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Alemtuzumab: New Indication for Multiple Sclerosis

By: Rosemary Persaud, Pharm.D.

Introduction: Multiple sclerosis is a progressive, immune-mediated disorder characterized by inflammation and extensive axonal injury that leads to disability.¹ Relapsing-remitting multiple sclerosis (RRMS) is the most common form of the disease, affecting about 85% of patients with MS. Patients with RRMS experience recurrent attacks or relapses that vary in frequency and severity, followed by partial or complete recovery periods. Unfortunately, some patients do not adequately respond to available therapies, leading to a need for other therapeutic options. Therefore, alemtuzumab was evaluated for the treatment of RRMS. Based on promising results in clinical trials, alemtuzumab, known as the brand name Lemtrada®, gained Food and Drug Administration (FDA) approval for the treatment of patients with RRMS in 2014.² Alemtuzumab is also marketed under the brand name Campath® which received FDA approval in 2001

for the treatment of B-cell chronic lymphocytic leukemia.³ It is important to note that Lemtrada® differs from Campath® in formulation, dosing, availability, and safety requirements.^{2,3}

How it Works: Alemtuzumab is a monoclonal antibody directed against the cell surface glycoprotein CD52, which leads to a depletion in T and B lymphocytes.⁴ The exact mechanism of action in MS is unknown, however it is believed to reduce central nervous system (CNS) inflammation secondary to an extended lymphocyte depletion and change in the composition of the lymphocytes that accompanies lymphocyte reconstitution. This reduced CNS inflammation is hypothesized to decrease the incidence of relapses associated with RRMS.

Clinical Trials: The FDA approval of alemtuzumab for use in MS was based

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New Gram-Negative Agents: Zerbaxa® and Avycaz®

By: Theresa Nerone, Pharm.D.

Introduction: Drug resistant Gram-negative bacteria are a growing health concern. The World Health Organization (WHO) antimicrobial resistance global report highlights increasing resistance in *Klebsiella pneumoniae*, *Escherichia coli*, and other bacteria to third-generation cephalosporins, fluoroquinolones, and carbapenems.^{1,2} Gram-negative bacteria can become resistant to antibiotics by several methods such as beta-lactamase production, changes in bacterial binding sites, loss of porins (openings in the bacterial cell which

allow antibiotic entry), and upregulation of efflux pumps which promote the extracellular removal of antibiotics.³ Due to concerns for antimicrobial resistance and the lack of new antibiotics to combat them, the Infectious Diseases Society of America (IDSA) has launched the "10 x '20" initiative" with the goal of developing 10 new antibiotics by 2020.⁴

New Gram-Negative Agents: Two new combination cephalosporin plus beta-lactamase inhibitor products,

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on the results of two phase 3 clinical studies: Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis (CARE-MS I and CARE-MS II) trials. The coprimary endpoints for both trials included rate of relapse and sustained accumulation of disability. In both trials, patients were randomized to receive alemtuzumab or interferon beta 1a (Rebif®). CARE-MS I included treatment-naïve patients with early, active RRMS, while CARE-MS II included patients who recently relapsed while taking a standard disease-modifying therapy.^{5,6} Overall, both of these trials found a statistically significant reduction in relapse rates with alemtuzumab therapy compared with 44 mcg of interferon beta 1a three times per week. The CARE-MS II study also found a significant reduction in sustained accumulation of disability over 6 months compared to interferon beta 1a. However, multiple adverse effects were identified in these trials, including mild-to-moderate infusion-associated reactions and infections. Serious adverse effects were autoimmune disorders, serious infusion-associated reactions, and malignancies. Based on these studies, the authors concluded that alemtuzumab is an effective treatment option for RRMS, however, suitable risk management strategies need to be employed in order to circumvent the drug's serious adverse effects.

Black Box Warnings and REMS: Alemtuzumab carries Black Boxed Warnings for the increased risks for autoimmunity, infusion reactions, and malignancies.² A rapid and profound lymphopenia caused by alemtuzumab returns to normal in only 80% of patients by 12 months. In clinical studies, autoimmune disorders developed following the last infusion.^{5,6} Therefore, patients receiving alemtuzumab must be monitored closely for at least 48 months following the last infusion. There is a Risk Evaluation and Mitigation Strategies (REMS) program requirement for alemtuzumab due to these risks that requires prescribers to enroll and complete training. Patients and infusion sites must also be enrolled in the program. Additionally, Lemtrada® is only available through a restricted distribution program.

Dosing and Administration: The recommended dosage of alemtuzumab is 12 mg/day administered by intravenous infusion for two treatment courses.² The dosing schedule is detailed in Table 1. Additionally, the manufacturer has data for efficacy of an extended dosing regimen. There is no dosage adjustment for renal or hepatic impairment. Due to the risk for infusion-related reactions, patients should be pre-medicated with high-dose corticosteroids immediately prior to the infusion.² Antihistamines and/or antipyretics may

also be used per the CCHS Lemtrada® Protocol. The medication is generally infused over 4 hours, but the infusion time can be extended based on patient tolerability to a maximum of 8 hours. Patients should be monitored for a minimum of 2 hours after each infusion. Details about an alternative infusion time based on patient tolerability can be found in the CCHS Adult IV Guidelines and the CCHS Lemtrada® Protocol.

Table 1: Dosing Schedule for Lemtrada®²

Treatment Course	Dosage
First	12 mg/day on five consecutive days
Second*	12 mg/day on three consecutive days

*Second course given 12 months after first treatment course.

The Bottom Line: In clinical trials, alemtuzumab demonstrated a significant decrease in relapse rates over 6 months compared with interferon beta 1a. However, due to its safety profile alemtuzumab should be reserved for patients who have had an inadequate response to at least two drugs indicated for the treatment of MS. Lemtrada® is currently on the CCHS Formulary restricted to the Department of Neurology for the management of MS for outpatient use only at the Mellen Center.

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ceftolozane-tazobactam (Zerbaxa®; Cubist Pharmaceutical) and ceftazidime-avibactam (Avycaz®; Forest Laboratories), have been approved by the Food and Drug Administration (FDA) in December 2014 and February 2015, respectively. Both products were designed to help combat multi-drug resistant Gram-negative bacteria and are FDA-approved for complicated urinary tract infections (cUTI) as monotherapy and complicated intra-abdominal infections (cIAI) used in combination with metronidazole. Ceftolozane is a novel fifth-generation cephalosporin and tazobactam is a beta-lactamase inhibitor. Ceftazidime is a third-generation cephalosporin and avibactam is a novel semi-synthetic beta-lactamase inhibitor that is partially reversible, allowing for recycling of the drug. Both products are only available as intravenous formulations.^{5,6}

Spectrum of Activity: Ceftolozane-tazobactam has activity against multi-drug resistant strains of *Pseudomonas aeruginosa*.³ It has minimal coverage and would therefore not be considered an optimal agent for *Acinetobacter baumannii* and *Burkholderia* species, anaerobes, and Gram-positive species. Ceftolozane-tazobactam is also not active against *K. pneumoniae* carbapenemases (KPC) or metallo-beta-lactamases.⁵ Avibactam inhibits various beta-lactamases such as extended-spectrum beta-lactamases (ESBL), AmpC, KPC, and some class D beta-lactamases (OXA), resulting in improved activity of ceftazidime against most species of *Enterobacteriaceae*. Ceftazidime-avibactam does not have improved activity against *Acinetobacter* species, Gram-positive organisms, or most anaerobic bacteria compared to ceftazidime alone. However, ceftazidime-avibactam has displayed activity against KPC.⁷

Dosing and Adverse Effects: Dosing for ceftolozane-tazobactam for cUTI and cIAI is 1.5 grams IV every 8 hours for patients with normal renal function. Dosage adjustments for patients with impaired renal function are listed in Table 1. The recommended therapy duration is 7 days for cUTI and 4 to 14 days for cIAI. The most common adverse reactions are nausea, diarrhea, headache, and pyrexia.⁵ Dosing for ceftazidime-avibactam for cUTI and cIAI is 2.5 grams IV every 8 hours for patients with normal renal function. Dosage adjustments for patients with impaired renal function are listed in Table 2. The infusion time for this product is unique in that it is recommended to be administered by intermittent infusion over 2 hours. Recommended therapy duration is 7 to 14 days for cUTI and 5 to 14 days for cIAI. The most common adverse reactions are vomiting, nausea, constipation, abdominal pain, elevated liver enzymes, and anxiety.⁶

Table 1: Ceftolozane-tazobactam Renal Dose Adjustments⁵

CrCl (mL/min)	Ceftolozane-tazobactam
>50	No dose adjustment necessary
30 to 50	750 mg every 8 hours
15 to 29	375 mg every 8 hours
<15	Not studied
ESRD on IHD	750 mg for one dose, followed by 150 mg every 8 hours*

ESRD=End-stage renal disease IHD=Intermittent dialysis

*Administer immediately after dialysis on dialysis days

Table 2: Ceftazidime-avibactam Renal Dose Adjustments⁶

CrCl (mL/min)	Ceftazidime-avibactam
>50	No dose adjustment necessary
31 to 50	1.25 grams every 8 hours
16 to 30	0.94 grams every 12 hours
6 to 15	0.94 grams every 24 hours
≤5	0.94 grams every 48 hours
ESRD on IHD	Administer based upon the patient's estimated renal function*

ESRD=End-stage renal disease IHD=Intermittent dialysis

*Administer immediately after dialysis on dialysis days

Availability and Cost: Ceftolozane-tazobactam is available as a 1.5 gram vial with a suggested wholesale price (SWP) of \$99.60.⁸ Ceftazidime-avibactam is available as a 2.5 gram vial with a SWP of \$342.

Formulary Status: Ceftolozane-tazobactam and ceftazidime-avibactam are on the CCHS Formulary restricted to use by Infectious Diseases physicians. Ceftolozane-tazobactam will be primarily reserved for the treatment of multi-drug resistant *Pseudomonas aeruginosa*, while ceftazidime-avibactam will be primarily reserved for the treatment of carbapenem-resistant *Enterobacteriaceae* infections.

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