

## Mellen Center Approach: Lemtrada (alemtuzumab)

### Q: What is the mechanism of action of Lemtrada?

A: Lemtrada (alemtuzumab) is a humanized anti-CD52 monoclonal antibody that causes cytolysis of T and B lymphocytes, NK cells, monocytes, and macrophages. After IV administration, there is rapid and profound lymphopenia that gradually recovers (return of absolute lymphocyte count to the lower limit of normal in 40% of patients at 6 months and in 80% by 12 months). Efficacy is thought to be due to depletion of circulating pro-inflammatory leukocytes and gradual immune reconstitution during which there is alteration in the lymphocyte profile and functional immunomodulation.<sup>1</sup>

### Q: What are the indications for Lemtrada (alemtuzumab)?

A: A Phase 2 and two Phase 3 trials.<sup>2-4</sup> demonstrated potent efficacy on relapses and MRI lesion activity compared to SC interferon beta-1a in relapsing MS. Benefit on worsening of disability was shown in the Phase 2 trial<sup>2</sup> and in the CARE-MS II Phase 3 study of patients with continued disease activity on other disease-modifying therapies,<sup>4</sup> but not in the CARE-MS I trial of treatment-naïve patients.<sup>3</sup> In early studies, there was no benefit on disability worsening in progressive MS.<sup>5</sup> Lemtrada generally has good tolerability. However, its use is associated with several safety concerns. Safety and efficacy in pediatric and geriatric patients have not been established.

Because of these considerations, the approved indication of Lemtrada generally is restricted to patients with active relapsing MS with an inadequate response to 2 or more disease-modifying medications.<sup>6</sup> The approved dose in MS is 12 mg IV daily for 5 consecutive days at Month 0 and daily for 3

consecutive days at Month 12. At the Mellen Center we agree with these restrictions. We use alemtuzumab for patients with active MS not responding to 2 or more disease modifying therapies, or who have not tolerated other medications.

Although not discussed in the Prescribing Information, there is anecdotal experience and data from the trials supporting the utility and safety of retreatment (3 days) after Month 12 (annually or less often PRN) in patients with return of MS disease activity.

Note that because of the importance of close follow up for this medication, particularly continued lab testing, we are careful at the Mellen Center to select candidates who are willing to follow up closely for their health and who are reliable agents in their ongoing care.

### Q: What is the pharmacology and immunogenicity of Lemtrada?

A: After IV administration, the elimination half-life of Lemtrada is approximately 2 weeks. Anti-Lemtrada binding antibodies develop in most patients (83%, 3 months after the 2<sup>nd</sup> cycle). Neutralizing antibodies also are common, detectable in 88-94% of binding antibody-positive patients 1-3 months after the 2<sup>nd</sup> cycle. Binding antibodies are less common 12 months after the first cycle prior to the 2<sup>nd</sup> cycle (detectable in 29% of patients), and neutralizing antibodies are uncommon (5% of binding antibody-positive patients). In the clinical trials, the presence of neutralizing antibodies had no apparent effect on efficacy, lymphocyte counts, or adverse effects.

### Q: What are the potential adverse effects of Lemtrada?

A: The main adverse effects of Lemtrada include:

#### *Infusion reactions*

Infusion-related symptoms are due to rapid cytolysis of circulating leukocytes and resultant cytokine release

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syndrome. Infusion-related symptoms develop in >90% of patients (without premedication) and can range from minimal to severe (in 3% of patients). Symptoms can develop during or after infusion. Typically, they are most prominent on Day 1 of the 1<sup>st</sup> cycle and are less severe on subsequent days and during the 2<sup>nd</sup> cycle.

Lemtrada should be infused in a setting with equipment, medications, and personnel to manage anaphylaxis and severe infusion reactions if needed.

In most cases, infusion-related symptoms can be effectively minimized by pretreatment with corticosteroids, antipyretics, and antihistamines. The Prescribing Information recommends IVMP 1000 mg daily for 3 days. However, in our experience, a significant proportion of patients then develop symptoms on Days 4 and 5. Therefore, unless contraindicated, we administer corticosteroid pretreatment for 5 days during the 1<sup>st</sup> cycle and for 3 days during the 2<sup>nd</sup> cycle (and subsequent cycles).

### *Antibody-mediated autoimmunity*

This phenomenon presumably is due to reconstitution of B lymphocyte populations faster than regulatory T lymphocyte populations. The risk of autoimmune disorders persists for 4-5 years after the last dose of Lemtrada.

1. Thyroid disease (34% of patients). Autoimmune thyroid disorders, associated either with hypothyroidism or hyperthyroidism, are common. Most cases respond to standard management. Thyroid ophthalmopathy is rare. The Prescribing Information recommends TSH prior to treatment and every 3 months until 48 months after the last administration.
2. Immune thrombocytopenia (2% of patients). This adverse effect can range from mild and self-limited to severe, including leading to hemorrhage and death. The Prescribing Information recommends CBC with differential prior to treatment and monthly until 48 months after the last administration. Note: severe thrombocytopenia can develop precipitously, within weeks of a normal CBC. Patients should be educated about the signs and symptoms of thrombocytopenia and should be evaluated emergently if they report them. Most cases respond

to standard management.

We encourage patient teaching to watch particularly for signs of a bleeding disorder (petechiae, hematomas) and to act immediately on any concerning signs.

3. Glomerular nephropathies (0.3% of patients). Glomerular nephropathies (membranous glomerulonephritis and anti-glomerular basement membrane disease) are rare but if left untreated can lead to renal failure. The Prescribing Information recommends urinalysis with cell count and Cr prior to treatment and monthly until 48 months after the last administration. Marked change in urine protein or cell counts, particularly if accompanied by a relative increase in Cr, is of concern and indicates the need to refer urgently to Nephrology. Mild abnormalities in UA are common in MS patients, including due to UTI and menses, so the significance of isolated abnormalities on urinalysis can be difficult to determine and requires clinical context.
4. Miscellaneous autoimmune conditions have been reported rarely (approximately 0.1-0.2% of patients each): hemolytic anemia, pancytopenia, acquired hemophilia, undifferentiated connective tissue disorders, rheumatoid arthritis, diabetes, vitiligo, and retinal pigment epitheliopathy.

### *Infection*

Increased risk of infection presumably is due to immunosuppressive effects of Lemtrada. In clinical trials, infections were common; serious infections were uncommon (3%). Lemtrada administration should be delayed in patients with an ongoing significant infection.

1. Herpes Virus.
  - a. In the clinical trials, Herpes virus infections occurred in 6% of Lemtrada-treated patients, and were serious in 0.1-0.2% of patients. Increased risk is greatest for 1-2 months after infusion but persists until CD4+ lymphocyte counts are >200/uL. Based on Lycke et al,<sup>7</sup> only approximately 50% of patients have a return of CD4+ count >200/uL 9 months after Month 0 and Month 12 cycles. Just over 80%

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have returned to  $>200/uL$  12 months after the Month 0 and Month 12 infusions. Therefore, we advise anti-herpes prophylaxis for 2 years beginning with the first cycle (assuming cycles are administered at Month 0 and Month 12). If there is a reason to discontinue prophylaxis sooner, it should be continued for at least 60 days after the last Lemtrada administration and until the CD4+ lymphocyte count is  $>200/uL$ .

- b. Patients should be screened for VZV immunity prior to initiation of Lemtrada. Patients who are VZV seronegative should receive the two-part Varivax vaccine, and Lemtrada dosing should be delayed until at least 6 weeks after vaccine administration.
2. Human Papilloma Virus. HPV infections, including associated cervical dysplasia occur in 2% of Lemtrada-treated patients. Annual HPV screening is recommended.
3. Tuberculosis. Active TB occurred extremely rarely in the clinical trials, but is a consideration in patients from endemic areas.
4. Fungal infections. In the clinical trials, fungal infections, most often oral and vaginal candidiasis, were relatively common (12% of Lemtrada-treated patients).
5. Listeria monocytogenes. Listeria meningitis has occurred in Lemtrada-treated patients. Patients should be advised to avoid foods that are potential sources (primarily unpasteurized dairy products).

### *Malignancy*

There is potential increased risk of malignancy, presumably due to immunosuppression with Lemtrada. Lemtrada should be administered with caution in patients with pre-existing or ongoing malignancy.

1. Thyroid cancer (0.3% of patients). Routine exam should include thyroid palpation.
2. Melanoma (0.3% of patients). Baseline and annual skin exams are recommended.
3. Lymphoproliferative disorders. Monthly CBC provides some screening, and routine exam should include LN palpation.

### *Pneumonitis*

In the clinical trials, pneumonitis of varying severity and including hypersensitivity pneumonitis and pneumonitis with fibrosis occurred in 0.5% of Lemtrada treated patients. Patients reporting new pulmonary symptoms should be evaluated as indicated.

### **Q: What is the effect on pregnancy and breastfeeding?**

A: Lemtrada is Pregnancy Category C. It may be directly toxic to the developing fetus. A pregnancy test should be obtained prior to Lemtrada administration, and women should be counseled to practice effective contraception during and for at least 4 months after administration.

Autoantibodies that develop in women treated with Lemtrada can be transferred transplacentally to the fetus during pregnancy.

It is not known whether Lemtrada is excreted in human milk. Therefore, we advise women not to breastfeed within 4 months of Lemtrada administration.

### **Q: What precautions are needed for immunizations when patients are using Lemtrada?**

A: Complete necessary immunizations at least 6 weeks prior to initiation of Lemtrada treatment.

### **NOTE: Do not administer live vaccines to patients treated with Lemtrada.**

### **Q: How much time should be allowed between therapies when switching to Lemtrada?**

A: There is no specific evidence for a washout period before instituting Lemtrada. At the Mellen Center, since the patients we will treat have highly active MS, we will minimize any washout period to avoid recurrence of disease activity during this period. A one month washout period for FDA approved therapies including natalizumab appears reasonable.

### **Q: What is the Risk Evaluation and Mitigation Strategy (REMS) Program for Lemtrada?**

A: Because of the safety concerns outlined above, the FDA mandated a REMS Program for Lemtrada, the components of which include:

1. To prescribe Lemtrada, clinicians must be certified with the program by enrolling and

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completing training (including passing a knowledge assessment).

2. Patients must enroll in the program and comply with ongoing monitoring requirements.
3. Pharmacies must be certified with the program and must only dispense Lemtrada to certified healthcare facilities.
4. Healthcare facilities must enroll in the program and verify that patients are authorized before infusing Lemtrada. Healthcare facilities must have on-site access to equipment and personnel trained to manage infusion reactions.

### REFERENCES

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3. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet* 2012;380:1819-28.
4. Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet* 2012;380:1829-39.
5. Coles AJ, Cox A, Le Page E, et al. The window of therapeutic opportunity in multiple sclerosis. Evidence from monoclonal antibody therapy. *J Neurol* 2006;253:98-108.
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### LEMRADA TREATMENT PROTOCOL

#### Pretreatment

1. Testing
  - a. CBC with differential.
  - b. Cr
  - c. LFTs.
  - d. TSH.
  - e. VZV IgG.
  - f. HIV testing.
  - g. Hepatitis serology.
  - h. Serum pregnancy test.
  - i. Urinalysis with cell count.
  - j. Skin exam to monitor for melanoma.
  - k. Gynecologic exam including screening for HPV and cervical dysplasia.
  - l. PPD or Quantiferon in patients from regions endemic for TB or with suspected exposure.
  - m. Brain MRI within 2 months prior to treatment.
2. Prescriptions (patient to begin in am morning of infusion day 1)
  - a. Cetirizine (Zyrtec) 10 mg PO daily for 14 days, beginning the morning of infusion Day 1.
  - b. Ranitidine (Zantac) 150mg PO daily for 14 days, beginning the morning of infusion Day 1.
  - c. Acyclovir (Valtrex) 200mg PO twice daily for 2 years (assuming cycles at Month 0 and Month 12), beginning the morning of infusion Day 1.
  - d. Sleep medication as indicated.
3. Complete Lemtrada forms.
4. Complete patient education.
5. Complete Mellen Lemtrada checklist.
6. Complete orders in EPIC.
7. Review and sign Informed Consent.

#### Administration

Administer Lemtrada 12 mg IV daily on 5 consecutive days at Month 0 then 3 consecutive days at Month 12.

#### *Infusion orders – each day*

1. Confirm patient took certirizine, ranitidine, and acyclovir.
2. Methylprednisolone (Solumedrol) 1000mg IV in 100ml 0.9% saline, infuse over 60 minutes.

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3. Acetaminophen (Tylenol)
  - a. 1000 mg PO 30 minutes prior to Lemtrada infusion.
  - b. 1000 mg PO every 4 hours as needed for fever, headache, itching.
4. Diphenhydramine (Benadryl)
  - a. 50 mg PO 30 minutes prior to Lemtrada infusion.
  - b. 25-50 mg PO every 4 hours as needed for mild fever, itching.
  - c. 25-50 mg IV as needed for more severe rash, itching, or shortness of breath. Repeat 25-50 mg IV as needed for rash, itching or shortness of breath every 30 minutes up to 4 doses.
5. Lemtrada
  - a. Using sterile technique, withdraw Lemtrada (12 mg, 1.2 mL) and inject into a 100-ml bag of 0.9% saline or D5W.
  - b. Infuse IV over a period of at least 4 hours
  - c. If not well tolerated, the infusion period may be extended, but the total infusion period on any day should not exceed 8 hours. If so, Lemtrada should be reconsidered.
6. Vital signs and monitoring for side effects
  - a. Prior to infusion
  - b. Every 15 minutes for the first 2 hours of infusion then every 30 min.
  - c. Every 30 min for 2 hours after completion of infusion
7. Discharge
  - a. Discharge if stable after the 2-hour monitoring period. Extend the monitoring duration if indicated.
  - b. Advise patients that side effects can develop after the 2-hour monitoring period.

### Long-term post-treatment monitoring

1. CBC with differential monthly until 48 months after the last dose
2. Urinalysis with cell count monthly until 48 months after the last dose
3. TSH every 3 months until 48 months after the last dose
4. Annual skin exam
5. Annual gynecological exam including screening for HPV and cervical dysplasia
6. It is appropriate to see patients in the office initially at least every 3 months, to evaluate for complications of therapy, verify clinical stabilization of MS disease activity, and to manage MS symptoms. Urgent office visits or emergent medical attention may be rarely indicated to evaluate for possible complications of therapy.
7. Brain MRI is generally performed at least every 6 months after treatment to monitor for disease activity, and as often as every 3 months in selected patients with very active disease prior to treatment.