B cells filling the subarachnoid space, which lasted for 56 days[16]. CD4+ and CD8+ T cells were roughly evenly distributed throughout the subarachnoid space, but CD79a+ B cells appeared to form discrete clusters. However, data demonstrated no features of lymphoid-like tissues in these clusters[17].

Even though most animal models for the study of meningeal FLS were based on EAE induction, our novel rat model of focal cortical inflammation, generated by the long-term expression of IL-1β in the cortex, also induced meningeal inflammation with FLS. These structures contained CD4+, CD8+, CD20+, CD23+ and CD39+ cells and were associated with cortical demyelination and neurodegeneration along with anxiety-like symptoms and short-term memory deterioration. Additionally, these cortico-meningeal structures could be visualized by MRI with gadolinium contrast[33].

Until now, the animal models described previously have represented the first step towards modelling the meningeal pathology associated with cortical damage. The development of a variety of animal models that mimic most of the characteristics of meningeal inflammation may help answer questions on the effect of the meninges in cortical tissue damage and, in turn, the effect of cortical damage on the inflammatory events occurring in the meninges.

EFFECT OF THERAPEUTIC AGENTS ON ANIMAL MODELS OF CORTICAL AND MENINGEAL ANIMAL MODELS

Although cortical pathology is important for the prognosis of patients, no new treatments have been specifically designed to target this aspect of disease. Thus, the evidence that some currently available drugs can also target cortical pathology provides valuable aid to the treatment of MS patients while waiting for the development of specific therapies targeting cortical pathology. A few previously approved drugs have already been tested in animal models of cortical pathology with the aim of showing their efficacy in cortical MS pathology, among them siponimod, glatiramer acetate and laquinimod.

Siponimod (BAF312) is a novel sphingosine-1-phosphate receptor modulator demonstrated to delay progression in PMS. The drug was recently approved by the United States Food and Drug Administration and the European Medicines Agency[37,49]. It was proposed that siponimod could reduce inflammation by sequestering lymphocytes in lymphoid tissues and could cross the blood-brain barrier by binding to its receptors on neurons, astrocytes and oligodendrocytes[50]. Siponimod was tested in a cortical model of MOG_{35-55}EAE C57BL/6J mice with the addition of intracortical administration of a cocktail of cytokines (TNF-α and IFN-γ). The authors demonstrated that demonstrated that oral, but not intracerebral, administration of siponimod diminished the infiltration of immune cells within both grey and white matter lesions. Siponimod administration partially restored cortical neuronal circuit function by exerting a neuroprotective effect after crossing the blood-brain barrier[49]. Moreover, the administration of siponimod significantly ameliorated subclinical MOG-induced EAE symptoms and improved subpial pathology concomitantly with selective reduction in the capacity of transferred T cells to induce Th17 cytokines[37]. In addition, they demonstrated that siponimod impaired the formation of meningeal tertiary lymphoid tissue, although it did not completely prevent the associated clinical symptoms of EAE. Siponimod diminished fibronectin network formation in the meninges by about 47% compared to control mice. The accumulation of B220+ and CD3+ cells was also significantly decreased compared to control animals, possibly due to the lack of fibronectin matrix support which is necessary for tertiary lymphoid tissue formation[37].

Glatiramer acetate is an immunomodulatory drug for RRMS that was demonstrated to have neuroprotective effects in two different EAE models, relapsing-remitting PLP-induced EAE disease and chronic MOG-induced EAE disease. The administration of glatiramer acetate alleviated cognitive impairment and cortico/hippocampal damage in these animals by downregulating pro-inflammatory pathways[51]. In addition, glatiramer acetate treatment in MOG_{35-55}-induced EAE mice potentiated neuroprotection by incrementing

neurotrophic factors (BDNF, NT-3, and NT-4)[51-53]. Additionally, BDNF expression in glatiramer acetate treated mice induced the differentiation/proliferation of neuronal progenitors that migrated into lesions in injured regions. These results indicate that the immunomodulator glatiramer acetate exerts anti-inflammatory, neuroprotective and regenerative effects in the diseased brain[52].

Laquinimod is a quinoline-3-carboxamide derivative that was demonstrated to inhibit the development of disease in inflammatory mouse models for MS such as EAE[54-56]. A focal model based on the combination of EAE induced with rat recombinant MOG, together with the injection of TNF-α and IFN-γ in the cortex and corpus callosum of the common marmoset, presented leukocortical demyelinating lesions at the site of the injections in both white and gray matter, as previously described. The prophylactic treatment with laquinimod completely prevented the leuko-cortical lesion formation in this model. The cortex of animals treated with laquinimod presented a lack of demyelinating lesions which could not be detected by MRI, and minor astrocytic and microglial reaction at the injection site. Thus, prophylactic modulation of the immune system by laquinimod prevents the development of focal EAE in marmoset[28]. Additionally, laquinimod demonstrated immunosuppressive and neuroprotective properties in a model based on a combination of neurodegeneration induced by cuprizone feeding and MOG_{35-55}-induced EAE in mice, which provokes an infiltration of myelin autoreactive T cells from peripheral lymphoid organs. The treatment with laquinimod was suspended two weeks prior to active EAE induction. Laquinimod ameliorated cuprizone pathology reduced demyelination, axonal loss, and microglial and astroglial activation but, at the same time, it decreased peripheral immune cell recruitment, particularly of lymphocytes[54-56]. This study demonstrated that ameliorating a primary degenerative CNS process might reduce the secondary inflammatory lesion development[56].

CONCLUSION

Grey matter lesions and meningeal inflammation are two of the most outstanding features of the progressive forms of MS and of RRMS, resulting in higher disease activity and poorer outcome. Animal models provide valuable insight into the knowledge of the role of cortical damage and its association with meningeal inflammation in MS. They also collaborated with the identification of the immune cells and molecules such as specific cytokines and chemokines involved in the development of cortical damage and meningeal inflammation pathologic processes. In addition, animal models helped to understand how immune molecules, either from cells within the cortex or from the inflammatory events in the meninges, impact glial activation, axonal degeneration, and oligodendrocyte death. Even though it was suggested that meningeal inflammation may play a role in the pathogenesis of cortical pathology ("outside-in" theory), it is also plausible that cortical damage induces meningeal inflammation ("inside-out" theory). In order to address this dichotomy, we need new information from animal models.

The importance of good preclinical studies is highlighted by the fact that research with animal models has already led to the development of three approved therapies for use in MS. However, most new therapeutic drugs showing promise in the preclinical studies end up failing in the clinical practice. One of the reasons that might explain this is the lack of development or evaluation of suitable animal models of MS. Still, there is no specific MS model that allows to study the entire pathology of the disease; several models reflecting the different aspects of the disease are available. The election of the right model to answer a specific question should be done in accordance with the specific aims of the study.

DECLARATIONS

Authors' contributions

Conceptualized and wrote the review: Silva BA, Ferrari CC
Wrote and corrected the manuscript: Miglietta E

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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