

A review of the evidence from U.S. Clinical Trials on Post-treatment Lyme Syndrome Columbia University Medical Center Brian Fallon, MD

Thank you

- Lyme Disease Action
- Patients who volunteer for research studies
- Research Assistants who do the daily hard work
- The donors & government agencies who support education & research

Preliminary Assumptions

- Some patients experience disabling chronic symptoms after Lyme disease – most do not
- The cause of these chronic symptoms is uncertain likely heterogeneous
- Terms –
 Post-treatment Lyme Syndrome vs Chronic Lyme
- Relatively few studies have been done of patients with chronic persistent symptoms.





Cost to Society of Lyme Disease Based on large samples



Outline of Talk

- Columbia Lyme Encephalopathy Study
 - Other U.S. Clinical Trials
 - Post-Trial Investigations
- Laboratory Testing in Patients with PTLS
- New Research: Implications & Questions

GOALS Lyme Encephalopathy Study (PTLE)

Lyme Encephalopathy – a more objective subcategory of Post-treatment Lyme (Fallon et al, Neurology 2008)

- To assess brain structure (MRI)
- To assess brain functioning (PET)
 Metabolism by FDG PET
 - Blood flow by O-15 PET (before & after hypercapnea)
- To assess improvement in response to 10 week of IV ceftriaxone vs IV placebo
 - Primary Measures cognition/memory

Randomized, Double-Masked Study Design

- Random assignment to 10 weeks of IV ceftriaxone vs 10 weeks of IV placebo
- Because of repeated neurocognitive testing, a healthy control group was included to assess the practice effect
- Primary outcome at 12 weeks Sustainability assessed at 24 weeks

These patients met highly conservative criteria for Post-treatment Lyme Syndrome

- Age 18-65
- Lyme patients:
 - Historically well-documented Lyme disease based on CDC surveillance clinical and laboratory criteria
 - Prior treatment with at least 3 weeks of IV ceftriaxone
 - Memory deficit (-1SD) confirmed by cognitive testing
 - Current positive IgG Western blot at our reference lab
- Healthy Controls: age-, sex-, educationmatched

Assessments

- Structural Imaging (MRI)
- Functional Imaging (PET)
 - FDG to assess metabolism
 - O-15 with hypercapnea to assess flow
- Primary Outcome: Neurocognitive Testing
- Secondary Outcomes (Self-reports):
 Fatigue, Pain, Functional Status



Final Study Entry Sample Size

• Total: 55

Lyme patients: 37

23 randomized to ceftriaxone, 14 to placebo Age 45; 59% female

Delay bet symptom onset and first treatment: 1.2 years

Healthy controls: 18

Design Issues that would negatively impact this study's ability to show a treatment effect

- Small Sample size of 37 Lyme patients
 - Only a treatment with a large effect size would be able to show a difference
- Prior Treatment was considerable therefore less likely to respond than a study with those who had received fewer prior treatments.
 - Mean IV: 2.3 months
 - Mean oral: 7.7 months

Baseline CSF Laboratory Results

- CSF (n=33):
 - Few Routine abnormalities:
 - 2 had mildly increased WBC & 4 had mild increased protein
 Oligoclonal bands: none
 - CSF Bb Antibodies: WCS Intrathecal Ab Index positive: 12.1% C6 Peptide Intrathecal Ab Index Positive: 62.5%
 - PCR Positive: None using OspA based PCR
 - Culture Positive: 1 sample (false positive)

Clinical Profile of Post-treatment Lyme Encephalopathy

- Cognitive: mild-moderate deficits
 - Verbal Memory (z=-1.0),
 - Verbal Fluency (z=-0.8)
- Psychiatric: mild depression & anxiety
- Systemic Symptoms are most debilitating:
 - PAIN comparable to post-surgical pain
 - FATIGUE comparable to M.S. patients
 - PHYSICAL DISABILITY comparable to congestive heart failure patients







Global Cerebral Blood Flow: is there a difference in vasodilation capacity bet pts and controls?

- Yes, The patient group showed a diminished ability to enhance blood flow compared to controls (8.2% for the patients v 28.1% for the healthy volunteers, p<.02)
 - This finding suggests vascular compromise in the patient group (not attributable to CVD risk factors)

FDG Imaging: are there regional metabolic differences between patients & controls? Yes.

- Large clusters of specific areas of decreased metabolism
- This was not a random distribution...most abnl areas on metabolic scan were also abnl on the 3 blood flow scans.

Patients have lower metabolism in 12 clusters (3049 voxels) Left Hemisphere: Temporal (1199v), Frontal (527V), claustrum (539V), Parietal (139V) Right Hemisphere: Cingulate (487 v BA 24/30), Parietal (265 v), Insula (154v) Patients have higher metabolism in 3 clusters (680 voxels)

What do these Neuroimaging findings mean?

- The brain is involved in the pathophysiology of symptom persistence
- Perhaps the brain is a new treatment frontier – if abnormalities in the brain function can be fixed, then symptoms may then resolve

None of the following predicted poor response to retreatment with IV

- Presence of positive titers for other infections (Anaplasma, Babesia, Bartonella)
- Positive Lyme IgM Western blot
- Low levels of NK CD 57
- Positive Immune or Inflammatory markers: ANA, CRP, or ESR
- Large Amount of prior IV or oral Abx

What was associated with greater likelihood of improvement?

Greater impairment at the start of treatment

- Worse Cognitive impairment
- Worse Pain, Fatigue, Physical Functioning
- Greater # of joints in pain on rheum exam
- Greater # of abnormal areas on neuro exam

Elevated C6 Peptide index (CSF/serum)

C6 ELISA Index: 4x more sensitive Than Whole Cell Sonicate ELISA (p<.001)

Positive C6 Index correlated with improvement in physical functioning for those given ceftriaxone at week 12 (r=.5, p=.04) & at week 24 (r=.5, p=.02)

AI= [OD CSF/OD Serum]/ [Total IgG CSF/Total IgG Serum]

Summary

Cognition: impaired memory & verbal fluency & speed

Brain MRI: White Matter Hyperintensities not helpful

PET Imaging: Decreased perfusion and metabolism

Treatment with Ceftriaxone

- Temporary improvement in cognition to week 12
- Relapse in cognition by week 24.
- Sustained improvement in pain and physical functioning

About ~40% of patients did not respond to retreatment with IV ceftriaxone

Other Studies from this Lyme Encephalopathy sample

- MR Spectroscopy study of Ceftriaxone's effect on CNS Glutamate
- Studies suggesting heightened immune activation
 - 1. Proteomic Study of CSF of PTLS
 - 2. Serum Anti-neuronal Ab
 - 3. Serum Interferon α-inducible genes

MR Spectroscopy before after 30 days of ceftriaxone or placebo

IV Ceftriaxone decreased the excitatory neurotransmitter glutumate Fallon et al, manuscript in prep.

The CSF Proteome: unique proteins differentiate post-Lyme vs CFS vs Normal

Strengths of the NINDS Lyme Encephalopathy Study

- Rigorously Defined Patients
- Quantitative methods for assessment
- Excellent Study Retention
- Age-, Gender-, and Education-matched controls
- Excellent collaborations
- Stored samples in Columbia repository

Limitations of the Study

- Generalizability was limited
 Enrollment criteria were so restricted
- Sample size was too small (n=37)
 Due to difficulty finding eligible subjects
 - Markedly reduced the power to detect treatment effects

Adverse Effects & Suggestion for future studies

- IV Ceftriaxone confers risk blood clots, blood stream infection, biliary stones/ cholecystitis, allergic reaction. Each of these occurred in our small study of 37 patients.
- Primary focus of future studies should not be on cognition...but on pain, fatigue, and functional impairment

Significance and Questions

Why do patients not sustain improvement in cognition?

- Would a less treatment refractory sample have done better?
- What alternative & safer non-antibiotic therapies may enhance patient response among those not responding to repeated antibiotics?

Can additional baseline predictors of response be identified?

What was the mechanism? Antimicrobial? Glutamate?

Other Randomized Placebo-Controlled U.S. Studies of PTLDS

STOP-LD Study (Krupp, Neurology 2003)

Klempner et al. (New England J Med 2001)

STOP-LD Study (Krupp et al, Neurology 2003)

- 55 patients with persistent fatigue after treated LD who had had at least 3 weeks of antibiotic treatment previously
- Fatigue severity for all enrollees had to be at least "moderate" on the Fatigue Severity Scale

STOP-LD Study Design

- Three primary outcome measures (fatigue, reaction time, CSF OspA) but only on one – Fatigue – were patients uniformly impaired.
- Random assignment to 1 month of IV ceftriaxone or placebo followed by 5 months of no treatment.
- Primary end-point: 6 months

Comparing Two PTLDS Studies – the Columbia results replicated the STOP-LD results

Prominent International Treatment Guidelines for PTLDS disagree with the prior summaries

- Infectious Disease Society of America: "antibiotic therapy has not proven to be useful"
- British Infection Association:
 "Studies of prolonged antimicrobial treatments of patients with Post Lyme Syndrome have not shown sustained benefit"

More Disagreement

• European Federation of Neurological Societies:

"American trials have demonstrated that additional prolonged antimicrobial treatment is ineffective in Post Lyme Disease Syndrome"

Klempner's 2 Studies of PTLDS NEJM 2001

- 129 seronegative & seropositive patients
 - Enrolled based on report of functional impairment – but no severity cutoff or severity measure was used for enrollment.
 - Did not require documentation of classic Lyme signs in the seropositive group
- Randomly assigned to:
 - 30 days of IV CFTX + 60 days of oral doxy
 - 30 days of IV placebo + 60 days of oral placebo

Results at 6 months Klempner et al, NEJM, 2001

• Primary Outcome:

- No difference in functional outcome between drug and placebo as assessed by the SF-36 measure
- Secondary outcomes:
 - No difference in change for cognition or depression.
- Result: Study stopped early due to lack of benefit.

Why were these results so different from the earlier studies?

- Strength of this study: sample size
- Limitations of this study:
 - Heterogeneity of patient sample
 - Not enrolled based on a pre-selected "severity level of impairment"
 - Statistical analysis did not adjust for differences in baseline severity on functional impairment

Fallon, Open Neurology 2012 Delong, Cont Clinical trials 2012 Klempner, AmerJMed, 2013

"Efficacy" vs. "Clinically Recommended"

- Krupp Fatigue Study:
 - Efficacy for IV ceftriaxone was shown for fatigue but IV treatment was not recommended due to risks associated with IV antibiotics
- Fallon Encephalopathy Study:
 - results showed non-sustained benefit on the primary outcome measure of cognition and IV risks – so IV treatment was not recommended for sustained improvement in cognition

Conclusions

- Guidelines should revise their assessment of the U.S. clinical trials - as retreatment with IV ceftriaxone reduces Fatigue in PTLDS
- Patients & Physicians should discuss together the risk/benefit ratio of retreatment.
- Alternative treatments are needed for those who are no longer benefiting from antibiotics
- Immune activation is present in many of these patients with PTLS – a potential clue

A Comparison of Lyme Disease Serologic Test Results From 4 Laboratories in Patients With Persistent Symptoms After Antibiotic Treatment

Brian A. Folios,¹ Martina Pavilicore,² Samantha W. Collino,² and Cerl Bremen⁴

Clinical Infectious Diseases Advance Access published October 13, 2014

Five Questions

- Do labs differ in the likelihood of detecting a sample as positive?
 Lyme specialty vs national commercial vs University lab
- Are the labs concordant with each other?

 ie, will a positive result at one lab also be positive at the next lab.
- Is the % of False Positives comparably low at the different labs?
- Do the in-house lab criteria for interpretation of a Western blot provide an advantage over the CDC criteria?
- How does the IgM Western blot perform from PTLDS samples?

Methods

- Serum from two groups:
 - 37 persistently symptomatic treated patients with well-documented prior Lyme disease (PTLDS)
 - 40 asymptomatic medically healthy controls without a history of Lyme disease diagnosis or treatment
- Samples from each subject sent to 4 labs:
 - University-based Lyme lab
 - Commercial Lab
 - Two Lyme Specialty Labs

Uncommonly, when ELISA is negative the WB IgG can be positive (using CDC criteria) WB only + IgG Specificity Commercial lab: 1/37 (2.7%) 100% 3/37 (8.1%) • University Lab: 97.5% Lyme Specialty Lab A: 2/37 (5.4%) 100% • Lyme Specialty Lab B: 2/37 (5.4%) 92.5%

• Clinicians may consider requesting an IgG Western blot if the ELISA is negative and the clinical picture & exposure history are supportive. For every test except the IgM WB when CDC criteria are used, % of False Positives (FP) are comparable across labs among 40 medically healthy controls

	ELISA (+/Ind)	IgG WB	2-Tier	C6 Peptide
University Lab	12.5%	2.5%	0%	
Commercial Lab	7.5%	0%	0%	
Specialty Lab A	2.5%	0%	0%	0%
Specialty Lab B	7.5%	7.5%	2.5%	0%

NOTE: The IgG WB, 2-Tier Assay, & the C6 Peptide ELISA performed well with few or no false positives

Limitations of the Study

- Were some of the medically healthy controls previously infected?
 - Possibly a small number
 - But these individuals felt healthy & had no prior diagnosis or treatment for Lyme disease.

Had these same individuals been fatigued, a physician relying upon a positive IgM serologic test for diagnosis may have erroneously initiated treatment for Lyme.

 <u>Antibody-based assays are problematic</u>. We need a sensitive & specific marker of active infection.

NEW RESEARCH DIRECTIONS

Slide courtesy of Stephen Barthold, UC Davis

Peer-reviewed articles demonstrating that Borrelia Persist – antibiotic tolerant

• Mouse Model:

- Hodzic et al, 2008; UC Davis, California
- Yrjänäinen, 2010; Univ Turku, Finland
- Bockenstedt, 2002 & 2012; Yale, Connecticut
- Rhesus Macaques:
- Embers et al, 2012; Tulane, Lousianna
- Dog Model:
 - Straubinger, 2000; Cornell, NY

 Borrelia spirochetes may not be detected unless the xenodiagnostic method is used

What have mouse models baught us?

Early results from the human xenodiagnostic study are intriguing

- 1 of 9 persons with PTLDS & C6+ tested positive, but only for DNA by PCR -- not by isolation of spirochete.
- Possible Explanations:
 - Persistent Infection
 - -Fully viable, disease inducing
 - -Reduced viability, disease inducing
 - -Non-disease inducing
 - A new infection from an unseen tick bite

What is the long-term fate of persisting spirochetes? What do they do?

"Resurgence of Persisting Non-Cultivable Borrelia burgdorferi following Antibiotic Treatment in Mice"

Emir Hodzic, Denise Imai, Sunlian Feng, Stephen W. Barthold

• PloS One January 23, 2014

What does this mouse research mean?

- Borrelia persist but often can't be cultured
 - Documented by DNA with RNA transcription
 - Spirochetes visualized by immunoflouresence
 - Spirochetes elicit a local cytokine response
 - Could this "finger-print" of pro-inflammatory cytokine expression be related to persistent fatigue, pain, and cognitive problems?

Not all Tick-borne Infections cause Lyme disease

- Babesia
- Anaplasma
- Ehrlichia
- Powassan Virus
- Borrelia miyamotoi
- Tick-borne encephalitis virus

Research questions to pursue

- Borrelia persisters (Zhang 2014, Lewis 2015)
 - Do the use of antibiotics shown to be effective against non-dividing stationery persisters (round forms) in vitro confer a better long term outcome in humans with later stage disease than doxycycline or ceftriaxone alone?
 - Is pulse dosing more effective than steady longer-term dosing?
 - What are the risks to the patient?

Research questions to pursue

- Immunomodulatory therapies
 - IV Immunoglobulin
 - -Can this help PTLS patients with neuropathic symptoms suggestive of autoimmune neuropathy?
 - Pilot data from U.S. (Katz 2009) suggests that some patients with PTLS have an immune mediated neuropathy
 - Abnormal small nerve fiber density is reversed by IVIg treatment.

Research Ouestions to Pursue

- Brain Imaging
 - Central Sensitization
 - Do post-Treatment LD patients with pain have abnormally activated brain circuits that remain hyperactive long after the infection is gone?
 - -Can the pain be treated by down-regulating these neural circuits with pharmacologic or brain stimulation treatments?

Clinical question of some urgency – how to add psychiatric care to the treatment plan

- About 40% of patients with PTLS have psychiatric symptoms that persist
 - Some avoid psychiatric care
- Results:
 - Persistent Despair, depression, anxiety
 - Sleep disturbance exacerbating fatigue
 - Cognitive impairment due to depression
 - Interpersonal distress loss of support
 - Suicidal thoughts in about 20% of PTLS pts

Breaking News: 10 Year Follow-up

A Preliminary Report tracking patients from our NIH trial of Posttreatment Lyme Encephalopathy

Primary Focus of Follow-up

- To what extent do you feel Lyme disease is affecting you now?
 - Not at all
 - A little (but not in a significant way)
 - Moderate Symptoms (but able to function)
 - Severe Symptoms & it impairs functioning

How many were reached?

- Information on 81.1% of 37 Lyme Pts
 - 1 Died
 - 6 Lost to follow-up
 - 1 Preferred not to participate
- Information on 11 of 18 Controls (61.1%)
 - 2 preferred not to participate
 - 5 lost to follow-up

- To what extent do you feel Lyme disease is affecting you now?
 - 28.5% Not at all (n=6) or a little bit (n=2)
 - 39.3% Moderately (but able to function)
 - 32.1% Severely & it impairs functioning

Pain-focused Therapies

Pain syndromes

- Pharmacologic:
 - Gabapentin, Pregabalin
 - Serotonin-Norepinephrine Reuptake Inhibitors
 - Low dose amitriptyline or naltrexone
- Immune Modulating
 - NSAIDS; Hydroxychloroquine; IV Ig
- Acupuncture
- Exercise e.g., pilades
- Meditation Yoga, Tai chi

Fatigue & Sleep Strategies

Improve Sleep

- Sleep hygiene
- Pharmacologic:
 - Amitriptyline
 - Trazadone
 - Gabapentin
 - Quetiapine ("Seroquel")
 - Mirtazipine ("Remeron")
- Neurofeedback

Brain Fog & Mood

Brain Fog

- Neurofeedback (e.g, Zengar Neuroptimal)
- Depression/Irritability/Anxiety
 - Bupropion
 - SSRIs/SNRIs
 - Transcranial Magnetic Stimulation
 - Psychotherapy

What is the role of nutrition, herbal therapies & the microbiome?

- Patients sometimes report benefit by modifying diet or herbal supplements:
 - Gluten-free diets
 - Anti-inflammatory diets
 - These need to be studied in a controlled fashion
- Do adjunctive probiotics enhance symptom reduction (in addition to restoring the microbiome)?

Key Questions

What happens over the long-term?

1.Compared to 10 years ago -Did they get better? Get worse? Stay the same?

2.Did their course over time differ from the course of the healthy controls – Are they more likely to worsen? To improve?

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Age and Gender at Follow-up

	Controls n=11	Patients n=28	P-value
Age	57.6 (10.8)	54.4 (14.0)	n.s.
% Female	81.8%	53.6%	P=.103
Education (yrs)	16.3 (2.3)	14.8 (2.6)	P=.098

Deep White Matter Hyperintensities in Brain of Controls vs Patients

What about new papers on morphology, Bb persisters, & differential treatment needs?

- Do the in vitro findings of "persisters" requiring different antibiotics for eradication have clinical relevance in vivo in humans?
- Would alternative treatments directed at these variants result in long-term improved clinical outcomes?

MRI: Treatment Results

 Change in Hyperintensities was not different between patients on drug vs placebo

Functional Imaging: Are there global differences at rest bet pts & ctrls?

No.

- Global Flow & Metabolism at Rest:
 No differences in resting blood flow
 - No differences in resting metabolism
 - No differences also within gray matter regions or white matter regions

Limitations of Study

- Small sample size
- Limited generalizability secondary to narrow entry criteria
 - Would seronegative pts who have persistent symptoms benefit?
 - Would pts who have had less prior antibiotic treatment do better?
- Can we do better identifying biomarkers to help guide treatment selection?

Summary of Background for Lyme **Encephalopathy Study**

- Symptoms may persist after standard courses of treatment for neurologic Lyme disease Ö
- Functional Imaging SPECT scans show patchy hypoperfusion (similar to vasculitis): multiple areas of decreased blood flow partially reversible. (Logigian et al). Objective measures of deficit are helpful.
- Structural imaging MR Scans show small white matter hyper-intensities
- Uncontrolled data suggested that re-treatment with IV Antibiotics may be helpful (Fallon 1999)

Positron Emission Tomography

- Cerebral Blood flow (O-15): CBF
 - Condition #1: at rest at room air

 - Condition #2: With snorkel at room air
 Condition #3: With vasodilation challenge (room air enhanced with 5% CO2).
- Cerebral Metabolism (FDG): CMR Condition #4: at rest

• Imaging Time Points:

- Patients & Controls at baseline, only Patients at weeks 12 and 24
- Analysis: SPM (Statistical Parametric Mapping) Subtraction images patients vs controls
 All significant at cluster size of 25 voxels & p<,01

What was the cognitive profile among evaluated Patients with Post-Treatment Lyme Disease & cognitive

complaints? (Keilp et al, 2006)

- 81 CDC-criteria pts vs 39 healthy controls
- Index Scores:
 - WAIS-III: Processing Speed slowed in LD (p<.01)
 Subtests: Digit Symbol and Symbol Search
 - WMS-III: Memory is affected in CLD (Auditory immed & delayed)
 - Subtests: Logical story memory (auditory) & family pictures (visual mem). Place demands on context & need to organize material
- Discriminant Analysis:
 - Logical memory subtest correctly classified 73.7% of Lyme and 75% of controls.

Disclosures & Grant Support

- Disclosures:
 - Roche Pharmaceuticals (supplied Ceftriaxone free of charge for NIH Study)
 - Immunectics (conducted C6 ELISA assays free of charge)
- Grant Support:
 - Primary: NINDS/NIH
 - Secondary studies:
 - Lyme Disease Association
 - Lyme Research Alliance, Inc.
 - National Research Fund for Tick Borne Diseases

Decline in Fatigue is significant at week 12 among the more impaired given antibiotic

Predictors of Response?

Adverse Events leading to hospitalization or drug discontinuation

 7 patients had treatment-related AE that led to drugdiscontinuation or hospitalization

Distribution:

- 1/14 (7.1%) on placebo vs 6/23 (26.1%) on drug
- PICC line:
 - Thrombus: 2
 - Line Infection: 1
- Drug-related:
 - Allergic reaction (hemolysis): 1
 - Allergic reaction (skin rash): 2
 - Biliary stones req cholecystectomy:

Does a positive C6 Ab Index have any clinical significance or any specific functional brain effects?

James Moeller, PhD

Recommendations for working with the patient with persistent symptoms who has been on antibiotics for prolonged periods

- Elicit the underlying fears
- Educate
 - Both antibiotics & healthy immune system help to fight

Additional Assessments

• Physical Exam: joints, neurologic

Blood

- Lyme: C6 Peptide ELISA, WCS ELISA, WB
- Other infections (Babesia, Anaplasma)
- Immune/inflammatory markers – CRP, ESR, ANA
 - Natural Kill cell CD57
 - Anti-neuronal antibodies
 - Interferon alpha activity

CSF Assessments

- WBC, Protein, Lyme Index
- Lyme PCR and Culture
- ELISA: Whole Cell Sonicate & C6 Peptide
- Later using a sub-sample of 25 CSF samples:
 - -Proteomic Investigation
 - Lead investigators: Steve Schutzer, Tao Liu
 - Pacific Northwest National Laboratory

Questions

- The C6 Brain pathway
 - Why is the magnitude of the C6 ELISA Index so tightly correlated with expression of a specific brain pathway?
 - Are the C6 Index AI positive patients truly those who benefit from antibiotic retreatment?
 - Does the expression of the C6 Brain map relate to treatment response?

Summary of Results at Wk 12

Did IV ceftriaxone result in specific improvement in memory?

• No, the improvement was spread across multiple domains and not specific to memory.

Did the IV Ceftriaxone show preferential response on other measures at wk12?

Yes, among the more impaired given IV ceftriaxone, greater improvement was noted in self-report measures of fatigue, pain, and physical functioning.

Summary of Efficacy Results

- Was there a significant difference in cognitive change across the 3 groups (Lyme pts on drug, Lyme on placebo, healthy controls) over the 24 weeks?
- Yes (p=.04). This was due to the greater improvement among the IV ceftriaxone treated patients noted at the primary efficacy time point of week 12.
- Was the drug-placebo difference at week 12 significant for cognition?
- Only the drug group had within group improvement (p<.01).
- The between group improvement (Drug vs Placebo) fell at the margin of significance (p=.053)...needs replication.
- Magnitude of improvement was moderate.

Was the improvement in the ceftriaxone group sustained to week 24 (after 14 wks of no treatment)?

No, for cognition. By week 24, there was no difference between groups in cognitive improvement over time.

Yes, for pain and physical functioning. At week 24, among the more impaired in severity at baseline, the improvement was sustained in pain and physical functioning (but not in fatigue).

Clinical Significance

- Adverse events associated with PICC lines and IV ceftriaxone are of concern
- For sustained cognitive improvement to week 24, given the risks & loss of benefit, it is not recommended to treat with 10 weeks of IV ceftriaxone followed by 14 weeks of no treatment
- For sustained improvement in pain and physical dysfunction, among the more impaired, repeated treatment with IV ceftriaxone may have a role in well-documented LD....but careful discussion with the patient about risks needs to occur.

Were clinical markers of Treatment Response suggested by this study of Persistent Lyme Encephalopathy?

Greater severity associated with improvement:

- Cognition
- Pain, Fatigue, Physical Functioning
- # of joints in pain on rheum exam
- # of areas with abnormality on a neuro exam

CSF

 Positive C6 Antibody index associated with acute & longterm improvement in physical functioning/fatigue

Neuro-imaging

- Expression of Lyme Brain Map on PET FDG
- CSF C6 AI and Brain Map together provided best predictor of who will benefit clinically (r=0.91)

Research Questions

- Why do patients relapse? What is the mechanism of action of ceftriaxone? an antimicrobial or a glutamate effect?
- What alternative treatments could be provided that might be safer and result in a more sustained response in cognition?
- Is the etiology of the persistent cognitive problem different from the etiology of the persistent pain, fatigue, physical dysfunction?

Additional Research Questions

- Is the C6 antibody index able to prospectively identify patients who will benefit from repeated treatment?
- Does expression of the Lyme brain map also help to prospectively identify patients more likely to respond to repeated treatment?

Limbic System Mediation

Parahippocampal gyrus

- Receives sensory input from outside world, integrates it, and projects it to the hippocampus (memory) and amygdala (fear, aggression, mood)
- Insula
 - Receives limbic input from amygdala.
 - Relays somatosensory info & pain reactions
 - Relays between Wernicke's and Broca's area (dysfunction contributes to aphasias & articulation deficits)

FDG PET: Metabolic Changes

Pathophysiology of CNS Lyme Disease

• Direct Damage by spirochete

 Invasion & attachment. Invades brain (rabbits, rhesus macaques) by penetrating CNS vascular endothelium and adhering to glial cells. In rat culture, Bb adheres to brain astrocytes, oligodendroglial cells & microglia, resulting in demyelination and neural cell cytotoxicity

• Indirect damage

- Cytokines from neurons. Exposure to Bb causes neurons to produce interleukin 6, TNF, nitric oxide. N.O. is cytotoxic and proinflamatory. Elevated IL6 can cause sx of fatigue & malaise. These Bb may be dormant or active.
- Immunologic damage. Bb's surface lipoproteins are proinflammatory and Bb glycolipids may elicit cross-reactive Ab. Quinolinic acid (NMDA excitotoxin) in LD encephalitis

Controlled Studies of the treatment of Chronic Lyme Disease

Baseline Clinical Cognitive: mild-moderate deficits Verbal Memory (z=-1.0), Working memory (-0.7), Verbal Fluency (z=-0.8) Psychopathology: mild mild depression & anxiety Neurologic exam:

- Mild sensory findings (73% Ly vs 22.2% C, p<.001)</p>
- Rheumatologic Exam:
 - Much joint pain (6.1 jts Ly vs 0.6 jts C, p<.01)</p>
 - Very few trigger points (1.8 Ly vs 0 C)

Hypoperfusion on SPECT is common: "Reversible Cerebral Hypoperfusion in Lyme Encephalopathy" (Logigian et al, 1996)

- Definite LE (13 pts) vs Possible LE (9 pts) vs 26 normals
- Results:
 - A. Significantly more deficits: LE>Possible LE> Normals B. Of 13 Pts with Definite LE treated with IV Ceftriaxone
 - 6 mons later: a partial reversal of perfusion deficits
- Conclusions:
 - SPECT deficits are worse with more severe disease
 - SPECT deficits may be seen even in absence of objective neuropsychological deficits
 - Perfusion deficits are <u>at least partially reversible</u>

Change from Baseline is significant for C6+ given drug vs others

O-15 Imaging: are there regional blood flow differences between pts and controls? Yes. (p<.001)

Areas of lower CBF in Lyme pts: L limbic parahippocampal, L&R temporal, R temporal, L & R occipital, L cingulate

• Co-investigators:

- Columbia: Carolyn Britton, MD, Ted Dwyer, MD, Jay Dobkin, MD, Ronald Van Heertum, MD, Robert Delapaz, MD
- NYSPI: Harold Sackeim, PhD, John Keilp, PhD, James Moeller, PhD, Mitch Nobler, MD, Shan Yu, PhD
- Study Coordinator: Kathy Corbera, MD
- Biostatisticians/Imaging Analysts: Eva Petkova, PhD, lordan Slavov, PhD, Jianfeng Cheng, PhD, Shan Yu, PhD, Brett Mensh, MD, Angela Lignelli
- Other Columbia: K Marder, Y Stern, D Bloomfield
- Facilities: Irving Center for Clinical Research, PET Center, NYSPI, Home Care Services (NJ), Roche Pharm., IRBs
- NINDS (A. Kerza, M. Nunn) & DSMB

Community practice in use of ELISA & WB tests varies

- Strict: apply CDC recommended lab criteria to avoid false positives
- Broad: apply a modified method to avoid false negatives
 - Positive IgM or IgG Western blot (without ELISA)
 - Laboratory-adopted criteria for WB vs CDC
 - Consider the serologic diagnosis of "possible" Lyme disease if the IgG Western blot is suggestive with 3 or 4 bands....attend to the 31 & 34 kd bands as these may be expressed in late infection

Testing (Aguero-Rosenfeld et al, 2005)

- Indirect assays:
 - good sensitivity and specificity for the more acute inflammatory phases of Lyme disease such as arthritis (100%)
 - lesser sensitivity for neurologic Lyme (64-87%) (Dressler 1993, Bacon 2003) and for convalescent phase after EM treatment (2 tier: 29-78%)
- Bb antibodies (IgM and IgG) may persist for many years after successful treatment of LB

Sample Size Screened

- Lyme (patients samples from 2 studies):
 - A. Lab/SPECT study screened 194 patients to find 13 (6.7%)
 - B. Screenings from prior NIH Study added stored samples from pts with well documented LD - all of whom had also had prior IV antibiotic therapy
- Healthy controls
 - A. Screened 315 people of whom 26 were
 - interested and eligible to participate (8.3%)
 - B. Stored serum from prior NIH Study added 7

Preliminary results from 3 Labs – expanded sample

 Across 3 Labs: (n=33 HC, n=20 Ly) 						
	Commercial		2 Lyme	e-specialty Labs		
	Sens	Spec	Sens	Specificity		
ELISA:	55%	91%	50-55%	82-94%		
C6 ELISA:			25%	100%		
IgM WB (CDC)	20%	100%	5-20%	91-97%		
IgM WB (Lab)			5%	96%		
IgG WB (CDC)	25%	100%	20-30%	97-100%		
IgG WB (Lab)			20%	100%		
CDC (2 tier IgG)	25%	100%	20-25%	100%		

Note:Very Similar performance across Laboratories.Note:C6 ELISA is comparable to IgG WB

