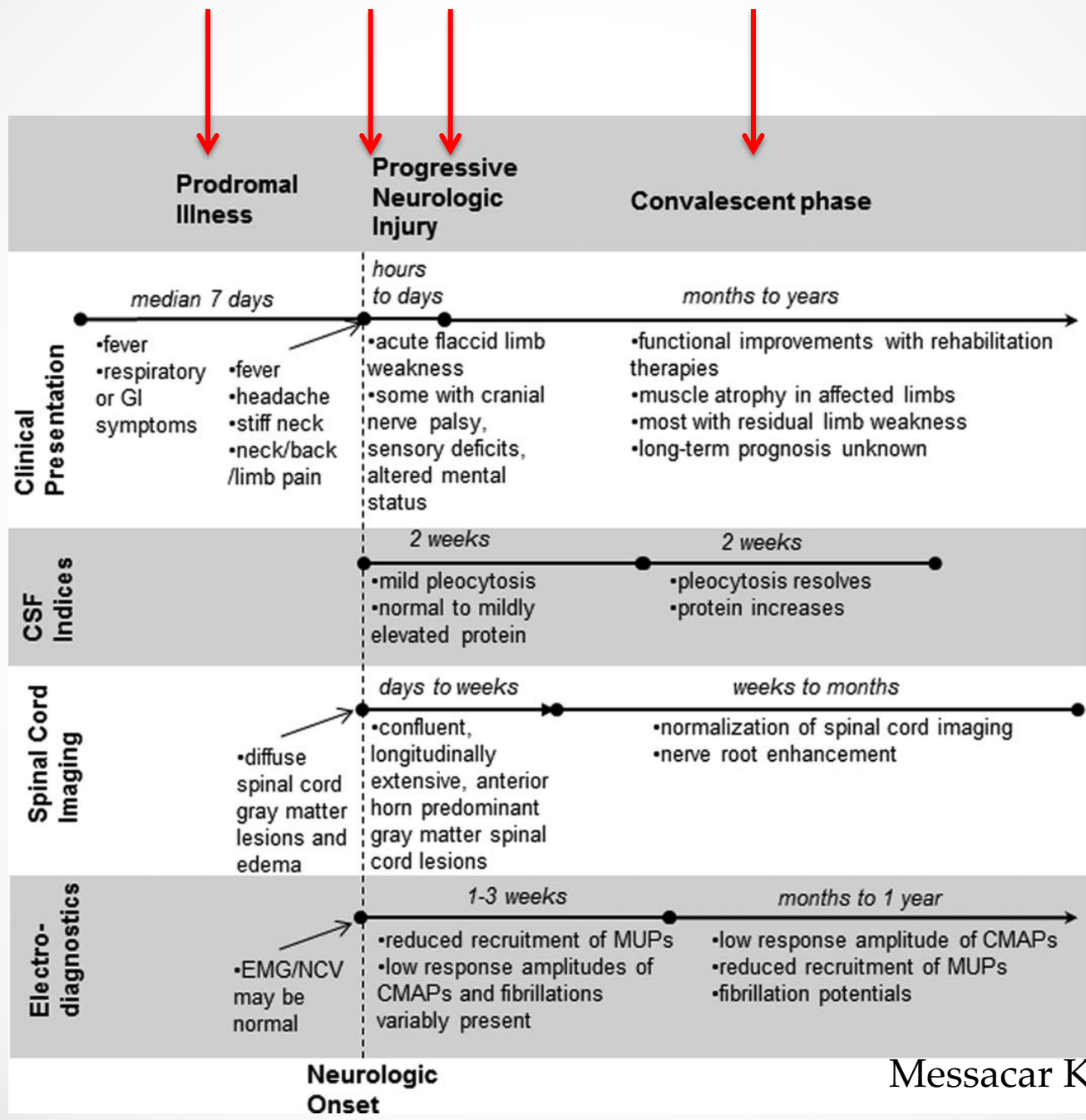


# What We Know About Treatment in AFM

Leslie Benson, MD  
Pediatric MS and Neuro-Immunology Program  
Boston Children's Hospital  
6/12/20

# Disclosures

- All treatments discussed are off label
- Biogen sponsored clinical trial – CONNECT
- Vaccine injury compensation program



# Treatment Overview

- Acute
  - Inflammation directed
  - Viral directed
  - ?Neuroprotective?
  - ?Restorative?
- Symptomatic & Supportive
  - Bone health
  - Psychotherapy
  - Bracing
  - Assistive devices
  - Pain management
  - Nutrition
  - Ventilation
- Chronic/Rehabilitation
  - THERAPIES – PT, OT, speech, feeding
  - Electrical stim “e-stim”
- Surgical
  - Nerve transfers
  - Muscle transfers
  - Tendon Transfers



# Acute Treatment

- Immune directed
- Anti-viral
- Neuroprotective?

# Acute Treatment

- **Immune directed –**
  - Predominated thus far
  - Extrapolated from autoimmune inflammatory myelitis treatment
  - Controversial
  
  - IVIG
  - Monoclonal/polyclonal antibodies
  
  - Steroids
  
  - Plasmapheresis/Plasma exchange (PLEX)

# Treatment Approach

TABLE 2. Diagnostic Findings, Treatment, and Course of Acute Flaccid Myelitis Cases in US Cohorts 2012–2015

| Source  | CDPH <sup>a</sup>    | CHCO <sup>b</sup>   | PCH <sup>c</sup>    | CDC <sup>d</sup>       |
|---|----------------------|---------------------|---------------------|------------------------|
| No. of cases  | 59                   | 12                  | 11                  | 120                    |
| <b>Treatment/course, %</b>  |                      |                     |                     |                        |
| Intravenous immune globulin   | 73                   | 75                  | 82                  | 73                     |
| Plasmapheresis  | 22                   | 17                  | 9                   | 15                     |
| Intravenous steroids  | 71                   | 42                  | 55                  | 54                     |
| Antivirals  | 3                    | 17                  | 0                   | NR                     |
| Response to treatment   | None noted           | None noted          | NR                  | NR                     |
| Intubation/ventilatory support  | 34                   | 25                  | 9                   | 20                     |
| Persistent motor deficits at last follow-up (no. with deficits/no. followed; median follow-up interval) | 84 (38/45; 9 months) | 75 (6/8; 12 months) | 90 (9/10; 6 months) | 95 (53/56; 4.2 months) |

# Acute Treatment

- Immune directed
  - IVIG
  - Steroids
  - Plasmapheresis/Plasma exchange (PLEX)
- **Viral directed**
  - **Pocapavir with no follow up evidence of anti EV-D68 efficacy**
  - **Fluoxetine**
  - **Others?**



# Acute Treatment

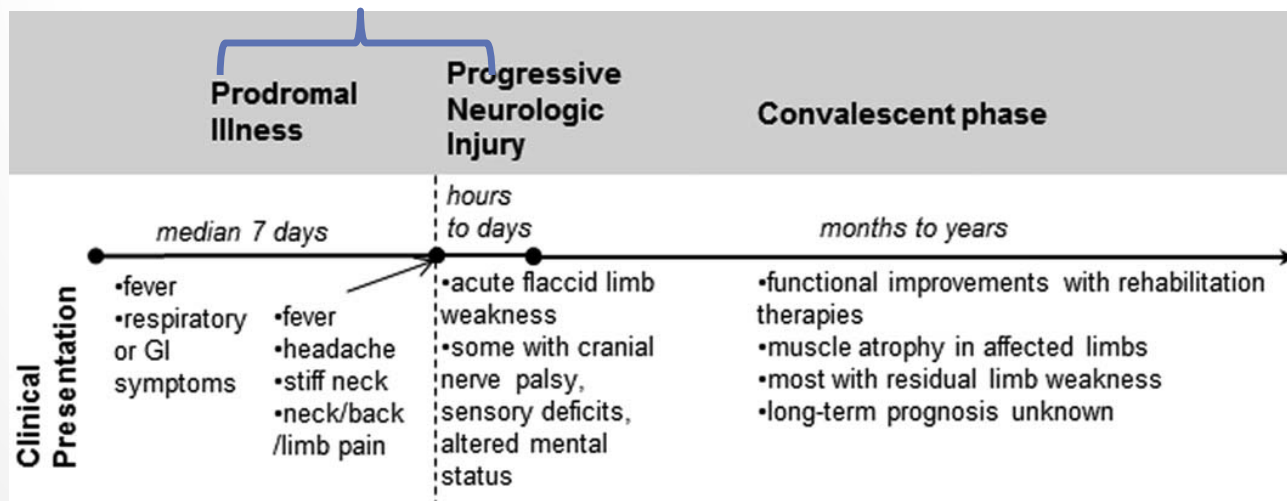
Rationale for the Evaluation of Fluoxetine  
in the Treatment of Enterovirus D68-Associated  
Acute Flaccid Myelitis



- Off label use 2016

# Challenges

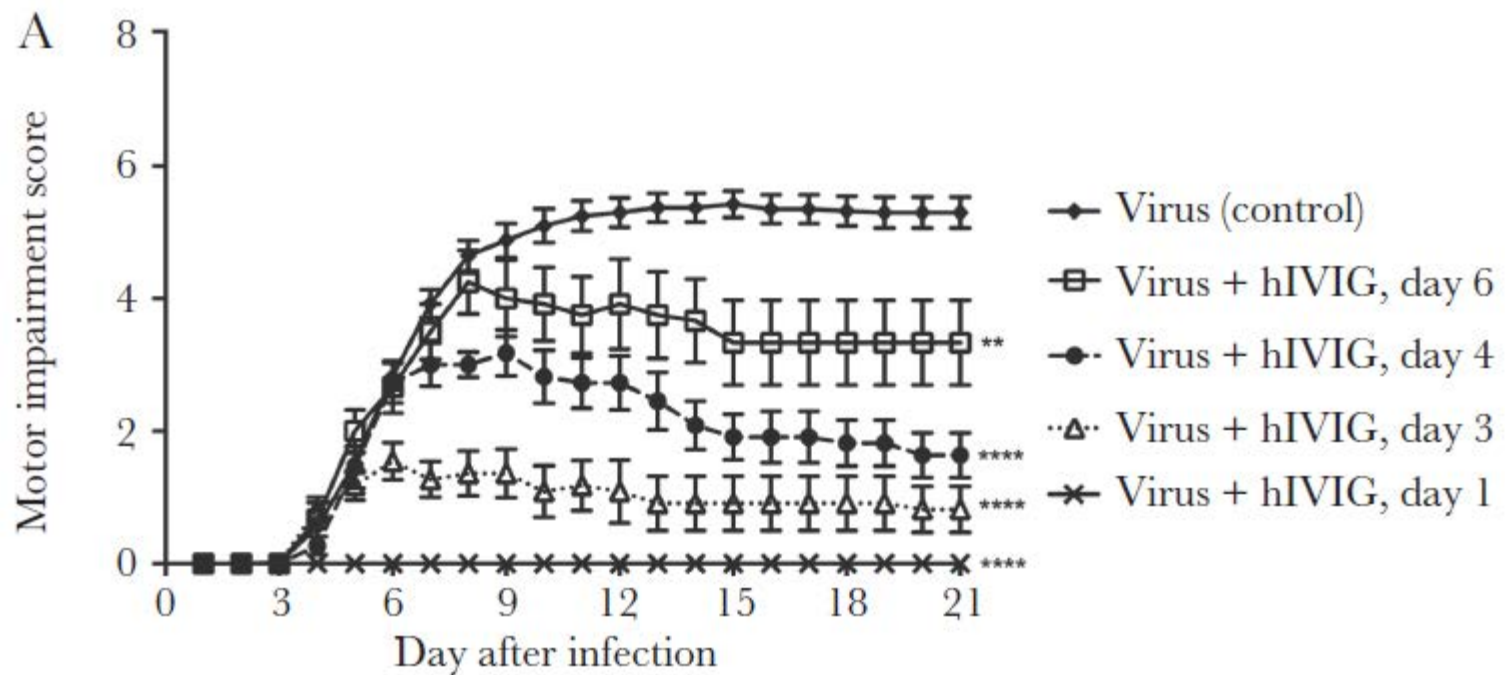
- Intervention before irreversible damage
  - Timely presentation
  - Timely diagnosis and confirmation
  - Effective treatment that works after neurologic onset vs during URI
- Rare disease
- Efficacy assessment with multiple interventions



# Acute Treatment

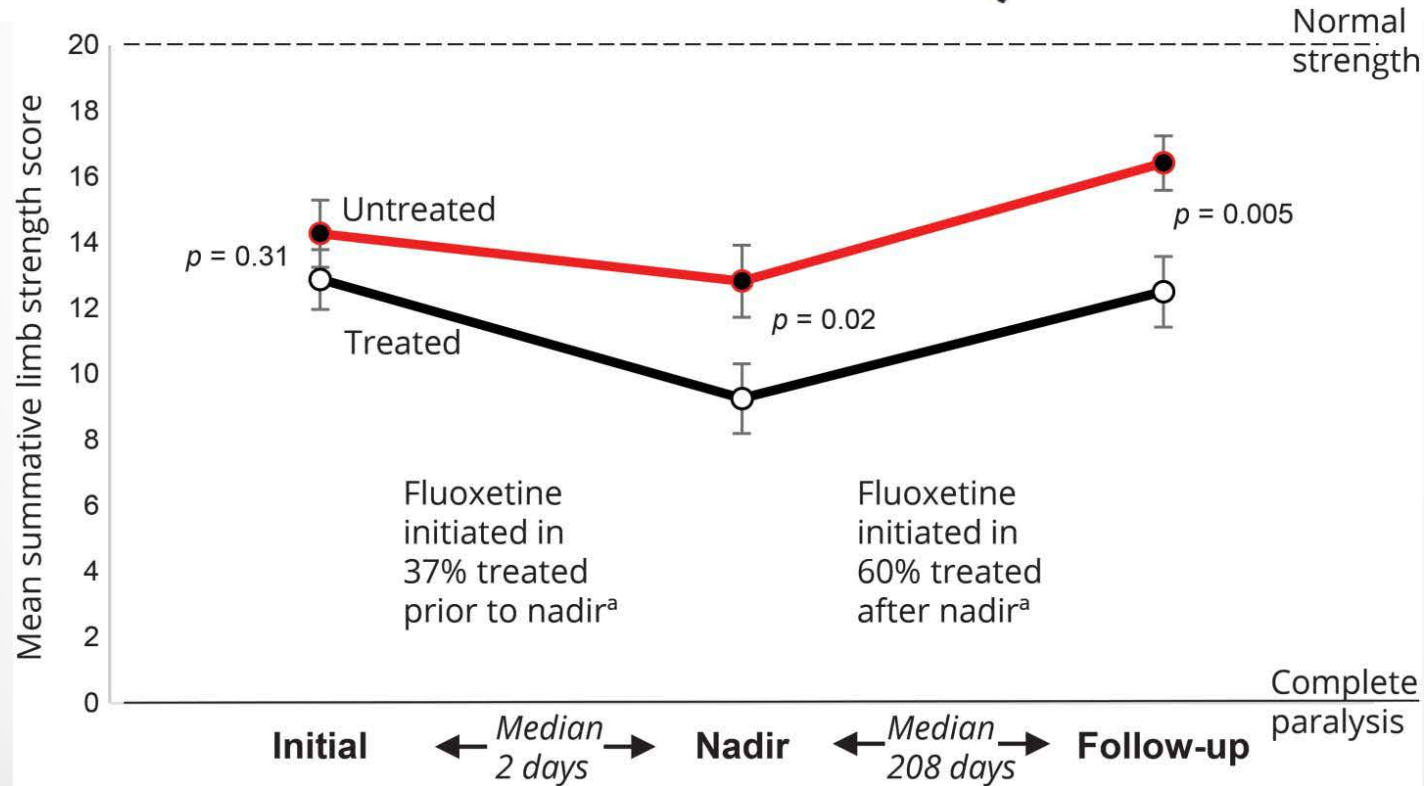
- Preliminary Mouse Data

- IVIG – GOOD



# Fluoxetine also doesn't clearly benefit humans

## Safety, tolerability, and efficacy of fluoxetine as an antiviral for acute flaccid myelitis



# Acute Treatment – NOW WHAT?

- Immune directed
  - IVIG
  - Steroids
  - Plasmapheresis/Plasma exchange (PLEX)
  - **Targeted antibodies?**
- Viral directed
  - Fluoxetine
  - **Telaprevir ?**
  - **Quinoline derivatives?**
  - **Capsid binding inhibitors - R856932**
  - **Others in development?**

# Acute Treatment – NOW WHAT?

Validating Enterovirus D68-2A<sup>pro</sup> as an Antiviral Drug Target and the Discovery of Telaprevir as a Potent D68-2A<sup>pro</sup> Inhibitor

- FDA Approved for HepC
- Telaprevir inhibits EV-D68 2A<sup>pro</sup>
- **Concerns:**
  - CNS penetration - unknown
  - Timing
  - Replaced by other protease inhibitors for cumbersome administration and adverse effects, low barrier to resistance, drug interactions

# Acute Treatment – NOW WHAT?

Journal of  
**Medicinal Chemistry**

Subscriber access provided by Strauss Health Sciences Library, University of Colorado Anschutz Medical Campus

Article

## Discovery of quinoline analogs as potent antivirals against enterovirus D68 (EV-D68)

Rami Musharrafieh, Jiantao Zhang, Peter Tuohy, Naoya Kitamura,  
Shreya Bellampalli, Yanmei Hu, Rajesh Khanna, and Jun Wang

*J. Med. Chem.*, **Just Accepted Manuscript** • Publication Date (Web): 26 Mar 2019

Downloaded from <http://pubs.acs.org> on March 27, 2019

- Optimized dibucaine
- Explored 2C inhibitors -> inhibits replication
- CNS penetration?
- Very early phase development

# Acute Treatment – NOW WHAT?

- Anti-viral R856932

ACS | Infectious  
Diseases

✓ Cite This: *ACS Infect. Dis.* 2019, 5, 1952–1962

Article

[pubs.acs.org/journal/aidcbc](https://pubs.acs.org/journal/aidcbc)

## A Novel Capsid Binding Inhibitor Displays Potent Antiviral Activity against Enterovirus D68

Chunlong Ma,<sup>†</sup> Yanmei Hu,<sup>†</sup> Jiantao Zhang,<sup>†</sup> Rami Musharrafieh,<sup>†</sup> and Jun Wang<sup>\*,†</sup> 

<sup>†</sup>Department of Pharmacology and Toxicology, College of Pharmacy, The University of Arizona, 1657 East Helen Street, Tucson, Arizona 85721, United States



# Exploratory Considerations

- **Neuroprotective – unexplored?**
- **Restorative – stem cells?**
  - Convalescent, chronic phase option
  - Provides a later option when early treatment fails
  - Useful for prior patients potentially
- **Prevention – vaccination?**

# Potential Future Directions

- Clarify effect of inflammation directed treatments?
- Anti-viral
- IVIG 2g/kg ASAP
  - Kawasaki disease protocol
- Combination Therapy
  - IVIG + anti-viral(s)
  - IVIG + anti-viral + other
- Neuroprotection?
- Vaccine?

# Q&A

- Click sessions tab on the left
- Click into the 1 session offered