Navigating the MAbs in Pediatrics: A special Class of Drugs

Suzette Stone, PhD, PNP, RN
Director of the Center of Advanced Practice Providers
St. Jude Children’s Research Hospital
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Speaker introduction

• Dr. Suzette Stone works as a pediatric nurse practitioner in pediatric stem cell transplant at Stanford Children’s Hospital and a professor at University of California, San Francisco in the pediatric nurse practitioner program. Dr. Stone completed her MSN at Yale University School of Nursing in both primary and chronic pediatric care and a masters of divinity from Princeton Theological Seminary and recently completed her PhD.

Disclosures

None

Learning Objectives

• Illustrate therapeutic uses of monoclonal antibodies within Pediatrics through three case studies of various biologic immunosuppressive agents.
• Describe the mechanism of action of monoclonal antibodies for prevention and treatment of Pediatric disorders.
• Define criteria for monitoring acute and chronic toxicity & side effects of monoclonal antibodies for Pediatric patients, including cytokine release syndrome.
• Recognize the future directions of monoclonal antibodies in Pediatrics.

Immune System

Normal Function
Balance of health and disease
Protects the host
Self, not-Self

Dysregulation of the Immune System
Overactive Immune Response
Autoimmunity
Genetic Factors
Environmental Factors

Dysregulation

Loss of Self-Tolerance
Failure of immune tolerance

Immune System

Autoimmune T & B cell responses
Monocyte/macrophage response
Inflammation
Tissue Damage

Types of Immune Reactions

<table>
<thead>
<tr>
<th>Hypersensitivity Type</th>
<th>Reaction</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Ab directed against cell surfaces or ECM</td>
<td>AI Hemolytic Anemia</td>
</tr>
<tr>
<td>II</td>
<td>Soluble immune complexes deposited in tissue</td>
<td>SLE</td>
</tr>
<tr>
<td>IV</td>
<td>Mediated by effector T cells</td>
<td>Multiple Sclerosis</td>
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Monoclonal Antibodies

What are monoclonal antibodies?
- Immune Modulators
- Proteins produced by hybridomas resulting from the fusion of a B lymphocyte (specific antibodies → antigen) & a myeloma cell capable of unlimited production of nonspecific antibodies

Naming of MAbs
Prefix-random
Designated Target
ba = bacterial
vi = viral
ci = cardio
ki = interleukins
os = bone
ta = tumor

Antibody Production*
u = human
o = mouse

Suffix of MAb
Example of Rituximab

Function
- Selective targeting of cytokines, chemokines, and their receptors, signaling molecules, mediators involved in leukocyte trafficking, and cellular targets such as activated T and B cells.
- Treatment of immunologic diseases, reversal of drug effects, and cancer therapy

Advantages
- Highly specific, binding to a single antigen
- Fewer side effects than conventional drugs

Examples of MAbs in Pediatrics for Autoimmune Diseases

<table>
<thead>
<tr>
<th>Anti-TNF</th>
<th>Infliximab</th>
<th>Crohn’s Disease</th>
<th>Lieroma Cutis</th>
<th>Rheumatoid Arthritis</th>
<th>Psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>Rheumatoid Arthritis</td>
<td>Plaque Psoriasis</td>
<td>Psoriasis</td>
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</table>

<table>
<thead>
<tr>
<th>Anti-C5</th>
<th>Eculizumab</th>
<th>Rheumatoid Arthritis</th>
<th>Lupus</th>
<th>Myeloma</th>
<th>Grass Pili</th>
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</thead>
<tbody>
<tr>
<td>Anti-CD20</td>
<td>Rituximab</td>
<td>Lupus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-IgG</td>
<td>Omalizumab</td>
<td>Asthma, Rhinitis</td>
<td></td>
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</tbody>
</table>

By 2020, analysts are expecting biologics to make up over a quarter of the entire pharmaceutical market.

A1 True
B2 False

Biologic agents have increased by 70% in the last five years to reach $232 billion.
Case #1

Use of Monoclonal Antibodies in Pediatrics

22 month-old male who is 11 months status post stem cell transplant for IPEX (Immunodysregulation Polyendocrinopathy Enteropathy X-linked) syndrome. From a transplant perspective, he is progressing nicely. No signs and symptoms of Graft-Versus-Host Disease and is rebuilding a new immune system as expected. He is free of any infections. No significant diarrhea & occasional spit ups. Unfortunately, he is not interested in eating or drinking and continues to lose weight. Due to the IPEX, he was always underweight (<10%), but is now below 1% for his percentile for age. The registered nutritionist was involved and many different formulas were tried including elemental formulas. GI was consulted and he underwent an upper and lower scope. Biopsies were taken.

What is on likely differential for failure to thrive?

A1 Ulcerative Colitis
B2 IPEX uncontrolled
C3 Eosinophilia
D4 Formula Intolerance
E5 Oral Aversion

Biopsy/Scope results
- Gross appearance confirmed GERD
- Biopsy with > 50 eos/hpf
- Threshold for diagnosis
  • GERD <5 eos/hpf
  • EoE 15 eos/hpf

Final Diagnosis: Eosinophilic Esophagitis

Next steps

Followed consensus guidelines for Eosinophilic Esophagitis (EoE) – 2017
- Initiated a PPI
- Initial response improved symptoms, but continued with FTT
- Initiate Immune Suppression
- Experimental Treatment

Mepolizumab (Nucala)
- Interleukin-5 Antagonist
- FDA Approved for Asthma (eosinophilic phenotype)
- Dosing
  • Children > 6 to 11 years: SubQ: 40 mg once every 4 weeks
  • Children > 12 years and adolescents: SubQ: 100 mg once every 4 weeks
  • No renal or hepatic adjustments
  • Contraindications
    • Hypersensitivity to Mab
    • Metabolism: Proteolytic degradation
    • Half-Life elimination: 16 to 22 days
Case #1

Outcome of the Case

- Never Reached Remission and maintenance on PPI alone
- Budesonide was not effective
- Nucala was given every month
- Within 3 months, patient was on the >10% percentile
- Remained on a normal diet – no restrictions
- Able to come off the PPI

Case #2

Use of Monoclonal Antibodies in Pediatrics

A 18 year-old patient presents with unilateral eye problems (photophobia, vision loss, abnormal pupil, redness, and orbital pain). Eye is watery, but no purulent discharge. No recent URIs. No recent sick exposures or focal signs/symptoms of infection. Patient has been taking Tylenol around the clock for pain. They tried baby shampoo to the eye and tea bags as compress. No improvement.

Patient’s parents are requesting abx for the eye.

Upon taking a patient history, you find the patient is + for irritable bowel syndrome and moderate back and neck pain. In addition, there was notable stiff neck and lower back.

Positive family history for multiple autoimmune disorders.

What labs would you send on this patient?
**Case #2**

Lab Results:
- Positive HLA B-27 & Elevated CRP of 8
  - Human Leukocyte Antigen B27 - highly associated
  - C-Reactive Protein – Inflammatory Marker – Non-Specific

Final Diagnosis: Ankylosing Spondylitis

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**Case #2**

Infliximab (Remicade)
- Tumor Necrosis Factor Blocking agent
- FDA Approved for Ankylosing Spondylitis, Crohn’s, Plaque Psoriasis, Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Refractory Kawasaki Disease & Ulcerative Colitis
- Dosing for Ankylosing Spondylitis
  - IV: 5 mg/kg* at 0, 2, and 6 weeks, followed by 5 mg/kg every 6 weeks
  - No renal or hepatic adjustments, but adjustment for heart failure
- Contraindications
  - Hypersensitivity to Mab
  - Pre-med recommended with Tylenol and Benadryl & PRN HCT
- Metabolism: Unknown
- Half-life elimination: 7 to 12 days

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**Case #2**

Outcome Of Case
- Initial Control with NSAIDS + Physical Therapy/Stretching
- Symptoms remain active
- Administered Infliximab 0, 2, & 6 weeks
- Relief of symptoms within 2 weeks of the first administration

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**Case #3**

Use of Monoclonal Antibodies in Pediatrics

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**Case #3**

10 year-old patient diagnosed with Acute Lymphoblastic Leukemia and has been on therapy protocol. Her last bone marrow showed “minimal residual disease.” They are now being admitted for Blinatumomab initiation.

After 14 hours, the patient developed fever & transient lower blood pressures - resolved w/o intervention. After 24 hours, the patient developed mild tremors & progressive sleepiness. They were able to answer questions appropriately, but was unable to to write her name.

What do you think is the cause of not being able to write her name?
- A1 Infusion Reaction
- B2 Tumor Lysis Syndrome
- C3 Cytokine Release Syndrome
- D4 Normal Effect of Blinatumomab
- E5 Neurotoxicity from Prior Therapy (ie Methotrexate)
Case #3

Final Diagnosis: Cytokine Release Syndrome

Initially the case was classified as Grade 1 CRS and Grade 2 Neurotoxicity

At hour 36, Neurology was consulted and increased the case to Grade 3 Neurotoxicity. Per protocol, Blinatumomab was stopped.

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Cytokine Release Syndrome

- Supraphysiologic response to immune therapy
- Systemic Reaction
- Role of Cytokines/Clinical Manifestations
  - IFN-γ: fever, chills, headache, dizziness, and fatigue
  - TNF-α: flu-like, watery diarrhea, vascular leakage, cardiomyopathy, and lung injury
- Treatment
  - IL-6 activation \( \rightarrow \) can use IL-6R antagonist called Tocilizumab
  - Steroids

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Onset: 1 – 14 days (2-3 days median)

Laboratory Evaluation
- CBC with Diff
- PT, PTT, Fibrogen, and D-Dimer
- Serum electrolytes, BUN/Cr, LFTs, Uric Acid and Lactate
- ? Of Arterial Blood Gas
- CRP, Ferritin, and Cytokine Panel

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Case #3

Cytokine Release Syndrome

- Onset: 1–14 days (2-3 days median)
- Laboratory Evaluation
  - CBC with Diff
  - PT, PTT, Fibrogen, and D-Dimer
  - Serum Electrolytes, BUN/Cr, LFTs, Uric Acid and Lactate
  - ? Of Arterial Blood Gas
  - CRP, Ferritin, and Cytokine Panel
- Consider CPR and supportive Oxygen

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Case #3

Infliximab (Remicade)

- Bispecific CD19-directed CD3 T-cell engager
- FDA Approved for MRD + B-cell precursor ALL or Relapsed or Refractory
- Dosing
- Based on Oncology Protocol
- No renal or hepatic adjustments
- Drug interactions – Suppress CYP450 enzyme activities
- Contraindications
- Hypersensitivity to Mab
- Pre-med recommended with Dexamethasone
- Metabolism: Unknown
- Half-life elimination: 2 hours

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Outcome of Case

- MRI/MRA to evaluate Neurotoxicity
- Treatment of CRS with Dexamethasone
- Blinatumomab was restarted at lower dose per guidelines
- Pre-medication with Dexamethasone continued for the rest of the course
- No more CRS or Neurotoxicity for the rest of the course
Monitor Monoclonal Antibodies
Use of Monoclonal Antibodies in Pediatrics

Side Effects of MAbs

- Fever &/or chills
- Flushing
- Itching
- Changes in HR and BP
- Dyspnea
- N/V/D
- Rash

Monitor MAbs

- Choosing Pre-Medications
- Monitoring for Anaphylaxis
- Vital Sign Monitoring and Mental Status Checks
- Re-Challenging Post Reaction

Primary Care Implications

- Vaccinations
- Bacterial Prophylaxis
- Increase risk of Infections

Future Directions of MAbs

- Shift to more biologics in Primary Care Settings
- Increase in assess to biologics with new compensations models & competition
- Niche Development for specific targets in broader categories
- Changing routes of administration