Dexamethasone markedly reduces the clinical deficit in relapsing-remitting experimental autoimmune encephalomyelitis in the rat

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Introduction

Multiple sclerosis (MS), an inflammatory, autoimmune and demyelinating disease of the central nervous system, affects about 2.5 million people worldwide. Relapsing-remitting MS (RRMS) is the most common disease course at the time of diagnosis. Approximately 85-90% of individuals with MS are initially diagnosed with RRMS.
MS is studied in the animal model experimental autoimmune encephalomyelitis (EAE). Various forms of EAE can be induced depending on the immunizing neuroantigen and the animal strain used. However, most EAE models develop monophasic feature of EAE disease which represents a major difference with the clinical setting of MS.
Dark-Agouti rats immunized with syngeneic spinal cord have been reported to develop relapsing-remitting form of EAE. Clear remission from the first attack and disease relapse can be observed in this rat strain. However, it is rarely used because most of EAE models implement Lewis rat strain, which is not prone to chronic EAE disease.

Materials and Methods

RR-EAE was induced by immunization of Dark-Agouti with an emulsion of homologous spinal cord homogenate in complete Freund's adjuvant.
The development of the neurological symptoms were monitored from day 7 to 24 post-immunization.
Clinical signs were scored on a scale from 0 to 5:

0 - no abnormality
0.5 - distal weakness of the tail
1 - complete weakness of the tail
2 - mild weakness in one or two hindlimbs
3 - moderate paraparesia of one or two hindlimbs
4 - severe paraparesia with incontinence
5 - total paraplegia.

Objectives

The aim of the present study was to characterize the RR-EAE induced in Dark-Agouti rats by syngeneic spinal cord. In particular, the disease relapse in respect to the treatment with anti-inflammatory drug such as Dexamethasone was scrutinized. Dexamethasone therapy was initiated at different stages of the disease: early disease symptom, peak of the first disease attack, early symptom of relapse. In addition, the severity of the disease relapse was assessed after discontinuation of Dexamethasone therapy at the remission from the first attack.

Results

In this model, rats develop visible clinical sign of EAE around days 8-9. The peak of symptoms (severe paralysis of lower back and hindlimb) is observed around days 12-14 post-immunization. This first attack is markedly resolved by day 16 post-immunization. Immediately after the remission, the disease relapses with a comparable intensity as in the first attack.

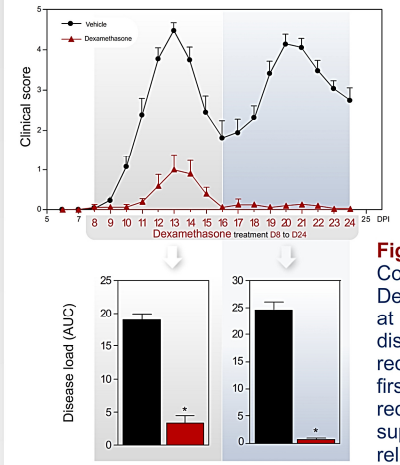

Figure 1 : Continuous treatment with Dexamethasone starting at the early sign of disease (D8) markedly reduce the severity of the first attack (80% reduction) and fully suppresses the disease relapse.

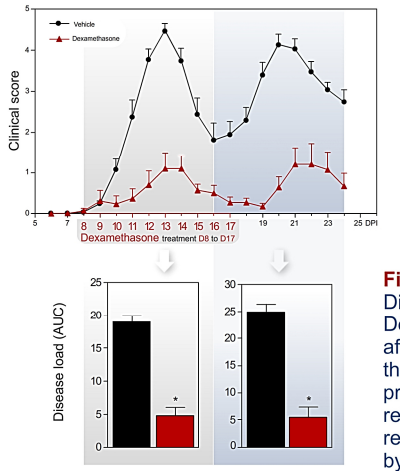

Figure 2 : Discontinuation of Dexamethasone therapy after the remission from the first attack did not prevent the disease relapse but significantly reduced the clinical deficit by 78%.

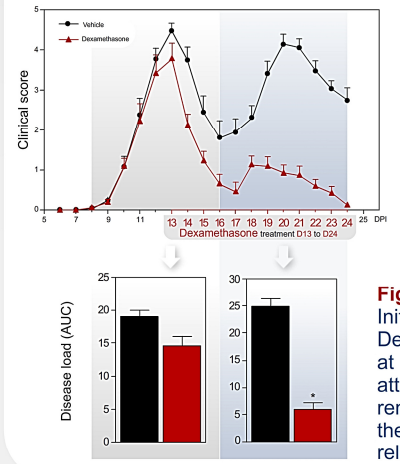

Figure 3 : Initiation of Dexamethasone therapy at the peak of the first attack accelerated the remission and reduced the severity of the disease relapse by 76%.

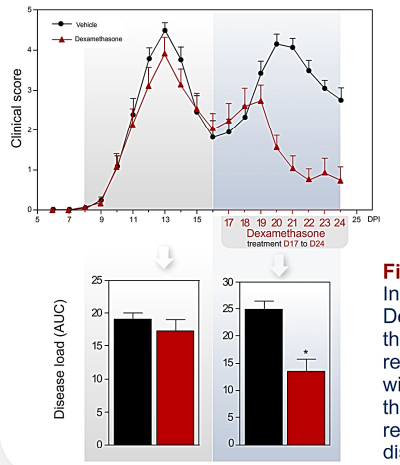

Figure 4 : Initiation of Dexamethasone therapy at the early sign of disease relapse was associated with marked decrease in the disease symptom and reduced the severity of the disease relapse by 46%.

Summary of key findings

- Relapsing-remitting course of EAE is confirmed in Dark-Agouti rats
- The severity of the relapse is comparable with that of the first attack
- Continuous treatment with Dexamethasone fully suppressed the relapse
- Treatment of first attack with Dexamethasone reduces the disease relapse
- Initiation of the Dexamethasone therapy at the first sign of relapse markedly reduce the severity of disease relapse