Glatiramer acetate is safe for a virus-induced demyelinating disease model

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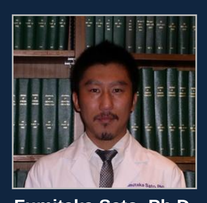

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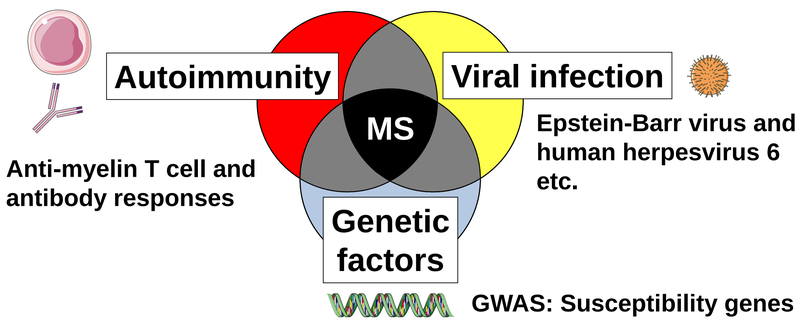
Abstract

[Objective] Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) associated with autoimmunity and/or viral infections. While most disease-modifying drugs (DMDs) for MS suppress disease activities by regulating uncontrolled immune responses (immunopathology), DMDs potentially inhibit anti-viral immune responses, leading to CNS viral reactivation syndromes, such as progressive multifocal leukoencephalopathy (PML). Among DMDs, glatiramer acetate (GA) has not been linked to PML. Here, a gap in knowledge exists of how GA can be effective in MS without causing PML. Thus, we aimed to determine the effects of GA in a viral model of MS, Theiler's murine encephalomyelitis virus-induced demyelinating disease (TMEV-IDD), in which both persistent viral infection and immunopathology in the CNS play pathogenic roles. **[Methods]** TMEV-infected SJL/J mice were treated daily with GA through the entire course or during the acute (early prophylactic) or chronic (late therapeutic) phase of TMEV infection. **[Results]** The early prophylactic GA treatment most efficiently decreased the clinical signs of TMEV-IDD. The early prophylactic GA treatment also enhanced the ratios of *Foxp3*/*Il17a* expression without increased CNS viral persistence or decreased anti-viral immunity. GA treatment induced GA-specific regulatory cytokine productions, including interleukin (IL)-4 and IL-10, which could be protective against immunopathology in TMEV-IDD. **[Conclusion]** This is the first findings to demonstrate that GA could be safe for MS patients with proven viral infection.

Background

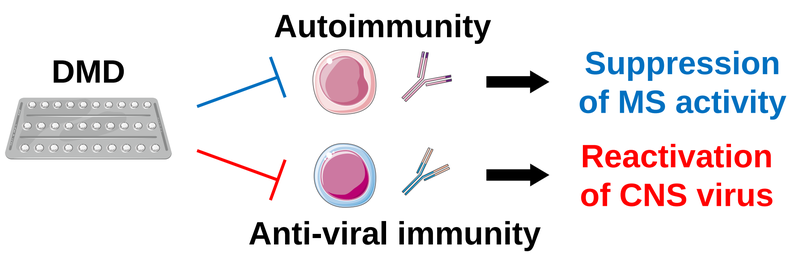
Multiple sclerosis (MS)

- Inflammatory demyelinating disease in the central nervous system (CNS)
- Caused by interactions among autoimmunity, viral infection, and/or genetic factors
- Approximately 20,000 patients in Japan with the ratio of women to men of 3 : 1



Disease-modifying drug (DMD)

- Has immunomodulatory effects
- Suppresses MS activities by regulating anti-myelin immune responses
- Potentially inhibits anti-viral immune responses
- Risk factor of CNS viral reactivation syndromes, such as progressive multifocal leukoencephalopathy (PML)

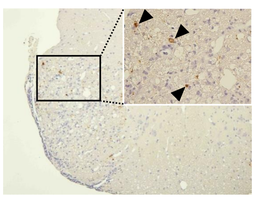


Glatiramer acetate (GA) & Gap in knowledge

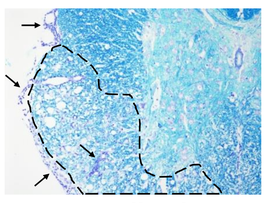
- Used as a DMD for MS, COPAXONE®
- Has anti-inflammatory effects:
  1) Enhances interleukin (IL)-4 and IL-10 production
  2) Increases regulatory T ells expressing the transcription factor Foxp3
- Effective in MS without causing PML

Theiler's murine encephalomyelitis virus (Theiler's virus)

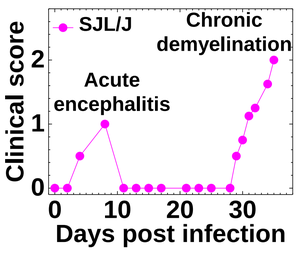
- Used as a viral model of MS
- Infects neuronal cells after intracerebral injection
- Induces acute encephalitis
- Causes chronic demyelination in the CNS due to direct lytic infection (viral pathology) and anti-viral immune responses (immunopathology)



Viral antigen



Demyelination



Aim & Methods

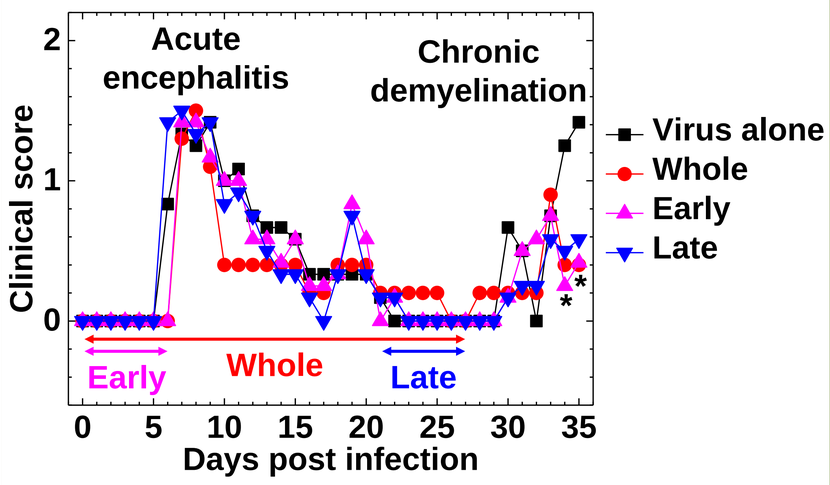
To determine the efficacy and safety of GA in the Theiler's virus model

Group	Theiler's virus infection	GA treatment (0.15mg/mouse)
Virus alone	+	–
Whole	+	Days 0–27
Early	+	Days 0–6
Late	+	Days 21–27

SJL/J mice were infected with Theiler's virus and treated daily with GA through the whole course or during the early (prophylactic) or late (therapeutic) phase of viral infection.

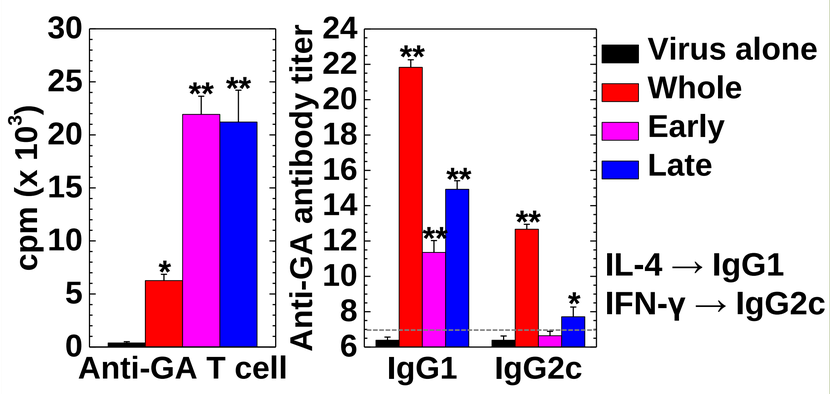
Results

All GA treatments reduce the clinical signs of chronic demyelinating disease



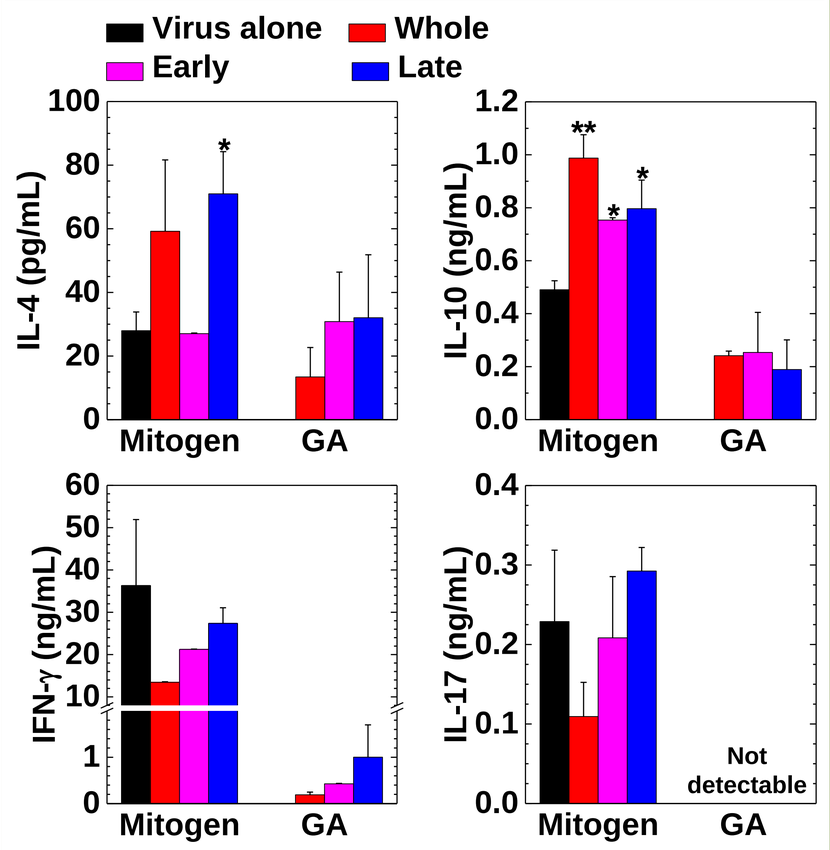
Clinical signs were evaluated by impaired righting reflex scores for 5 weeks. * $P < 0.05$.

GA treatment induces immune responses to GA



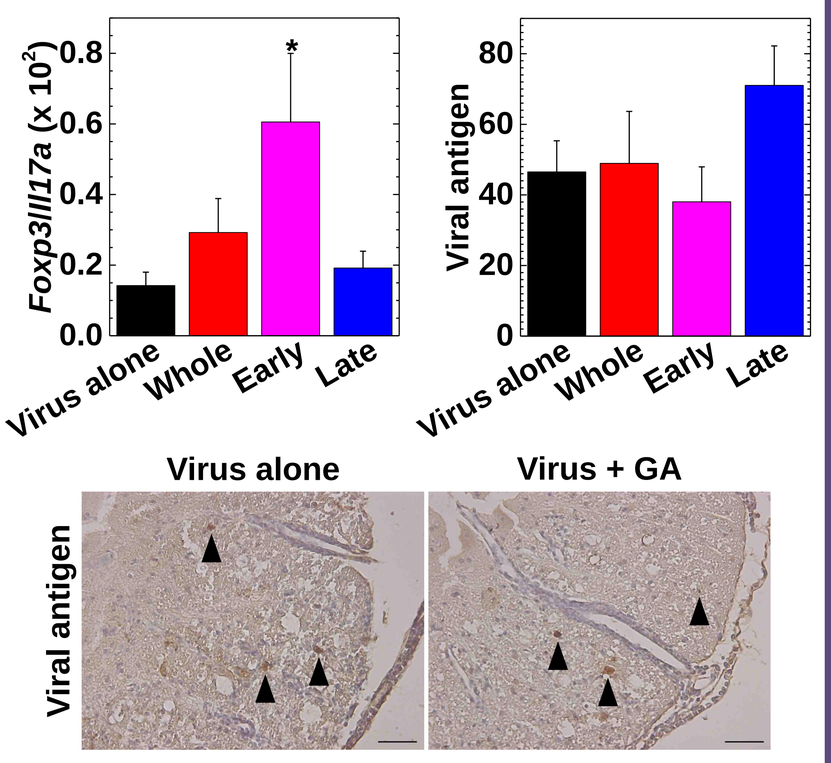
Anti-GA T cell and antibody responses were quantified by [³H]thymidine incorporation assays and enzyme-linked immunosorbent assays (ELISAs), respectively, at 5 weeks. The dotted line is the detection limit. * $P < 0.05$, ** $P < 0.01$.

GA treatment enhances regulatory but not pro-inflammatory cytokine production



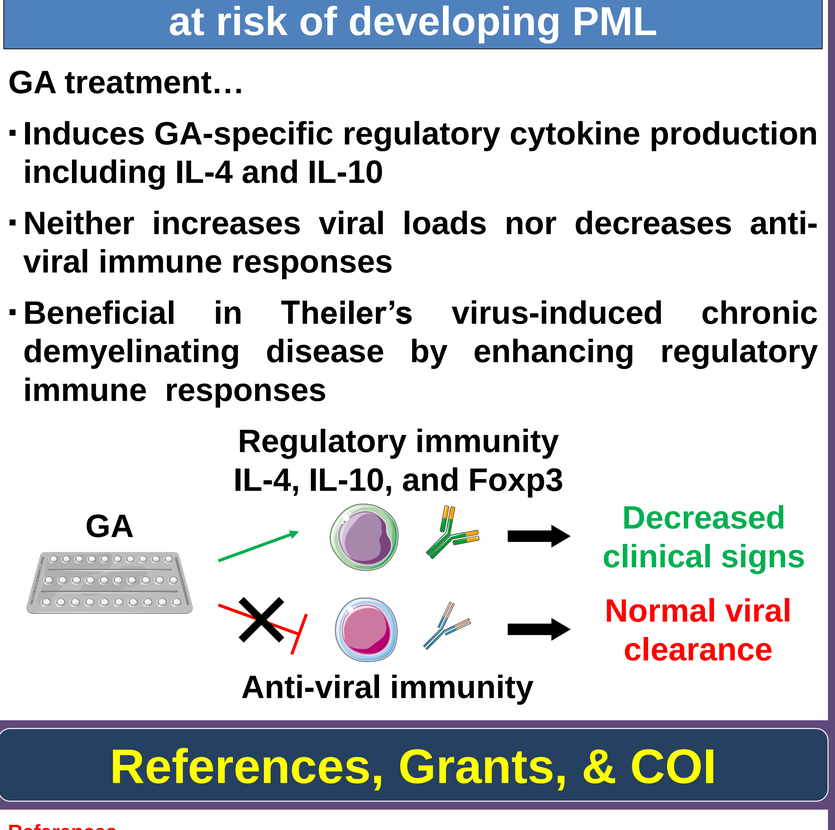
Spleen mononuclear cells were stimulated with a mitogen or GA at 5 weeks. Amounts of cytokines were quantified by ELISAs. * $P < 0.05$, ** $P < 0.01$.

GA treatment enhances the ratio of *Foxp3*/*Il17a* without increasing viral loads



Foxp3/*Il17a* ratios and viral antigens (arrowheads) in the spinal cord were quantified by real-time PCR and immunohistochemistry, respectively, at 5 weeks. * $P < 0.05$.

GA treatment does not suppress immune responses to Theiler's virus



Anti-viral T cell and antibody responses were quantified by [³H]thymidine incorporation assays and ELISAs, respectively, at 5 weeks. The dotted line is the detection limit.

Conclusions

GA could be safe for MS patients who are at risk of developing PML

GA treatment…

- Induces GA-specific regulatory cytokine production including IL-4 and IL-10
- Neither increases viral loads nor decreases anti-viral immune responses
- Beneficial in Theiler's virus-induced chronic demyelinating disease by enhancing regulatory immune responses

References, Grants, & COI

References

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