Serious Adverse Events, Autoimmunity, and Infections Following Alemtuzumab Therapy in a Large, High Disability, Treatment-Refractory MS Clinic Cohort

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Abstract

Background: Alemtuzumab (ALE), an anti-CD52 IgG therapy provides powerful, long-term, disease-modifying effects with a liability for infusion-related, infectious, and autoimmune liabilities. We have a large clinic cohort of highly treatment-refractory, older, higher disability subjects with long-term data regarding these complications.
Objectives: Report rates of complications of hospitalization, infection, autoimmunity, and malignancy following ALE in highly treatment refractory long-term and short-term cohorts.
Methods: NCT01624714 Retrospective and prospective data collection of subjects in open label phase I clinical trial for treatment refractory MS. Total of 61 subjects were follow for a mean 54 months, or total of 254 patient-years (PY) post-ALE. Treatment was received at a median age of 49 (32-68) years. The long-term (LT) cohort had a mean of 83 months follow up (FU), and short-term (ST) mean of 25 months FU.
Results: 41 Serious adverse events, nearly entirely hospitalizations, occurred at a rate of 0.16 events per PY; only 1 for MS relapse. Serious events differed for LT 0.10/PY and ST 0.35/PY. Serious infections caused 16 hospitalizations, 0.063/PY. Major infections included 4 opportunistic infections (fungal osteomyelitis 1, disseminated histoplasmosis 2, granulomatous fish handlers' disease 1. Other infections included Urinary: UTI (2), UTI with paraparesis pseudorelapse (1); Pulmonary: pneumonia (2), pneumonia and sepsis (1); Gastroenteritis: C.difficile (1), rotavirus gastroenteritis (1), fecal impaction with enteritis (1) and Other: post-operative MRSA osteomyelitis (1), and pseudofolliculitis (1). Serious infections also differed in rate between long-term 0.04/PY and short-term 0.1/PY. Autoimmunity occurred, not usually needing hospitalization: 5 Grave's disease, 5 hypothyroidism, 2 goiter/nodule, 2 hemolytic anemias, 1 ITP, 1 recurrent alopecia totalis. The total thyroid autoimmunity rate of 12/61 (20%) subjects or 0.047 events/PY. Autoimmunity caused 4 hospitalizations (7% of subjects), and were thyrotoxicosis (2), ITP with mild pancytopenia and hemolytic anemia, and hemolytic anemia. Autoimmunity rate was similar between the LT 0.061/PY and ST 0.08/PY. One anemia resolved but recurrent infections after rituximab led to study withdrawal, hospice care, and death. Malignancies other than basal cell carcinoma (BCC) did not occur, 3 BCC were excised (0.01 per PY).
Conclusions: Safety of ALE in this challenging and refractory cohort is similar to previously reported, but infections and hospitalizations occur. Histoplasmosis occurred multiple times in our cohort and is an endemic pathogen in our region. Serious infection rate is likely higher than expected and weighted towards the first two years of treatment. Thyroid autoimmunity appears less common overall, judging from the thyroid complication rate over a very long follow up period.
Study Supported by: Genzyme-Sanofi via a grant to NeuroNexus Center

Protocol

- **Phase I retrospective and prospective:**
  NCT01624714: clinicaltrials.gov
- **Inclusion Criteria**
  - **ALE-experienced Inclusion criteria**
    - Off-label treated, refractory, MS clinic cohort, MS with documented relapses
    - Prior treatment experience with approved disease modifying agents
    - ≥1 cycles of prior ALE therapy
  - **ALE-naive Inclusion criteria**
    - Prior treatment experience 1 or more DMTs, refractory, MS clinic cohort, MS with documented relapses
    - Prior treatment experience with approved disease modifying agents
- **Exclusion:** pregnancy, neoplasm, infection, uncontrolled autoimmunity

Alemtuzumab total 60mg first course slow i.v. over 3-5 days. Repeat yearly course total 30-36 mg annually divided over 3 days. In each course 3 days i.v. methyl-prednisolone 1 g were given. Pretreatment with acetaminophen, hydroxyzine, and ranitidine or equivalent were used.

Second course at 12 months. Other courses as indicated.

Background

Are novel complications seen in long-term highly treatment experienced cohorts?

Do complications changes over time?

Are complications different in a more disabled, treatment-refractory cohort?

We describe the prevalence and types of hospitalizations, serious infections, autoimmunity and malignancy.

This data was not collected in phase II/III trials but in "real-world" high disability, treatment-refractory, high disability, MS patients.

Study Cohort

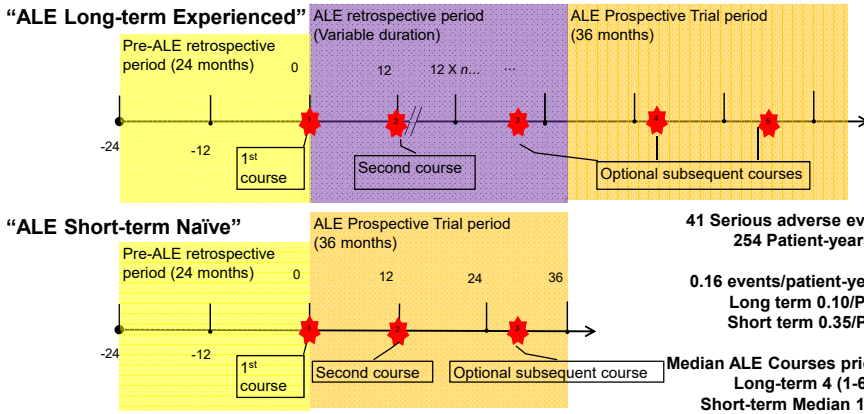
Patients:	61 subjects, 41 female, 20 male >= 12 months post ALE, Previously documented relapses
Age at First ALE Infusion:	Mean 49 years, range 32-68 years
EDSS at ALE (Median, range):	Total 5.0 (2.5-7.5, *n*=58) Long-term 5.5 (2.0-7.5, *n*=30) Short-term 5.0 (2.5-7.0, *n*=28)
Total Courses ALE:	Median 3 (1-7, *n*=61 subjects) Short-term 2 (1-3, *n*=30) Long-term 4 (3-7, *n*=31)
Follow-up:	254 patient-years total Long-term/ Experienced 83 mos Short-Term/Naïve 25 mos
Prior therapies	1 DMT: 8 subjects 2 DMT 19 subjects 3+ DMT 34 subjects
Prior Treatment Experience entire history	2 Cyclophosphamide 2 Dimethylfumarate 17 Fingolimod 21 Glatiramer 61 Interferon-beta 5 Leflunomide/Teriflunomide 3 Methotrexate 5 Mitoxantrone 3 Mycophenylate 29 Natalizumab 4 Regular MP, DXM 1 Other cytotoxic agents

Malignancy

Basal cell Carcinoma was only malignancy	3/61 subjects had basal cell carcinoma excised (0.01/ patient year)

Fish Handlers' Disease (*Mycobacterium marinum*)

Trial Design and Results



41 Serious adverse events in 254 Patient-years

0.16 events/patient-year (PY)
Long term 0.10/PY
Short term 0.35/PY

Median ALE Courses prior to SAE
Long-term 4 (1-6)
Short-term Median 1 (1-2)

Infection SAE

17 infections **16 hospitalizations** **0.063/PY**	**SAE Infection Rate** **Long-term 0.04/PY** **Short-term 0.1/PY**
4 opportunistic infections fungal osteomyelitis 1 disseminated histoplasmosis 2 fish handlers' disease 1	**Pulmonary:** pneumonia 3 pneumonia and sepsis 1
Urinary: UTI 2 UTI with paraparesis pseudorelapse 1	**Gastroenteritis:** Appendix perforation 1 *C.difficile* colitis 1 Rotavirus enteritis 1 Enteritis with fecal impaction 1
Other Infection: post-op MRSA osteomyelitis 1 pseudofolliculitis 1	
Noninfectious-nonimmune SAE:	**17 hospitalizations** **0.067/PY**
Vascular-Cardiac 7 (arrhythmia 3, PE 1, CEA 1, syncope 2)	**GI** 2 (pancreatitis, illeus) **Metabolic** 2 (hypo Na, dehydration)

Autoimmunity

Autoimmunity **16 events 4 hospitalizations** **15 (7%) subjects**	**All autoimmunity:** **Long-term 0.061/PY** **Short-term 0.08/PY**
Thyroid events: Grave's disease 5 Hypothyroidism 5 Goiter/nodule 2	**Total thyroid autoimmunity:** 12/61 (20%) subjects 0.047 events/PY
Hematologic Autoimmunity: Immune thrombocytopenia 1 Hemolytic anemia 2 (1 HA anemia with ITP case) Hospitalization 2	**Thyroid Hospitalizations:** Thyrotoxicosis 2
Other: Alopecia totalis, relapse 1	**SAE Autoimmunity** **4/254 PY** **0.02/PY**
Noninfectious-nonimmune SAE (continued):	
Psychiatric 5 (psychosis 2, depression 1, overdose-suicide attempt 2)	**Neuro** 3 HA 1, Seizure 1, MS relapse 1

Histoplasma Capsulatum

Histoplasma capsulatum, a dimorphic fungus, is endemic where humidity, soil acidity, and bird/bat droppings promote growth. Contact with mycelia in soil and caves aerosolizes the microconidia, infecting humans as granulomas containing encapsulated budding yeast. Positive histoplasmin skin tests occur in as many as 90% of the people living in areas where *H. capsulatum* is common, such as the eastern and central United States, causing an estimated 500,000 pulmonary infections a year. Infection is treated with i.v. and oral antifungals.

Ryan KJ, Ray CG, eds. (2004). Sherris Medical Microbiology (4th ed.). McGraw Hill. pp. 674–6. ISBN 0-8385-8529-9.

Chang, Ryan. "Histoplasmosis." 19 Sep 2005. emedicine. 25 Aug 2007 <http://www.emedicine.com/MED/topic1021.htm>.

Conclusions

- We report serious events in an aggressively treated high disability, treatment-refractory clinic cohort, with long-term use of ALE
- Autoimmunity is fairly stable over time.
- SAE were infrequent, occurring in a small minority
- Serious infections were infrequent, although some unusual.
- Serious infection rate declined over time.
- No malignancy signal was appreciated.
- Histoplasmosis has not been previously described, but is not surprising.
- MS hospitalizations were rare.