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Mepolizumab for Eosinophilic Granulomatosis with Polyangiitis

By: Jordan D. Long, Pharm.D., MBA

Background: Eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg-Strauss Syndrome, is a rare vasculitis affecting small and medium-sized vessels, usually accompanied by asthma and eosinophilia.[1] In EGPA, any organ system can be affected through eosinophil infiltration, granuloma formation, or vasculature inflammation. The annual incidence of EGPA is 0.5 to 6.8 new cases per million inhabitants with a much higher incidence in asthmatics. Systematic glucocorticoids are considered the mainstay for EGPA, however most patients become steroid-dependent and many experience frequent relapses.[2,3] Other immunosuppressive agents (e.g., cyclophosphamide, azathioprine, methotrexate) are often needed to treat relapses and prevent permanent organ damage, however these therapies have questionable efficacy. Therefore, mepolizumab (Nucala®;GlaxoSmithKline), which was previously approved by the Food and Drug Administration (FDA) in November 2015 for severe eosinophilic asthma, was evaluated for the treatment of EGPA in adult patients and became the first drug approved for this indication in December 2017.[4]

Mechanism of Action: Eosinophil-induced inflammation is thought to be involved in the pathogenesis of EGPA.[2,4] Interleukin-5 plays a significant role in the maturation and survival of eosinophils. Mepolizumab is an interleukin-5 (IL-5) antagonist which inhibits the binding of IL-5 to its receptor which subsequently reduces the production and survival of eosinophils.

Key Clinical Trial: Mepolizumab's FDA approval for EGPA was based on a randomized, double-blind placebo-controlled, Phase III multicenter trial.[2] The study objective was to evaluate the efficacy and safety of mepolizumab versus placebo as add-on therapy in

AbobotulinumtoxinA for Pediatric Lower Limb Spasticity

By: Christine Li, Pharm.D.

Background: Cerebral palsy (CP) is a complication following injury to the developing brain resulting in a non-progressive brain lesion which produces difficulties in neuromotor control; it can occur prenatally, perinatally. or postnatally.[1,2] The prevalence rate of CP has been estimated to be two to five per 1000 live births.[1] Clinical manifestations of CP include spasticity, dyskinesia, rigidity, ataxia, and decreased muscle tone.[2,3] Muscle spasticity is a debilitating CP complication and is the main cause of secondary problems such as static muscle contractures and bony deformities.[3] Botulinum toxin type A (BoNT-A) has been utilized to improve motor function and development in pediatric patients with muscle spasticity.[2] BoNT-A has been used for CP-induced muscle spasticity at varying doses as an off-label indication. The three commercially available formulations of BoNT-A: onabotulinumtoxinA (Botox® ; Allergan, Inc.), abobotulinumtoxinA (Dysport®; Ipsen Ltd), and incobotulinumtoxinA (Xeomin®; Merz Pharmaceuticals) have

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patients with relapsing or refractory EGPA over a 52 week period. The study included 136 patients who were ≥ 18 years of age with either relapsing or refractory EGPA for at least 6 months and were receiving a stable dose of prednisone/prednisolone (≥7.5 mg to ≤ 50 mg per day). Patients with any signs of granulomatosis with polyangiitis or microscopic polyangiitis, organ- or life-threatening EGPA, malignancy, liver disease, infection, previous mepolizumab therapy or hypersensitivity to mepolizumab were excluded. After a 4 week screening period, participants were randomized 1:1 to mepolizumab (n=68) or placebo (n=68). The active treatment group received mepolizumab 300 mg subcutaneously every 4 weeks, in addition to standard care (glucocorticoids with or without immunosuppressives). The two primary endpoints were: 1) total accrued weeks of remission (defined as a Birmingham Vasculitis Activity Score (BVAS) of 0 [BVAS range is 0 to 63 with higher scores indicating more severe disease activity] and receipt of a prednisolone or prednisone dose of ≤4 mg/day over the 52 week period), and 2) percentage of patients who achieved remission at both weeks 36 and 48. More patients in the mepolizumab group achieved at least 24 weeks of remission compared to placebo, 28% versus 3%, respectively (95%CI:2.68-13.03;p<0.001). Additionally, more participants in the mepolizumab group were in remission at weeks 36 and 48 than placebo, 32% versus 3%, respectively (95%CI:3.61-77.56;p<0.001). Mepolizumab was found to have greater efficacy in patients with higher eosinophil counts (>150/mm^3). Based on the results of this trial, the authors concluded treatment with mepolizumab resulted in a significantly greater frequency and duration of remission allowing for reduced glucocorticoid use.

Safety: The most common adverse reactions associated with mepolizumab reported in the Phase III clinical trial included: headache (32%), nasopharyngitis (18%), arthralgia (22%), and upper respiratory tract infection (21%).[2] Exacerbation or worsening of asthma was the most frequent serious adverse event occurring in 3% of the mepolizumab group and 6% in the placebo group. Systemic reactions, both allergic and non-allergic, were seen in 6% of patients receiving mepolizumab and 1% of patients receiving placebo. The incidence of local injection site reactions was similar between study groups.

Dosing and Administration: The recommended dose of mepolizumab for the treatment of EGPA is 300 mg administered subcutaneously as three separate 100 mg injections every 4 weeks.[4] It is important to note that this differs from its dosing regimen for the treatment of severe asthma which is 100 mg subcutaneously every 4 weeks. A 100 mg vial of mepolizumab is reconstituted with 1.2 mL of Sterile Water for Injection to achieve a concentration of 100 mg/mL; it is recommended not to shake the reconstituted solution during this process, since this can result in foaming or precipitation. If the reconstituted solution is not used immediately, it may be stored below 30°C (86°F) (not frozen) but must be used within 8 hours. Mepolizumab must be administered by a health-care professional in order to ensure monitoring for hypersensitivity reactions. Each 100 mg injection should be given subcutaneously into either the upper arm, thigh, or abdomen. Injections should be administered at least 5 centimeters apart if administered at the same site.

Availability and Cost: Mepolizumab is available as a 100 mg single-dose vial which contains sterile, preservative-free, lyophilized powder for reconstitution. The vial should be stored below 25°C (77°F) but cannot be frozen. Prior to use, it should be kept in its original packaging to protect from light. The average wholesale price for one 100 mg vial of mepolizumab is approximately $3442, therefore, the cost of a 300 mg dose would be about $10,326.[5]

Formulary Status: The restriction for mepolizumab was modified to state: Restricted to Rheumatology, Allergy and Immunology, and Pulmonary Medicine. Rheumatology was added due to the FDA-approval for use of mepolizumab for EGPA.

References:

1. Mouthon L, Donogue B, Guillevin L. Diagnosis and classification of eosinophilic granulomatosis with polyangiitis (formerly named Churg-Strauss syndrome). J Autoimmun. 2014;48-49:99-103.
2. Weschsler ME, Akuthota P, Jayne D, Khour P, Klion P, Langford CA et al. EGPA Mepolizumab Study Team. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. N Engl J Med. 2017: 376 (20):1921-32.
3. Groh M, Pahnou C, Baldini C, Be Bottero, Cottin V et al. Eosinophilic granulamotosis with polyangiits (Churg Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. Eur J Intern Med. 2015;25:545-53.
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different neurotoxin A protein contents and are not interchangeable.[4] In June 2016, the Food and Drug Administration (FDA) approved abobotulinumtoxinA for the treatment of lower limb spasticity in patients ≥ 2 years of age.[5]

Mechanism of Action: AbobotulinumtoxinA inhibits the release of acetylcholine from the peripheral cholinergic nerve endings.[3] This reversible chemical denervation of the treated muscle results in a reduction of limb spasticity. Recovery of neurotransmission gradually occurs as new nerve endings are formed.

Key Clinical Trial: Delgado and colleagues conducted a randomized Phase III multicenter, double-blind study comparing a single dose of abobotulinumtoxinA with placebo for CP-associated equinus foot deformity, a complication associated with spasticity in the lower leg muscles.[6] The study included patients (n=241) 2 to 17 years of age diagnosed with spastic hemiparesis, paraparesis, diparesis, or tetraparesis, secondary to CP, and dynamic equinus foot deformity. Additional inclusion criteria involved a Gross Motor Function Classification System (GMFCS) level of I–III, a Modified Ashworth Scale (MAS) score of C2, and a spasticity grade (Y) of 2–4 on the Tardieu Scale involving the ankle of the most affected leg. The MAS score is used to assess resistance to passive movement and to describe muscle tone. The Tardieu scale measures spasticity by assessing the muscle's response to stretch at a range of velocities. Patients were randomized 1:1:1 to abobotulinumtoxinA 10 units/kg/leg (i.e., 20 units/kg for bilateral injections) (n=79), 15 units/kg/leg (i.e., 30 units/kg for bilateral injections (n=79), or placebo (n=77). Patients were stratified by age (2 to 9 years of age and 10 to 17 years of age) and by previous use of abobotulinumtoxin at baseline. The primary endpoint was the change in the MAS score at the ankle joint of the affected leg. At week 12, abotulinumtoxinA-treated patients had improvements in MAS scores compared to placebo, with differences of -0.49 (-0.75 to -0.23; p<.001) in the 15 units/kg/leg group and -0.38 (-0.64 to -0.13; p=0.003) in the 10 units/kg/leg group. Of note, a tertiary endpoint included change in Tardieu scores at 4 weeks. Tardieu Scale spasticity grades improved with both dosing regimens, but only the 15 units/kg/leg group had significant improvement of -0.4 (-0.5 to -0.3; p<0.001). One-hundred forty-four patients reported ≥1 treatment-related adverse effect with the most common being pyrexia and local muscular weakness. The authors concluded that single injections of abobotulinumtoxinA 10 units/kg/leg and 15 units/kg/leg significantly reduced muscle hypertonia and spasticity and was well tolerated in CP patients.

Safety: The most frequent adverse reactions occurring in ≥10% were upper respiratory tract infection, nasopharyngitis, influenza, pharyngitis, cough, and pyrexia. The product may contain milk protein and thus is contraindicated in patients with a milk protein allergy.

Dosing and Administration: The dose should be selected based on the target muscle, spasticity severity, and patient's prior response and tolerability of botulinum toxins.[5] AbobotulinumtoxinA has been approved for the injection into the calf muscles, specifically the gastrocnemius (6 to 9 units/kg) and soleus (4 to 6 units/kg) muscles. The total recommended abobotulinumtoxinA dose for a single treatment session is 10 to 15 units/kg per limb. The maximum dose should be 15 units/kg/leg or 1000 units, whichever is lower. The dose should ideally be distributed between multiple injection sites in a single muscle with the maximum volume for any single injection site as 0.5 mL. Doses for re-treatment should not be administered less than 12 weeks apart.

Cost and Availability: AbobotulinumtoxinA is available in 300- and 500-unit vials.[5] AbobotulinumtoxinA has an average wholesale price of $589.50 per 300 unit vial and $982.20 per 500 unit vial.[7] With one treatment cycle occurring every 12 to 16 weeks, the annual cost for a typical 30 kg patient would be approximately $7,000.

Formulary Status: AbobotulinumtoxinA was added to the CCHS Pediatric Formulary restricted to the Departments of Pediatric Neurology and Physiatry for outpatient use only in patients at least 2 years of age with lower limb spasticity.

References:

1. Taft, LT. Cerebral Palsy. Pediatr Rev. 1995;16(11):411-18.
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3. Molenaers G, Van Campenhout A, Fagard K, De Cat J, Desloovere K. The use of botulinum toxin A in children with cerebral palsy, with a focus on the lower limb. J Child Orthop. 2010;4:183-195.
4. Brin MF, James C, Maltman J. Botulinum toxin type A products are not interchangeable: a review of the evidence. Biologics: targets & therapy. 2014;8:227-41.
5. Dysport® [package insert]. Wrexham, United Kingdom: Ipsen Biopharm Ltd; June 2017.
6. Delgado MR, Tilton A, Russman B, Benavides O, Bonikowski M, Carranza J, et al. AboboulinumtoxinA for equinus foot deformity in cerebral palsy: a randomized controlled trial. Pediatrics. 2016;137(2):1-9.
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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Aminolevulinic acid hydrochloride (Gleolan®)	Optical Imaging Agent	Visualization of malignant tissue during surgery in patients with glioma	Restricted to the Department of Neurosurgery, Brain Tumor, or Neuro-Oncology for use only by physicians who have completed the Gleolan® training program
Avelumab (Bavencio®)	Monoclonal Antibody	Treatment of metastatic Merkel Cell carcinoma	Restricted to the Department of Hematology and Oncology for metastatic Merkel Cell in the outpatient setting
Cholera Vaccine, Live, Oral (Vaxchora®)	Vaccine	Prevention of cholera	Restricted to outpatient use (Travel Clinics only)
Diatrizoate meglumine and diatrizoate sodium Enema (Gastrografin®)	Radiopaque Contrast Agent	Management of DIOS	Restricted to Pulmonary and Critical Care Medicine and Interventional Radiology for CF patients who have failed or who are not candidates for enteral Gastrografin®
Hepatitis B Vaccine Recombinant, Adjuvanted (Heplisav-B®)	Vaccine	Prevention of Hepatitis B	Restricted to patients ≥ 18 years of age who are immunocompetent and not receiving dialysis
IV/Subcutaneous Golimumab (Simponi®Aria™/ Simponi®)	Monoclonal Antibody	Treatment of PsA and AS	Restricted to Rheumatology for the management of PsA and AS in the outpatient setting
Rifapentine (Priftin®)	Antitubercular Agent	Active PTB and LTB Infections	No Restrictions
Tisgenlecleucel (Kymriah®)	Chimeric Antigen Receptor (CAR) T-cell Immunotherapy	Treatment of ALL	Restricted to Department of Hematology/Oncology and Bone Marrow Transplantation
Zoster vaccine, recombinant, adjuvant (Shingrix®)	Vaccine	Prevention of Herpes Zoster Infection (Shingles)	Restricted to: 1) Immunocompetent patients ≥ 50 years of age 2) Immunocompetent patients ≥50 years of age undergoing pre-transplant evaluation 3) Post-transplant HSCT, solid organ transplant, and immunocompromised patients pending formal ACIP recommendations on a case-by-case basis in collaboration with Infectious Diseases

DIOS=Distal intestinal obstruction syndrome CF=Cystic fibrosis IV=Intravenous PsA=Psoriatic arthritis
AS=Ankylosing spondylitis PTB=Pulmonary tuberculosis LTB=Latent tuberculosis ALL=Acute lymphoblastic leukemia
HSCT=Hematopoietic stem cell transplantation ACIP=Advisory Committee on Immunization Practices

Change in Restrictions of Medications on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Change in Restriction**
Aerosolized ribavirin (Virazole®)	Antiviral Agent	Treatment of RSV	Restricted to Infectious Disease Physicians for: 1) Severe RSV lower respiratory tract infection in non-intubated HSCT recipients 2) RSV upper respiratory tract infection with a high risk of lower airway progression in HSCT recipients
Clobazam Oral Liquid (Onfi®)	Benzodiazepine	Lennox-Gastaut Syndrome	Clobazam tablets will be used in adults (tablets can be crushed) and clobazam liquid and tablets will be used in pediatric patients
Eculizumab (Soliris®)	Monoclonal Antibody	Refractory Myasthenia Gravis	Modified restriction to include Neurology (Neuromuscular) for outpatient use only in patients with refractory, generalized myasthenia gravis positive for anti-acetylcholine receptor antibodies. For this indication, eculizumab can only be administered at Main Campus
Filgrastim (Neupogen®) and Sargramostin (Leukine®)	Colony Stimulating Factor	Neutropenia	Modified restriction to include Solid Organ Transplant Services for patients with an ANC <1000 cells/mm^3 for a one-time dose within a 24-hour period and dose will be ≤ 5 mg/kg (rounded to the nearest vial size). These restrictions do not apply for Hematology, Oncology, or Bone Marrow Transplant patients
Infliximab (Remicade®)	TNF Inhibitor	Crohn's Disease Ulcerative Colitis Rheumatoid Arthritis	Modified restriction to allow APPs to initiate and continue infliximab (following all other formulary restrictions) under the direction of a Staff Physician

RSV=Respiratory syncytial virus HSCT=Hematopoietic stem cell transplantation ANC=Absolute neutrophil count
TNF=Tumor necrosis factor APP=Advanced practice provider

Change in Restrictions of Medications on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Change in Restriction**
Meningococcal Group B Vaccine (Bexsero®)	Vaccine	Prevention of Meningitis	Restriction will be modified to the following: 1) Patients > 10 years of age with anatomical or functional asplenia, including patients with sickle cell anemia, complement deficiency, or at risk for meningococcal B disease outbreaks 2) Patients receiving eculizumab 3) Healthy adolescents aged 16-18 years
Mepolizumab (Nucula®)	Monoclonal Antibody	Treatment of EGPA	Modified restrictions to include: Restricted to Rheumatology for outpatient use only
Neuromuscular Blockers (e.g., succinylcholine) and Etomidate	Neuromuscular Blockers and General Anesthetic	Intubation	Modified restrictions on neuromuscular blockers (e.g., succinylcholine) and etomidate to include: 1) APNs under the House Officer Program who are privileged in AAM and deemed competent by the Medical Director at their institution may prescribe these medications 2) ACNPs privileged in AAM and deemed competent by the Medical Director at each Hospital may prescribe these medications
Pulmonary Hypertension Medications (bosentan, ambrisentan, macitentan)	Vasodilators	PAH	Modified restrictions on bosentan, ambrisentan, and macitentan to include: If a patient brings in their own home supply of the medication, then the inpatient order may be written by any prescriber, including those not registered with the REMS program. This is permitted by the REMS program.
Trepostinil Extended-Release Tablets (Orenitram®)	Prostacyclin	PAH	Modified restrictions to include: Initiation of therapy by providers from the Respiratory Institute
Ziconotide (Prialt®)	Non-opioid analgesic	Severe Chronic Pain	Modify restriction to include: For outpatient use only

EGPA=Eosinophilic granulomatosis with polyangiitis APN=Advanced practice nurse ACNP=Acute care nurse practitioner
AAM=Advanced airway management PAH=Pulmonary arterial hypertension REMS=Risk evaluation mitigation strategy

Dose Rounding and Standardization Changes on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Change**
IV Acetaminophen (Ofirmev®)	Analgesic	Pain Relief Fever	**Scheduled doses** of IV acetaminophen will be allowed to be rounded to 1000 mg by pharmacists
Vincristine	Antineoplastic	Various Cancers	Vincristine doses will be allowed to be rounded to the nearest 0.1 mg if the dose is >0.96 mg by pharmacists
High Molecular Weight Viscoelastic Hyaluronate Agents	Viscosupplements	Osteoarthritis	The supply of viscosupplements on the CCHS Formulary will be standardized to: 1) For multiple injections: Euflexxa® and Hyalgan® 2) For single injections: Synvisc-One® and Gel-One® **All other viscosupplements are non-formulary**

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Atenolol (Tenormin®)	Beta-Blocker	Treatment of Hemangiomas	Restricted to test doses administered in Cardiology or Dermatology outpatient clinics for treatment of hemangiomas
Diatrizoate meglumine and diatrizoate sodium Enema (Gastrografin®)	Radiopaque Contrast Agent	DIOS	Restricted to Pedatric Pulmonary and Pediatric Critical Care Medicine and Pediatric Radiology for CF patients who have failed or who are not candidates for enteral Gastrografin®
Tisgenlecleucel (Kymriah®)	Chimeric Antigen Receptor (CAR) T-cell Immunotherapy	Treatment of ALL	Restricted to Department of Pediatric Bone Marrow Transplantation for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse and CD19+

DIOS= Distal intestinal obstruction syndrome CF=Cystic fibrosis ALL=Acute lymphoblastic leukemia

Changes in Restrictions of Medications on the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Change in Restriction**
Infliximab (Remicade®)	TNF Inhibitor	Crohn's Disease Ulcerative Colitis Rheumatoid Arthritis Graft vs. Host Disease	Restriction will be modified to allow APPs to initiate and continue infliximab (following all other formulary restrictions) under the direction of a Staff Physician
Meningococcal Group B Vaccine (Bexsero®)	Vaccine	Prevention of Meningitis	Restriction will be modified to the following: 1) Patients > 10 years of age with anatomical or functional asplenia, including patients with sickle cell anemia, complement deficiency, or at risk for meningococcal B disease outbreaks 2) Patients receiving eculizumab 3) Healthy adolescents aged 16-18 years

TNF=Tumor necrosis factor APP=Advanced practice provider

Dose Rounding and Standardization Changes on the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Change**
Generic Vigabatrin (Sabril®)	Anticonvulsant	Infantile Spasms	Brand vigabatrin (Sabril®) powder packets will be switched to the generic product. This conversion does not affect brand Sabril® tablets.
Vincristine	Antineoplastic	Various Cancers	Vincristine doses will be allowed to be rounded to the nearest 0.1 mg if the dose is >0.96 mg by pharmacists