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Effect of (chloro-4-phenyl) thiomethylene bisphosphonic acid (SR 41319) on the autoimmune disease activity in MRL/1 mice

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Abstract

MRL – lpr/lpr (MRL/l) mice spontaneously develop an autoimmune pathology including arthritic lesions. SR 41319, a bisphosphonate, having previously shown to be active in *in vitro* and *in vivo* models of arthritis, the aim of this study was to search for its possible effect on the pathology of the MRL/1 mice. Results showed that SR 41319 reduced the severity of the disease in its early stages and increased mean life span. Further investigation would be necessary to define the effect of the drug during later stages when major changes in immune status occurred.

Introduction

MRL-lpr/lpr (MRL/l) mice spontaneously develop an autoimmune pathology with autoantibodies, immune complexes, lymphoproliferation, vasculitis and polyarthritis. This animal pathology was proposed as a model for studying systemic lupus erythematosus and rheumatoid arthritis [1–2]. SR41319, a compound belonging to the class of bisphosphonates, was previously shown to be active in the rat adjuvant arthritis [3] and *in vitro* on the release of collagenase and neutral proteases by chondrocytes or synoviocytes stimulated by MCF [3], the aim of this study was to evaluate the effect of SR41319 on the autoimmune disease of MRL/l mice.

Methods

Female MRL/l mice were obtained from CNRS (Orléans, France) and used in two experiments. In the first experiment, 40 animals were randomly assigned into two groups of 20 mice; the first one orally received SR41319 at 0.16 mmol/kg, 3 days a week beginning on the 5th week of life until death and the second group received only water. Percentage of mortality and clinical alterations (measured by an arbitrary score ranging from 0 to 12) were evaluated. In the second experiment, 60 mice were divided into the same two groups as in the first experiment. Five mice of each group were sacrificed at various times between the 8th and the 16th week of age (3 to 11 weeks of treatment). At each sacrifice, erythrocyte sedimentation rate (ESR) and spleen, thymus, adrenal and kidney weights were determined.

Results

In the first experiment, clinical signs of pathology in the control group appeared approximately on the 15th week of age. These signs (lymphadenopathy, exophthalmia, oedema of paws etc.) progressively increased until reaching a maximum from the 25th week to the end of experiment.

SR41319 treatment reduced the severity of the disease throughout the experiment but did not prevent the pathology from progressing (Fig. 1 a).

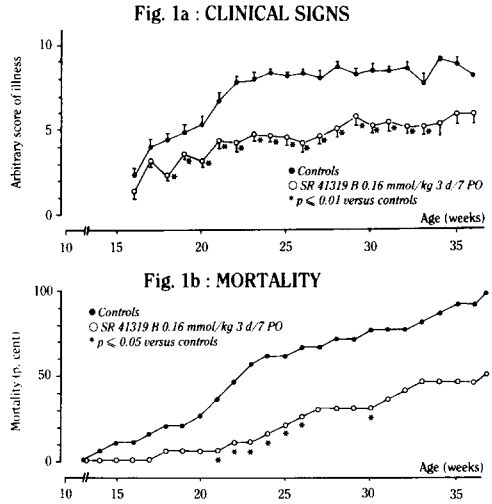

Figure 1
Percentage mortality and clinical alterations in MRL/l mice. Effect of SR41319.

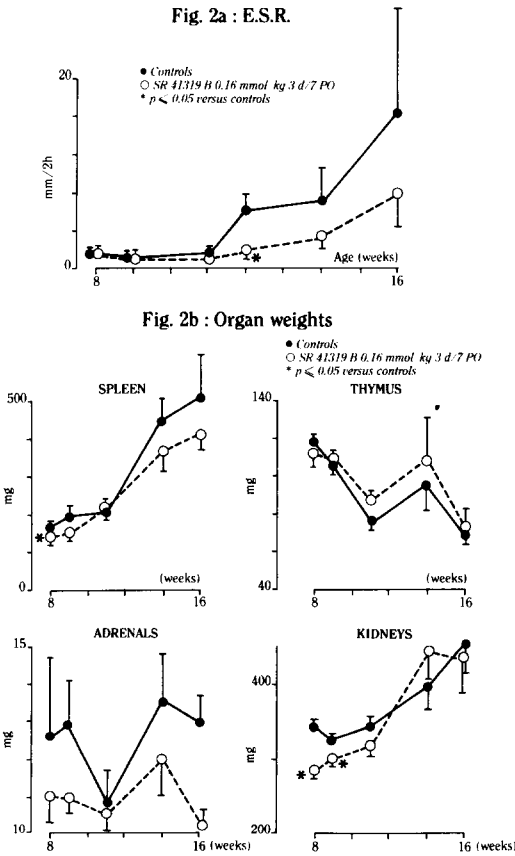

Figure 2
Effect of SR41319 on the erythrocyte sedimentation rate and organ weights in MRL/l mice.

This effect can be seen from the mortality rate: fifty percent of mortality was reached on the 23rd week of age for controls whereas it occurred on the 37th week of age for SR41319-treated mice when almost all control mice were dead (Fig. 1b). In the second experiment, for the control group there was a progressive increase in ESR from the 12th week to the 16th week. SR41319-treatment delayed this increase but because of scattering of control values, variations became significant only on the 12th week (Fig. 2a). Similarly, SR41319-treatment induced slight modifications in the very early stages of the pathology with a significant decrease in spleen and kidney weights. In the latter stages, no effect was observed. This was due, especially for spleen and adrenal weights, to variability in the physical state of the mice (Fig. 2b).

Discussion and conclusion

Data obtained with control MRL/l mice are in accordance with those previously described for mortality [1] and ESR [4]. SR41319 prophylactically administered delays onset of the disease expressed as a clinical index, increases life span and decreases ESR. SR41319 exerts slight effects on the weights of organs but only in the early stages of the pathology when polyarthritis has developed [5] without major changes in immune status which appear approximately on the 12th week [6]. In order to define its mechanism of action, more precise and more specific evaluations of SR41319 effects in this model are under investigation.

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