptin): HER2+ breast ca
- **Bevacizumab** (Avastin): Breast, colorectal, kidney, NSCCL, glioblastoma, ovarian ca
- **Infliximab** (Remicade): RA, Crohn's, psoriasis, UC, AS
- **Insulin glargine** (Lantus): Diabetes
- **Pegfilgrastim** (Neulasta): Neutropenia
- **Interferon-beta 1A** (Avonex): Multiple sclerosis
- **Ranibizumab** (Lucentis): Age-related macular degeneration

Biologics for Diabetes

- Certain insulins were granted biologic status in May, 2020.
  - Insulin glargine (Lantus); the first biosimilar to this agent was introduced in 2020—Insulin glargine—ygfn (Semglee). It is also classified as an interchangeable agent
  - *Highly significant for 2 reasons: Biosimilars are very difficult to bring to market--this is the first biosimilar from a different sponsor (company) than the maker of Lantus. It is an interchangeable agent, meaning prescribers may substitute it for Lantus*
  - *Cost is less for biosimilar insulin glargine: As Lantus, $500 for 3 pens. As Semglee, $177 for 3 pens.*
  - Dulaglutide (Trulicity); Liraglutide (Victoza)

Biologic Medications with Increasing Use

- Alirocumab (Praluent) and Evolocumab (Repatha) are 'mabs that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9)
  - PCSK9 reduces the liver's ability to remove LDL-C from the blood. Useful for HoFH and HeFH when diet, high-dose statins and other lifestyle changes do not work to lower LDL
- Evinacumab-dgnb (Evkeeza) is a new add-on biologic for HoFH
  - Binds to angiopoietin-like protein 3 (ANGPTL3). ANGPTL3 slows the function of certain enzymes that break down fats in the body.

Biologic Medications with Increasing Use

- Omalizumab (Xolair: targets IgE), Mepolizumab (Nucala), Reslizumab (Cinqair), Benralizumab (Fasenra--all target eosinophils; Mep and Ben may be self-administered), Dupilumab (Dupixent) targets inflammatory cytokines; may be self-administered
- Bezlotoxumab (Zinplava): Binds to C.diff toxin B
- Watch for Teplizumab: seeking FDA approval as a treatment to delay T1DM

Biologics with Increasing Use

- Biologics for migraine are becoming increasingly popular
  - Most require prior authorization and a stepwise plan to treat migraine
- Eptinezumab-jjmr (Vyepti): IV given once every 3 months. Must be reconstituted in 100 mL 0.9% NS and given by a HCP; $1600/3 months
  - Nasopharyngitis and hypersensitivity were main SE
- Erenumab-aooe (Aimovig): $600 for 70 mg/month; $1200 for 140 mg/month
- Fremanezumab-vfrm (Ajovy): $640/month
- Galcanezumab-gnlm (Emgality): $653/month

Controversial Biologics

- Aducanumab (Aduhelm): Used to treat Alzheimer's disease in patients with mild cognitive impairment or mild dementia
  - Data were controversial: some studies showed mild improvement, some showed no improvement in patients with mild cognitive impairment due to Alzheimer's
  - *Currently, Medicare will only cover patients using Aducanumab as part of a clinical trial*
- Any biosimilar!!

‘Mabs in Development

- Orthopedic biologics including allografts and chitosan gel to enhance wound healing
- Tralokinumab for atopic dermatitis
- Lebrikizumab for AD
- Nemolizumab for pruritis in AD
- Tezepelumab which blocks cytokine release
- Sphingosine 1-phosphate receptor modulators to decrease the movement of lymphocytes out of nodes

Side Effects, Adverse Drug Reactions, Ease of Use and Acute Incidents with Biologics

DO BENEFITS OUTWEIGH RISKS?

An Eye on the Biologics

- Biologics were first introduced in 1999; achieved wide use by 2001
- Since then:
  - Average cost is $30,000-$40,000/year
  - 34,000 deaths due to use
  - Approximately 500,000 serious adverse events
    - *Death, disability, hospitalization, permanent damage, life-threatening complication*
    - *Histoplasmosis is a serious complication for which many biologics have a BBW*
  - Approvals of some biologics with limited efficacy has come under scrutiny (Aducanumab for Alzheimer’s)

How Easy are Biologics to Obtain?

- Require authorization to fill because of cost
- Average time for authorization to dispensing the drug is 44 days
  - Both insurance review and specialty pharmacy dispensing each took about 22 days
  - Has led to an increase in hospitalizations in patients with asthma, migraine, skin conditions
- *Will the patient fill the Rx when faced with the cost?*

How Does the Pharmaceutical Industry Affect Cost and Availability?

- Exploitation of the drug development and patent system to maintain patent rights (seen with Adalimumab and Ibrutinib)
  - Consistent increase in drug price
  - Blocking the ability of biosimilars to come to the market
  - Adalimumab (Humira) started at $522 per 40 mg syringe. Current price is $2984 per 40 mg syringe—Medicare beneficiaries are paying the cost.
    - US patients pay at least $760 more per syringe than other patients worldwide
    - Biosimilar entry into the market has been blocked until 2023; the manufacturer owns 257 patents for Humira; these expire in 2037 (“patent wall”)

QUESTION

- Which patient is not a good candidate for a biologic drug?
- A. The 32-week pregnant female with a chief complaint of migraine headache
- B. The 18-year-old male with eczema
- C. The 68-year-old female with age-related macular degeneration
- D. None of the above patients are candidates for biologic therapy

General Use Parameters of Biologics

- Biologics typically have storage and reconstitution requirements
  - Follow reconstitution directions
  - *Store properly, do not shake; use when ordered*
  - Usually administered by IV or SubQ injection
  - *If patient self-administers, education is important*
  - Adherence is extremely important
  - *Patients must be made aware of safe medication storage!*
    - *Drug efficacy is directly related to storage conditions*

Safe Use of Biologics

- Safety in breastfeeding and pregnancy has not been established
- *Screen for latent TB and serious infections before using*
- Do not use biologics in patients receiving live vaccines
- *Consider patients with pre-existing GI, skin, liver toxicities*
- Injection may cause anaphylaxis or serious allergic event

General SE of Biologics

- Most biologic drugs have the potential to cause allergic hypersensitivity reactions.
- Biologic drugs that are used for rheumatoid arthritis, psoriasis, and other immune related disorders may modulate the immune system and increase the risk of infections.
- Biologic drugs given by injection may also can cause injection site reactions.
- Biologic drugs given intravenously may cause infusion reactions.

What to Watch For During Biologic Use

- Patient monitoring
  - Record VS during infusion, 15-30 min before and after
    - *Infusion reactions include headache, dizziness, chest tightness, rash, hypotension*
    - *Infusion reactions are reduced by slowing or stopping infusion; treat with acetaminophen, antihistamines, corticosteroids, epinephrine*
  - Delayed infusion reactions include arthralgia, myalgia, malaise, fever, urticarial rash, fatigue and GI symptoms: flu-like syndrome that is difficult to predict by agent and patient
  - Common infections may include URIs, UTIs and rare infections (TB, histoplasmosis, coccidiomycosis, hepatitis B).
    - *Especially in patients receiving anti-TNF alpha agents*

Serious SE of Biologics

- Allergy
- Cancer: overall prevalence rate of 3.85%; for skin cancer, 2.55% in patients with psoriasis
- Hypotension
- Thyroiditis
- Bleeding; blood clots
- Mucositis; stomatitis
- Hepatitis; other infections
- GI perforation

QUESTION

- A patient using a ‘mab presents to the ED with emergent symptoms. Which of the following is a reason to discontinue the ‘mab?
- A. A rash that looks infected
- B. Severe colitis
- C. Liver enzymes 2X ULN
- D. Cytokine release syndrome
- E. All of the above are reasons to discontinue

SE and ADRs of 'Mabs

- ***A reason for a patient to present to the ED***
- **Immunogenicity**: development of adverse immune reactions including anaphylaxis. Prior exposure and route of administration (except for IV) seems to sensitize
- **Nonacute reactions**: delayed hypersensitivity including serum sickness (fever, rash, hemolytic anemia, myalgias). Steroids may be used to treat
- **Cytokine Release Syndrome**: occurs when cytokines are released from WBC after drug administration. Cytokines involved are IL-6, IL-1 and IL-2. NVD and rash are seen; hypotension, tachycardia, tachypnea, seizure, delirium may present. Tocilizumab (an anti-IL-6 mab) is used to treat

Cytokine Release Syndrome

- Cytokine Release Syndrome may be seen after infusion with biologics.
  - Grade 1: Fever, flu-like symptoms
  - Grade 2: Hypotension responding to fluids or low-dose pressors; select organ toxicities
  - Grade 3: Shock requiring high-dose pressors; hypoxia; extensive organ toxicities
  - Grade 4: Mechanical ventilation required

Toxicities of 'Mabs

- **Dermatologic**: 'mibs and some 'mabs may target Epidermal Growth Factor Receptor (EGFR). EGFR regulates differentiation and migration of keratinocytes to the surface of the skin. Blockade of EGFR causes fissures, rash, pruritis and xerosis which predispose the patient to MRSA or herpes simplex. Tx is topical steroids, retinoids, topical or PO antibiotics
- **Gastrointestinal**: diarrhea and severe colitis may occur. Ipilimumab (used for melanoma) and pertuzumab (used for breast cancer) are the most common culprits. Tx is stopping the drug and administering steroids
- **Hepatic:** usually occurs 6 weeks after therapy via hepatocyte necrosis and damage to the biliary tree. Liver enzymes are typically 5x ULN. D/c the drug.

Use of Biologics in Acute Care

- What if a patient needing acute care is also prescribed biologics?
  - Maintain treatment while in ICU
  - Use substitute treatment if needed (insulin, alternate treatments for migraine, non-biologic anti-inflammatory drugs)
  - Consider withholding treatment in patients also receiving high-dose or chronic steroids
  - Always withhold treatment if the patient has severe hepatotoxicity (liver enzymes 5X ULN), severe GI distress

Prevalence of ADRs

- Adalimumab – 169,000 adverse event reports with 13,000 related deaths.
- Etanercept – 135,000 serious adverse event reports and 8,000 related deaths.
- Infliximab – 98,000 serious adverse event reports and 6,000 deaths.
- **Note: these agents make up 10% of the market, yet they are among the most-cited by the FDA for adverse events**
- Demand is HUGE
  - Screen patients for active or risk for infections, other risk factors

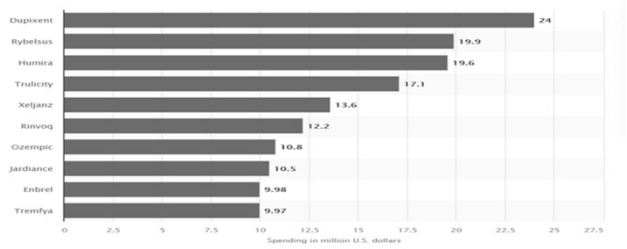
Biologics to Date and Summary

DATA ON BIOLOGIC USE, COST

Drug Advertising and Biologics

- Biologics are among the top-advertised drugs on television and social media
  - Social media does not have the constraints on it that television advertising does
- How many countries allow DTCA?
- Do ads increase drug use? YES
  - Increased prescribing of brand-name drugs
  - In 2016, $6 bn was spent on DTCA; $20 bn was spent on advertising to doctors

Television Ad Spending in Millions, 2021



Ethical Issues Around Biologic Use

- Does direct-to-consumer advertising spur the provider-client interaction?
  - Will the drug work for this patient?
    - Example: Aducanumab for Alzheimer's
  - Those 65+ are the most vulnerable
  - Stay informed of uses, mechanism, SE/ADRs and affordability
  - Patients might be able to access drugs through coupon programs, compassionate use and PBMs. But then?
  - Dilemmas of beneficence occur with some biologics

Biologic Considerations: Cost

- Insurance coverage for biologics varies
- Recently, Alirocumab price was decreased to $5850/year
- Adalimumab and Etanercept each cost $1662-5000/month
  - Methotrexate is $13-80/month
- Trastuzumab cost is between $28,000-50,000 for breast or colon cancer treatment
- Infliximab infusion cost for Crohn's or RA is between $1300-2500
- Andexanet alfa cost is $23,000; not covered by insurance
- Aducanumab cost is $56,000/year (recent label change for patients with mild/moderate cognitive impairment)
  - **Alzheimer's treatment could cost $29 bn; in 2019, Medicare Part B drug cost for ALL patients was $37 bn**

Biologics and the QALY

- With biologics, the Quality Adjusted Life Year assessment should be taken into account
  - QALY takes into account years of life x utility
  - A patient who lives for 1 year, but with 0.5 utility value has 0.5 QALY
  - If a drug positively impacts either duration of life or quality (utility), the QALY goes up.
  - A recent drug combination for melanoma priced the QALY at willingness to pay of $150,000/year
    - In practice, the drug QALY was $276,000/year
    - The drug would have to be taken several years
    - It would have to protect the patient for 20-30 years to be cost-effective.

Summary: Biologics

- Use of biologics and patient demand are increasing at an impressive pace—biologics are revolutionary!
  - Cost does not appear to be too much of a deterrent, but accessibility is limited in patients with no insurance or on Medicare, or once coupon programs lapse
    - Compassionate use; GoFundMe
- Patients in both outpatient and in hospital settings care may require biologics (bleeding disorders, C diff, migraine, etc.) or may present due to severe side effects associated with biologic use (anaphylaxis, colitis, hepatotoxicity)
- Biologic use and development are both expanding; data on biologic drugs may be found at the FDA's website, **(FDA.gov/Purple Book Database)**

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