An Introduction to Biologics: The science and use for patient success
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Disclosure Statement
• Abbvie Speaker’s Bureau

Objectives
• By the end of the presentation, the participant will be able to:
  – Describe and understand the role of cytokines and interleukins in the pathophysiology of psoriasis and list approved treatments for psoriasis that target these specific proteins.
  – Understand efficacy data and safety issues associated with biologics.

Objectives (continued)
• By the end of the presentation, the participant will be able to: (cont.)
  – Differentiate TNF-α inhibitors with each other and with other therapies based on the mechanism of action, efficacy, safety and clinical use.
  – Describe the effects of comorbidities associated with psoriasis and how biologics relate to them.

What is psoriasis?
• Hyperactive skin cell production
  – Normal cycle is 311 hours
  – In psoriasis – 36 hours
• Formerly considered skin disease only
  – Now understood as a specific skin presentation due to elevated levels in the body of a protein known as TNF-α

References
Additional references at end of presentation
No Shortage of OTC “Cures”

Persistent Inflammation

Scalp Psoriasis

Psoriasis on the Trunk

Nail Pitting and Onychorrhexis

Psoriatic Arthritis
Chronology of Psoriasis Treatments

- **1890s**
  - Topical iron and cod liver oil application

- **1920s**
  - Topical 5% coal tar followed by UVB radiation (Goeckerman regimen)

- **1950s**
  - Oral, topical, IV steroids

- **1970s**
  - Oral methotrexate

- **1980s**
  - Oral retinoids

- **1990s**
  - Topical calcipotriene and oral cyclosporine

Classic Psoriasis Step Treatment

- Topical: Calcipotriene and steroid
- Targeted laser or phototherapy
- Oral regimen
- TNF-α or interleukin antagonist (biologic)
- Oral with biologic

Topical Treatment in Psoriasis

PUVA Treatment

Laser Treatment in Psoriasis
Oral Treatments

Biologics

Basics on Biologics
- Fastest growing class of drugs in the pharmaceutical industry
  - Enormous strides in cancer and autoimmune disorders with intense targeting and selectivity of disease
  - Staggering costs, crippling adverse effects
- 1982 recombinant insulin first biologic

How Biologics are Made
- Disease-fighting protein spliced into cells of a living organism
  - Cells extracted from living organism
  - Cells multiply into large quantities
- Finally, the desired proteins are extracted and purified into a biologic medicine, and reintroduced into host

The 1994 Psoriasis/TNF Connection
  - Revealed high levels of TNFa in psoriasis samples
  - Using anti-TNFa antibodies showed conclusive evidence of lessened inflammation
The Challenge of Treatment

Tumor Necrosis Factor

- Tumor necrosis factor (TNF) is a cell-signaling protein AKA cytokine, that is involved in systemic inflammation.
  - TNF is one of the cytokines that make up the "acute phase" response.
  - TNF is produced by many types of cells including white blood cells, neutrophils, mast cells and eosinophils.

The Good News of TNF

- TNF works against bacteria, viruses, tumors, parasites and in cancers by inflammatory and suppressive means
  - It stimulates proliferation of other anti-inflammatory cytokines.
- TNF has a very important and active role in a healthy immune system.

The Bad News of TNF

- Overexpression of TNF disrupts the normal immune response.
- Elevated levels of TNF are found in multiple chronic immune-mediated diseases.

Tumor Necrosis Factor-alpha

- Although initially discovered as an anticancer agent, TNF-α and its family members have now been linked to an array of conditions, including cancer, neurologic diseases, cardiovascular diseases, pulmonary diseases, autoimmune diseases and metabolic diseases when overexpressed.

TNF Implicated in Multiple Conditions
The Proliferation of TNF

Interleukins
- Much like TNF-a, these are also proteins or cytokines that are expressed in the inflammatory process of psoriasis.
- Generally a smaller group than TNF-a
- Very specific target in attempt to lessen the adverse effects profile

The FDA Definition of a Biologic
- "Biologics are genetically-engineered proteins derived from human genes (living cells). They are designed to inhibit specific components of the immune system that play pivotal roles in fueling inflammation, which is a central feature of psoriasis."

The Goldilocks Conundrum
- How can we balance an immune system dysfunction with an immunomodulator, without inducing any immune-system adverse effects?
- The key is: TARGETING

Biologics
Why IV or injections?
- Because they do not have preservatives, biologics are extremely sensitive to heat and light.
- Biologics are easily destroyed by gastric acid, which negates the oral route.
- Generally safe in breast-feeding

"Biologics Affect the Immune System"
- Hopefully, yes.
  - The over expression of TNF is ruinous to the body long-term.
- Hopefully, no.
  - Because biologics suppress the immune system response, patients taking these drugs have an increased risk of infection.
Drugs vs. Biologics
- A drug is a chemical synthesis between specific ingredients.
  - Biologics are manufactured in living systems (i.e., cells, using DNA technology)
- The “product is the process.”
  - Sensitive cells can affect final product and how it functions in the body.
- Extremely expensive for consistency

Quick Goals to Attain
- Most trials report patients feeling better as early as their first or second injection.
- Biologics are not a cure, but slow the progression of the disease.
- Main goals are to reduce plaques, lessen morning joint stiffness and tenderness.

Can biologics be combined?
- Great question
- No
- Never
- Next slide

What can be used with biologics?
- Methotrexate
  - Discussion
- Steroid
  - Discussion
- Cyclosporine
  - Not recommended due to renal toxicity
- Any patient on concomitant therapy has increased risks of multiple infections or serious disorders.

Biologics and Vaccines
- Live vaccines are contraindicated when using biologics because of lower vaccine immunogenicity.
  - Initiate vaccinations three months prior to beginning biologics
- Vaccines OK during treatment if not live or inactivated, ie, pneumococcal, influenza, tetanus toxoid

Biologics with Surgery, Conception and Pregnancy
- A difficult discussion
- General practice is to stop biologic therapy up to a month before and after surgery.
- Conception and pregnancy is a discussion of risk and benefit but a review of studies deems generally safe.
Preparing the Patient for a Biologic

• PPD/QuantiFERON TB Gold test
• CBC, CMP, lipid panel
• Why not ESR/ANA/SS-A or SS-B?
• Chest x-ray
• Hepatitis B, C

Traditional Systemic (Oral) Treatments for Psoriasis

• Acitretin (Soriatane®)
  – Adults with severe psoriasis not planning to conceive
  – Two forms of birth control for women of childbearing potential
  – 10 mg to 50 mg/day, once a day
  – Teratogenicity, liver, renal and hyperlipidemia considerations

Lab Orders

• Baseline CBC, CMP, and lipids
• HIV, Hep B and Hep C
• Chest x-ray and when to repeat
• PPD/QuantiFERON
• Methotrexate/cyclosporine/acitretin
• When to repeat?

Established Biologics

• Adalimumab (Humira®)
  – Ten indications currently from age 2 years and up, and when other systemic indications are not appropriate
  – Indicated in psoriasis and psoriatic arthritis
  – 80 mg subcutaneous first week and then 40 mg subq q other week

Traditional Systemic (Oral) Treatments for Psoriasis (continued)

• Cyclosporine (Neoral®)
  – Severe recalcitrant psoriasis
  – 2.5 mg/kg/day in two divided doses
  – Nephrotoxicity, hypertension, contraindicated with PUVA, coal tar and immunosuppressant agents

Traditional Systemic (Oral) Treatments for Psoriasis (continued)

• Methotrexate (Rheumatrex®)
  – Severe recalcitrant disabling psoriasis, classic DMARD
  – 5–25 mg weekly with daily 1 mg folic acid
  – Myelosuppression, hepatotoxicity, nausea, fatigue, pulmonary fibrosis

Lab Orders

• Baseline CBC, CMP, and lipids
• HIV, Hep B and Hep C
• Chest x-ray and when to repeat
• PPD/QuantiFERON
• Methotrexate/cyclosporine/acitretin
• When to repeat?
Established Biologics (continued)

- **Alefacept (Amevive®)**
  - Blocks T-cells
  - 15 mg IM weekly for 12 week cycles
  - Moderately successful for psoriasis
  - No activity against psoriatic arthritis

- **Etanercept (Enbrel®)**
  - 50 mg subq twice a week for three months, then weekly
  - Very commonly used in conjunction with methotrexate
  - Temptation to use 50 mg subq after three month period

Established Biologics (continued)

- **Golimumab (Simponi®)**
  - 50 mg monthly subcutaneously
  - Not approved for plaque psoriasis
  - Most likely used in rheumatology

Traditional Systemic (Oral) Treatments for Psoriasis (continued)

- **Infliximab (Remicade®)**
  - 5 mg/kg by IV at week 0, 2, 6, and then every 8 weeks
  - Hospital setting or infusion center
  - Continues to show strong performance over the years in chronic severe plaque psoriasis

Traditional Systemic (Oral) Treatments for Psoriasis (continued)

- **Ustekinumab (Stelara®)**
  - An interleukin and targets IL 12 and 23 for psoriasis and psoriatic arthritis
  - Weight based at 45 mg and 90 mg subcutaneously every three months after initial bolus
  - Remarkably low serious adverse effects profile

Traditional Systemic (Oral) Treatments for Psoriasis (continued)

- **Secukinumab (Cosentyx®) and ixekizumab (Taltz®)**
  - New interleukins which target IL 17a
  - Secukinumab
    - Weight based 150 mg/300 mg subq once a week for 5 weeks, then once a month for psoriasis and psoriatic arthritis
Secukinumab and ixekizumab (cont.)

- Ixekizumab is subq two weeks for first 12 weeks, then every four weeks
- Most common adverse effects in clinical trials
  - Injection site reactions, upper respiratory infections, nausea and fungal skin infections
  - Ps/PsA coverage, high clearance rates

Comment on Nonbiologic Apremilast (Otezla®)

- Unique oral PDE4 inhibitor, apremilast maintains increased level of cAMP (cyclic adenosine monophosphate)
- Antagonistic effect on prior production of TNF-α and IL-2
- Interrupts the inflammatory cascade earlier as “small molecule”

The Risks of Biologics

- Serious infections much increased with concomitant immunosuppressants (i.e. methotrexate and corticosteroids)
- TB, fungal infections, bacterial and viral
- Avoid pt with history of chronic infections
- Lymphoma in pediatric population

Most Common Biologic Adverse Effects

- Injection site reaction
- Sinusitis
- Headache following injection
- Diffuse rash on trunk

Why do some biologics lose efficacy?

- Immunogenicity
  - All foreign proteins are immunogenic by definition, even those given for therapeutic reasons.
  - These are called anti-drug antibodies (ADA) and rates are listed in literature.
- Patient weight

Why do some biologics lose efficacy? (continued)

- Suboptimal dosing
- Lower serum drug levels
- Intermittent or episodic therapy
- Evolving theory
  - Disease evolves within patient, requiring evaluation of the pathway treatment
When should we consider changing to another biologic agent?

- The adverse effect profile is not tolerated.
- Lack of improvement after four months
- Multiple flares
- It doesn’t make sense to move from a TNF-a antagonist that is not performing to another TNF-a
  – Consider the newer interleukins

The Saga of Psoriasis

- Most likely confused with leprosy throughout history
- Classic “skin” disease with serious systemic consequences
- What does constant inflammation mean?

Classic Psoriatic Comorbidities

- Cancer
- Obesity
- Atherosclerosis
- Metabolic disease
- Increased mortality
- Dyslipidemia
- Hypertension
- Complications with diabetes
- Myocardial infarction
- Stroke
- Sexual dysfunction
- Depression
- CVD

The Risk of Status Quo

- We need to move from seeing psoriasis as a skin disorder with occasional flares, to treating psoriasis/psoriatic arthritis as it’s own serious disease akin to diabetes, congestive heart failure or COPD. The longer a systemic condition is undertreated, the greater the damage to the organs of the body.

Key Unintended Discovery

- The comorbidity, malignancy and death rate in psoriatic patients is higher than average in US population.
- In trials of patients on biologic therapy, all rates referenced above decreased to expected norms associated with the general population.

TNF and the Golden Spice

- Curcumin (diferuloylmethane) is isolated from turmeric.
  – Study shows it can block TNF-a and suppress TNF production
- Also shown to inactivate TNF-a by binding
  – Currently in clinical trials
Observation on Biosimilars

- A generic drug is chemically identical to the branded counterpart.
  - A biosimilar is not
- Biologics can never be exactly replicated due to their inherent variability and status as living cells derived from DNA technology.

Observation on Biosimilars (continued)

- No less expensive to create
- Safety will be projected and assumed.

Knowledge is power.

Summary

- TNF is a potent source of systemic inflammation and in psoriasis
- A lifetime condition requires a lifetime treatment.
- Psoriasis often underrated
- All conversations must begin and end with risk vs. benefit
- Biologic science very much the future

End of Presentation
Thank you for your time and attention.
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References

References (continued)


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Biologic manufacturing is complex.
The Challenge of Treatment

TOXICITY

LIFESTYLE CHANGES

Diet
Exercise
Stress reduction

Salicylic acid
Corticosteroids
Anthrannil
Coal tar

PUVA UVB

PHOTO

PUVA UVB

SYSTEMIC

Hydroxyurea
Biologics
Tioguanine
Cyclosporin
Methotrexate
Retinoids

EFFECTIVENESS

What you eat can drastically affect psoriasis and oftentimes has as much effectiveness as the toxic alternatives.
TNF Implicated in Multiple Conditions

**Autoimmune diseases**
- Ankylosing spondylitis
- Multiple sclerosis
- Eczema
- Hidradenitis suppurativa
- Inflammatory bowel disease
- Atopic dermatitis
- Rheumatoid arthritis
- Psoriasis
- Sarcoidosis
- Scleroderma
- Systemic lupus erythematosus

**Neurologic diseases**
- Alzheimer's disease
- Epilepsy
- Bipolar disorder
- Parkinson's disease
- Depression

**Osteoporosis**

**Cancer**

**Non-alcoholic fatty liver disease**

**Metabolic diseases**
- Obesity
- Diabetes, type 2

**Pulmonary diseases**
- Asthma
- Chronic obstructive pulmonary disease

**Cardiovascular diseases**
- Atherosclerosis
- Myocardial infarction
The Proliferation of TNF

Aberrant activation of osteoclast formation
- Osteoclast
  - Interfer with metabolism
  - Adipocyte
    - Increased differentiation
  - Monocyte
    - Increased cell infiltration
    - Increased angiogenesis
  - Endothelial cells
  - Increased cell infiltration
  - Increased angiogenesis
- Myocyte
  - Myocardial dysfunction and cardiac myocyte death
- Glia
  - Modification of synaptic transmission
- Fibroblast
- Apoptosis
- T-cells proliferation
  - T-cells
    - Antibodies
      - B-cell
        - Increased acute phase response
        - Hepatocytes

TRENDS in Pharmacological Sciences

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