Malignancy Following the Use of Biologics
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No conflicts of interest to disclose.

Objectives
• Explain the common biologics used for the treatment of various autoimmune disorders and their mechanisms of action.
• Compare the side effect profiles of various biologics.
• Discuss the risk of a secondary malignancy associated with the prescribing of a biologic medication.

UIHC Specialty Pharmacy
Pediatric Clinical Pharmacy Specialist
Gastroenterology
– Inflammatory Bowel Disease
– Hepatitis C Infection
– Eosinophilic Esophagitis
Rheumatology
– Juvenile Idiopathic Arthritis
– Systemic JIA
– Periodic Fever Syndromes
– Ankylosing Spondylitis
– Psoriatic Arthritis
– Chronic Recurring Multifocal Osteomyelitis
**Biologics**

- Genetically-engineered proteins manufactured in a living system such as a microorganism, plant or animal cell.
  - Biologics are very large, complex molecules or mixtures of molecules.
  - Requires state of the art knowledge in molecular biology, recombinant biotechnology and cell culture techniques.
- Typically used in a smaller population of patients compared to drugs.

**Tumor Necrosis Factor Inhibitors**

- Adalimumab (Humira)
  - Subcutaneous administration
  - Prefilled syringes or autoinjector
- Certolizumab (Cimzia)
  - Subcutaneous administration
  - Single use vial or prefilled syringe
- Etanercept (Enbrel)
  - Subcutaneous administration
  - Single or multiple use vials, prefilled syringes, autoinjector
- Infliximab (Remicade)
  - Intravenous infusions over about 4 hours
- Golimumab (Simponi)
  - Subcutaneous administration
  - Prefilled syringe or autoinjector

**Interleukin-1 Inhibitors**

- Anakinra (Kineret)
  - Subcutaneous administration
  - Prefilled syringes
- Canakinumab (Ilaris)
  - Subcutaneous administration
  - Single use vial
- Rilonacept (Arcalyst)
  - Subcutaneous administration
  - Single use vial
**IL-1 Inhibitors**

Treatments include:
- Anakinra: Treats rheumatoid arthritis, cryopyrin-associated periodic syndromes.
- Canakinumab: Treats systemic JIA, periodic fever syndromes.
- Rilonacept: Treats cryopyrin-associated periodic syndromes.

**Mechanism of Action**
- **Anakinra**: Blocks the biologic activity of IL-1 alpha and beta by competitively inhibiting IL-1 binding to the IL-1 type 1 receptor, which is expressed in a wide variety of tissues and organs.
- **Canakinumab**: Human monoclonal anti-human IL-1 beta antibody of the IgG1/κ isotype; binds to human IL-1 beta and neutralizes its activity by blocking its interaction with IL-1 receptors.
- **Rilonacept**: Blocks IL-1 beta signaling by acting as a soluble decoy receptor that binds IL-1 beta and prevents its interaction with cell surface receptors.

**IL-6 Inhibitor**

Treatments include:
- Tocilizumab (Actemra): Treats rheumatoid arthritis, giant cell arteritis, polyarticular JIA, systemic JIA, cytokine release syndrome.

**Mechanism of Action**
- Binds to both soluble and membrane-bound IL-6 receptors and has been shown to inhibit IL-6-mediated signaling through these receptors.

**CTLA-4 Inhibitors**

Agent includes: abatacept (Orencia).

**Mechanism of Action**
- Subcutaneous administration:
  - Prefilled syringe
  - Autoinjector
- Intravenous infusion
**CTLA-4 Immunoglobulin**

Treatment option for: rheumatoid arthritis, juvenile idiopathic arthritis, adult psoriatic arthritis

- **Mechanism of Action**
  - A selective costimulation modulator, inhibits T cell activation by binding to CD80 and CD86, thereby blocking interaction with CD28.

  [Image of CTLA-4 mechanism action]


**Rare but Severe Adverse Effects**

- **Anti-TNF Agents**
  - Demyelinating disease
  - Lupus-like reaction
  - Increased risk of infections
  - Malignancy
  - HF exacerbation
- **Interleukin-1 Inhibitors**
  - Increased risk of infections
  - Malignancy
- **Interleukin-6 Inhibitors**
  - Demyelinating disease
  - Increased risk of infections
  - Malignancy
- **CTLA-4 Immunoglobulin**
  - Increased risk of infections
  - COPD exacerbation
  - Malignancy

**Pre-screening for all agents:**
- TB screening
- Hepatitis B
- Hepatitis C
- Liver function
- CBC with differential

**Additional items to consider:**
- No live vaccines while on therapy
- Should be up to date on vaccines
- Should be notified of changes to medications
- Should be notified of illnesses

**Biologics and Secondary Malignancies**

**Inflammatory Bowel Disease**

- **Ulcerative Colitis**
  - Long-lasting inflammation and sores in the innermost lining of your large intestine and rectum
  - May be curable via surgery
- **Crohn’s Disease**
  - Inflammation of the lining of your digestive tract, which may spread deep into affected tissues
  - Not a curable disease and will require life-long therapy
- **Complications**
  - Both: colon cancer; skin, eye, or joint inflammation; primary sclerosing cholangitis; blood clots
  - Crohn’s disease: bowel obstruction; ulcers; fistulas; anal fissures; malnutrition
  - Ulcerative colitis: toxic megacolon; dehydration


**Additional items to consider:**
- No live vaccines while on therapy
- Should be up to date on vaccines
- Should be notified of changes to medications
- Should be notified of illnesses
Inflammatory Bowel Disease
Incidence of malignancy in the adult population

Risk of Lymphoma Associated With Combination Anti-Tumor Necrosis Factor and Immunomodulator Therapy for the Treatment of Crohn’s Disease: A Meta-Analysis
Corey A. Simon1, J. Badie M. Marden1, Sarah M. Persing1, Robin J. Larson1, and Bruce E. Band1

Study Aim:
• To determine the rate of non-Hodgkin’s lymphoma in adult Crohn’s disease patients who have received anti-TNF therapy
• To compare this rate with that of a population-based registry and a population of Crohn’s disease patients treated with immunomodulators

Results: Incidence of Lymphoma
Expected rate of non-Hodgkin’s lymphoma in the Surveillance Epidemiology and End Results database: 1.9/10,000 PYF

Immunomodulators monotherapy: 4/10,000 PYF
Anti-TNF therapy in adult IBD: 6.1/10,000 PYF
• Confidence Interval = 1.5-6.9 compared to “expected rate”
• Confidence Interval = 0.5-7.1 compared to immunomodulator monotherapy

Rate of Lymphoma
• Male patients consistently had higher rates of non-Hodgkin’s lymphoma
• The crude rate non-Hodgkin’s lymphoma rate among anti-TNF exposed subjects increased by age, the age- and gender-specific standardized incidence ratio was significant for male patients between the ages of 20-54 – confidence interval = 1.3-18.1

Characteristics of Patients with Lymphoma
• Mean patient age = 52 years
• 12 patients were treated with infliximab; 1 patient received adalimumab

Things to Consider
1. The majority of patients in the anti-TNF group had previous immunomodulator exposure.
   a. Therefore, reported rates in the anti-TNF group are truly rates of combination anti-TNF and immunomodulator therapy
   b. Are the major contributors to the increased risk the immunomodulators or anti-TNF drugs?
2. Radiation exposure received by patient’s diagnosed with Crohn’s disease.
3. Incomplete dosing data or duration of exposure (i.e. 4 patients received only 1 dose of infliximab)
Inflammatory Bowel Disease
Incidence of malignancy in the pediatric population

Primary Outcome:
absolute rate of serious infection, lymphoma
and death with anti-TNF therapy in pediatric IBD

Results: Incidence of Lymphoma
• Rate of lymphoma seen in pediatric patients prescribed an
  anti-TNF agent: 2.1/10,000 PYF
• Rate of lymphoma compared in the general pediatric
  population: 0.58/10,000 PYF (p=0.18)
• Thiopurine monotherapy: 4.5/10,000 PYF (p=0.48)

Hepatosplenic T-Cell Lymphoma

Aim: investigated the medications, duration of therapy, and ages
of patients associated with Hepatosplenic T-Cell Lymphoma

Things to Consider
1. Approximately 80% received concomitant therapy with an
   immunomodulatory agent
  • Does the risk of lymphoma still exist when pediatric IBD patients are
    taking anti-TNF monotherapy or methotrexate instead of a
    thiopurine?
2. The majority of patients had an average follow-up time of
   shorter than 2 years
  • Both pediatric lymphomas developed 3 years after anti-TNF
    exposure to infliximab
  • Is the lymphoma risk with anti-TNF therapy exposure-dependent
    or a cumulative risk that is dependent on duration of therapy?
Hepatosplenic T-Cell Lymphoma

Results: up to 200 cases of HSTCL have been reported with 36 cases involving IBD patients receiving thiopurines since 1996

- 20 cases received concomitant anti-TNF therapy
- All receiving infliximab
- 4 patients receiving adalimumab
- 1 patient receiving natalizumab
- 16 cases receiving thiopurine monotherapy

- Patients were 12-58 years old, with a median age of 22.5 years
- Only 2 females of the 31 patients whose gender was known

- Subtype of IBD
  - 9 UC
  - 1 Indeterminate Colitis
  - 26 CD

- Average thiopurine exposure time
  - Combination therapy: 5.5 years
  - Monotherapy: 6 years

What’s the absolute risk?
All patients on thiopurines = 1:45,000
Men <35 years of age = 1:7,404
Concomitant anti-TNF and thiopurine therapy = 1:22,000
Concomitant anti-TNF and thiopurine therapy AND men < 35 years of age = 1:3,534

“More than 99.99% of patients on either monotherapy or combination therapy will NOT develop HSTCL, with the exception of men < 35 years of age”

Rheumatologic Diseases

Arthritis (specifically RA and JIA): joint pain or joint disease
- Joint symptoms include:
  - Swelling, pain, stiffness, and decrease range of motion
  - Impacts patients of all ages, gender, and races
  - Leading cause of disability in America

Systemic Onset JIA: fever plus rash, lymphadenopathy, enlarged spleen or liver, or serositis, in combination with joint involvement; clinical diagnosis
- Complication: macrophage activation syndrome – mortality of up to 8%

www.arthritis.org
Objective: to ascertain the relationship between anti-tumor necrosis factor therapy, methotrexate and the risk of lymphoma in patients with rheumatoid arthritis.

Results: Incidence of lymphoma

- 95 lymphomas diagnosed in 89,710 PYF
- Risk of lymphoma is increased in rheumatoid arthritis with a standardized incidence ratio of 1.9 (Confidence Interval=1.3-2.7)

Things to Consider

1. If rheumatoid arthritis severity is related to the risk of developing lymphoma and if patients with the most severe RA are more likely to receive anti-TNF therapy, then lymphoma risk could represent the treatment plus the risk associated with disease activity.
Objective: to summarize the current evidence in order to help health professionals properly advise patients and their families about the possible risk of malignancies in JIA treated with biologic agents.

- Review of the article by Diak et al. that led to the 2008 FDA black box warning
- Review of newer data assessing the risk of malignancy in patients with a diagnosis of JIA

Results: Incidence of malignancy

- Malignancy rate in general pediatric population: 16.8/100,000
  - Lymphoma only: 2.4/100,000
- Total number of malignancies = 48 cases
  - Infliximab use = 31
  - Etanercept use = 15
  - Adalimumab use = 2
- Rate of malignancy for infliximab: 66/100,000
  - Lymphoma only: 44/100,000
- Rate of malignancy for etanercept: 22/100,000
  - Lymphoma only: 11/100,000

Characteristics of patients diagnosed with malignancies

- 88% of the reported cases received anti-TNF therapy concomitantly with an immunomodulator
- 25 had inflammatory bowel disease
  - Most patients receiving infliximab had IBD; therefore, also received an immunomodulator
  - A large number of patients treated with etanercept for JIA also were prescribed methotrexate

Diak et al. Conclusion

- Although TNF blockers might increase the risk of malignancy, a clear causal relationship could not be established

Conclusion

- Although TNF blockers might increase the risk of malignancy, a clear causal relationship could not be established

Simard et al.

- Evaluated the risk of cancer occurrence in a nationwide Swedish population-based cohort of 9020 JIA patients matched with five general-population comparators
  - Relative risk of malignancy in the JIA population diagnosed in 1987 or later was 2.3 for all malignancies and 4.2 for lymphoproliferative malignancies

- Conclusion: there was an elevated risk of malignancy among biologic therapy-naive patients with JIA identified during the last 20 years
**Rheumatologic Diseases**

Incidence of malignancy in pediatric population

What about agents other than the anti-TNF medications?

<table>
<thead>
<tr>
<th>Malignancies reported</th>
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<tbody>
<tr>
<td>Abatacept phase III trial, enrolled 190 patients – 1 acute lymphoblastic leukemia; follow-up trial had no reports of malignancy</td>
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<tr>
<td>IL-1 inhibitors: trials have not reported any malignancies</td>
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<tr>
<td>IL-6 inhibitors: trials have not reported any malignancies</td>
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**Summary**

IBD patient population receiving anti-TNF therapy with/without an immunomodulator

**Questions**

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