LIMITATIONS ON THE MOST USED EXPERIMENTAL MODELS FOR DEVELOPING THERAPIES IN MULTIPLE SCLEROSIS AND THE ESTABLISHMENT OF ENDPOINTS

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Introduction

The incidence of neurological dysfunctions worldwide has been increased during the last years, for this reason it is necessary to search new therapeutic strategies focused on the neuroprotection and the neuroregeneration of damaged tissues. Multiple sclerosis (MS) is the most frequent inflammatory chronic disease of the central nervous system and the second cause of disability in young adults. Searching effective therapies for MS, defining appropriate therapeutic windows, as well as establishing better diagnostic and prognostic biomarkers have remained being a challenge for researchers. The development and evaluation method of preclinical studies assessed in animal models could underlie the fail of effective therapies in the clinical application. Validation of an animal model is so much more complicated unless the knowledge of the etiology of the disease under study is known, however in these cases, bio-models are usually used to reproduce most of the symptoms and it is necessary the use of several animal models for studying the pathology. In this scenario, the development of effective therapies, the definition of appropriate therapeutic windows, as well as the achievement of better diagnostic biomarkers and mainly prognosis MS continues being a challenge. This work studies the most critical aspects in the development of experimental models, drawing up recommendations to unify the methodology, establishments of endpoints and to propose standard requirements on the application of the animal models in use for the different laboratories of animal experimentation using MS.

Objective:

To describe the establishment of experimental models based on their classification, define their limitations, determine the number of humanitarian endpoints and some recommendations on their application in preclinical studies. Our team has carried out a detailed assessment of the appropriate experimental models, their limitations and their application according to the pursued objective, incorporating standard and indispensable approaches in a preclinical study. These are the autoimmune model (AM) and virus-induced models.

Results

These are the autoimmune model (AM) and virus-induced models. The AM pattern is the most used experimental model and one of the oldest. This can be induced in a great variety of species and used with different purposes, but certain concern exists on if the pattern reflects in a precise way the development of the illness and, more important, if it can drive to results and mistaken conclusions when it is used to evaluate possible therapies. Another additional group of models of AM is since those that denominate spontaneous models, they don't require the induction of the illness so that the clinical signs are developed.

Limitations

- low incidence of the disease and the long periods until the clinical signs appear.

<table>
<thead>
<tr>
<th>Specie/Strain</th>
<th>Model of AM</th>
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<tbody>
<tr>
<td>Rata Lewis</td>
<td>Monofasic</td>
</tr>
<tr>
<td>Rata Brown Norway</td>
<td>chronic and soft</td>
</tr>
<tr>
<td>Mouse C57BL6</td>
<td></td>
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</tbody>
</table>

The virus-induced models, the temporary rule of demyelination of the spinal cord is very well established and the early axonal damage is possible to study

Limitations

- the model adequately it is an incomplete development of the disease, taking into account the viral etiology and to what extent approved therapies in EM is effective in it.
- The most widespread viral model is the EM Theiler's murine encephalomyelitis virus considered as a model of EM in its progressive primary variant.
- An important characteristic in this model is the frame of time in which the infection with the virus should be carried out preferably between four to six weeks of age. This point supports the hypothesis that the origin of the EM could be due to a viral infection during the childhood or early adolescence. It is very established the temporary rule of desmielination in the spinal marrow and it is possible to study the damage early axonal.

Conclusions

The success of the therapeutic progression of the MS involves the acquisition of methods in the experimental models, so that the adequacy of each pattern to the study and its objectives are optimized. The established recommendations as: the demand of appropriate controls, sample size, randomization, the necessity to be a blind study, the control of the animal origin, clinical assessment scales, additional behavioral tests or the inclusion of humane endpoints, could help to generate preclinical data useful in clinical practice. The effective use of endpoints requires general and study-specific observations of experimental animals and at most appropriate times.