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# Prophylactic and Therapeutic Effect of Kynurenine for Experimental Autoimmune Encephalomyelitis (EAE) Disease

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## ABSTRACT

**BACKGROUND:** The essential amino acid, tryptophan, is predominantly metabolised through the kynurenine pathway (KP) to generate kynurenine, an aryl-hydrocarbon receptor (AhR) pro-ligand that exerts its effects in a ligand-dependent manner. Interaction between kynurenine and the AhR is an effector mechanism of immunosuppression. We previously found that the KP is involved in multiple sclerosis (MS) disease progression. We postulated that AhR activation by kynurenine might be neuroprotective by encouraging differentiation of Tregs. In this study, we assess both the prophylactic and therapeutic efficiency of kynurenine on disease severity and progression in mice with experimental autoimmune encephalomyelitis (EAE), an MS model.

**METHODS:** Myelin oligodendrocyte glycoprotein induced EAE mice (n=6 per group) were treated with 200 mg/kg L-kynurenine once daily for 10 days beginning on either day 1 of EAE induction (prophylactic) or once they demonstrated motor weakness (therapeutic). Clinical disease severity measured by disease score, time on rotarod, and body weight.

**RESULTS:** The prophylactic kynurenine treatment significantly ( $P < .0001$ ) prevented the development of a more severe disease course with mice demonstrating diminished relapse rate and improved clinical and behavioural outcomes. However, therapeutic kynurenine did not significantly ( $P = .4463$ ) decrease the clinical signs until 36 days following induction of disease; after 36 days, it also significantly ( $P = .0479$ ) reduced disease relapse. Mean body weight measurements only correlated with time on rotarod ( $r = -.6410$ ;  $P = .0007$ ) but not clinical scores ( $r = .1925$ ;  $P = .3674$ ).

**CONCLUSIONS:** Kynurenine ameliorates EAE disease progression prophylactically and reduces relapses therapeutically. Further investigations are needed to elucidate the molecular mechanism explaining the therapeutic role of kynurenine for MS.

**KEYWORDS:** Tryptophan, kynurenine, kynurenine pathway, aryl-hydrocarbon receptor, ligand, pro-ligand, multiple sclerosis, immunosuppression

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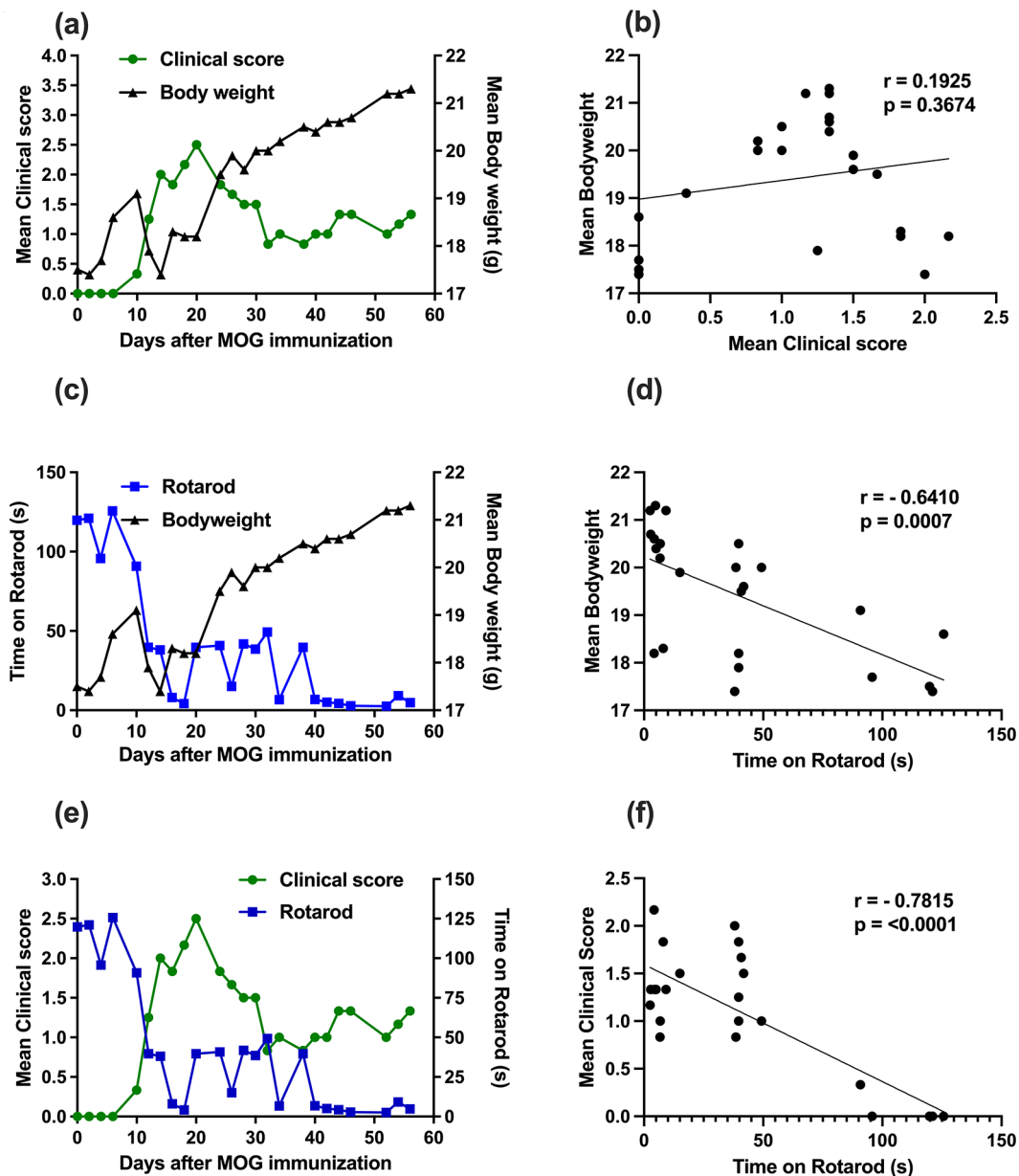
## Background

Multiple sclerosis (MS) is a debilitating neuroinflammatory and neurodegenerative disease of the central nervous system. The aryl hydrocarbon receptor (AhR) is a transcription factor activated by endogenous and exogenous ligands

such as kynurenine and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD).<sup>1</sup> These ligands can alter innate and adaptive immune responses including effects on T-cell differentiation. Many ligands including those from the kynurenine pathway (KP)<sup>2</sup> known to efficiently activate the transcriptional activity of AhR, have already been associated with MS.

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**Figure 1.** Comparison of clinical scoring, bodyweight and time on rotarod (s). (a) Line diagram depicts mean clinical score and body weight (grams (g)) of EAE induced mice ( $n=6$ ) for 58 days. (b) Correlation between mean clinical score and bodyweight (g). (c) Comparison of time on rotarod (s) and mean body weight (g). (d) Correlation of mean bodyweight (g) and time on rotarod (s). (e) Comparison of mean clinical score versus time on rotarod (seconds (s)). (f) Correlation between mean clinical score and time on rotarod (s).

The essential amino acid tryptophan (TRP) is metabolised through the KP (Supplemental Figure 1), generating kynurenine, an AhR ligand.<sup>3</sup> Five percent of tryptophan is also metabolised along the serotonin pathway. In the KP, indoleamine 2,3-dioxygenase 1 (IDO1) and tryptophan 2,3-dioxygenase (TDO2) are the 2 first and rate limiting enzymes<sup>4</sup> responsible for metabolising tryptophan to kynurenine, which is then hydroxylated into 3-hydroxykynurenine by the enzyme kynurenine monoxygenase (KMO)<sup>5</sup> followed by hydrolysis of 3-hydroxykynurenine by kynureninase (KYNU) into 3-hydroxyanthranilic acid. Further down the pathway, 3-hydroxyanthranilic acid dioxygenase cleaves the ring of 3-hydroxyanthranilic acid to generate  $\alpha$ -amino- $\beta$ -carboxymuconate- $\epsilon$ -semialdehyde,

a compound that non-enzymatically catabolises to quinolinic acid (QUIN),<sup>6,7</sup> an NAD<sup>+</sup> precursor<sup>8</sup> and to picolinic acid (PIC).<sup>9</sup>

QUIN has multiple mechanisms for neurotoxicity including NMDA receptor agonist activity,<sup>10-13</sup> inhibition of reuptake of glutamate, generation of reactive oxygen species, destabilisation of the cellular cytoskeleton, promotion of tau phosphorylation and disruption of autophagy.<sup>10-13</sup> Furthermore, kynurenine is degraded into kynurenic acid (KYNA) by kynurenine aminotransferase (KAT). KYNA as a neuroprotective molecule competitively inhibits ionotropic glutamate receptors. KYNA also acts as an AhR ligand that synergistically regulates immune homeostasis leading to recruitment of

the AhR nuclear translocator and induction of IL6 expression. Induction of IL6 may also occur through interaction of KYNA-AhR with NF- $\kappa$ B.<sup>14</sup> Although IL6 promotes inflammation, it also has anti-inflammatory activities in cells through activation of STAT3-mediated signalling pathways.<sup>15</sup>

The KP plays a key role in the progression of MS.<sup>16</sup> Animal studies using the experimental autoimmune encephalomyelitis (EAE) mouse model, the most used animal model of MS, have also shown KP involvement.<sup>17</sup> The activities of AhR and IDO1/KP metabolites are linked and are important in immunoregulation<sup>2</sup> and in MS pathogenesis. These findings are consistent with studies using the xenobiotic 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), which is the most potent ligand of AhR. Systemic administration of TCDD ameliorated EAE disease progression in mice.<sup>18</sup> However, TCDD cannot be used as a therapeutic molecule in humans as it has a half-life of 7.6 years and prolonged exposure can have deleterious effects.

Several studies have reported that number of endogenous tryptophan derivatives including kynurenine have a high affinity for AhR. Although the roles of IDO1/KP metabolites in MS have been extensively studied, the timed administration of kynurenine to determine its role in prophylaxis and therapy in autoimmune demyelinating disease have not yet been explored. This study aims to address these 2 issues using the EAE model.

## Materials and Methods

### Animals

Mice used for experiments were 6 to 8-week-old C57Bl/6 females purchased from Charles River (L'Abresle, France). All mice were housed in an A2 animal facility. All animal studies were carried out under protocols approved by the Institutional Animal Care and Use Committee at University of Bordeaux. All efforts were made to minimise animal suffering and the number of animals necessary to produce reliable results.

### Reagents

Desiccated, killed *Mycobacterium tuberculosis* H37Ra was obtained from Bioscientific Pty Ltd. Complete Freund's adjuvant (CFA) was purchased from Sigma-Aldrich (Missouri, USA). Myelin oligodendrocyte glycoprotein (MOG<sub>35-55</sub>; Amino Acid (21) Sequence: H-Met-Glu-Val-Gly-Trp-Tyr-Arg-Ser-Pro-Phe-Ser-Arg-Val-Val-His-Leu-Tyr-Arg-Asn-Gly-Lys-OH) and pertussis toxin were obtained from Sapphire Biosciences. Interchangeable syringes were obtained from Cadence Inc (Virginia, USA). L-kynurenine (10 mg/mL) was diluted in PBS.

### Induction of EAE

For EAE induction, mice (female, strain C57BL/6J, 18-20 g, 6-8 weeks) were inoculated using a well-established protocol.<sup>19</sup>

Briefly, animals were intradermally injected with complete Freund's adjuvant containing 1 mg/mL *Mycobacterium tuberculosis* (strain H37Ra) and 100  $\mu$ g of the MOG<sub>35-55</sub> peptide. Immunisation with MOG<sub>35-55</sub> was followed by i.p. administration of 200 ng of Pertussis toxin on day 0 and after 48 hours. Clinical scores (0 = healthy; 1 = limp tail; 2 = paresis of hindlimbs; 3 = partial hindlimb paralysis and/or paresis of forelimbs; 4 = both hindlimb paralysis and forelimb paresis; 5 = moribund or death) and body weights were recorded daily.

### Drug treatments

Mice were randomly assigned to the following groups: Vehicle control, Prophylactic kynurenine treatment and Therapeutic kynurenine treatment. L-kynurenine, supplied by Sigma Aldrich was given intraperitoneally, 200 mg/kg once daily. While studying the effect of 'prophylactic' administration of kynurenine, mice with EAE were injected with kynurenine from the start of the EAE induction (day 1) and continued until day 10. When studying the effect of the administration of kynurenine starting from the acute stage of the disease EAE score  $\geq 2$  and remaining the same for 2 consecutive days), kynurenine was injected at 200 mg/kg dose intraperitoneally for 10 days; this group was termed the 'therapeutic' treatment group. After kynurenine treatment, both prophylactic and therapeutic groups were monitored for disease severity for 60 days. Clinical severity was measured based on the clinical scoring described above. Animals treated with TCDD or vehicle were used as positive or negative controls, respectively.

### Rotarod assay

Motor coordination was assessed with a rotarod treadmill for mice at a fixed speed of 40 rotations per min (rpm). Animals were provided training before testing. The fall-off latency was averaged from 3 tests, and the cut-off time was 2 minutes. The fall-off latency and final rpm were averaged from 3 tests.

### Statistics

All statistical analyses were performed using GraphPad Prism version 8 software. Results were expressed as mean  $\pm$  SEM. For clinical scores, significance between 2 groups was expressed as area under curve (AUC). The linearity of the correlation between rotarod, clinical score and mean body weight was tested with Pearson correlation. The strength of the correlations was quantified using the *r* squared. The required sample size was calculated based on the similar experiments and analyses carried out previously. Sample normality distribution was tested using the Kolmogorov-Smirnov normality tests. The vehicle, kynurenine, TCDD treated were compared using one-way ANOVA with Tukey's multiple comparison post-hoc test. Statistical significance was considered for  $P < .05$  (\*),  $P < .01$  (\*\*) and  $P < .001$  (\*\*\*)

## Results

### *Comparison of EAE clinical score, body weight, and rotarod score to assess the severity of EAE*

We first assessed the relationship between body weight, clinical scores, and rotarod scores in mice at different stages of EAE. Using our EAE protocols, we found that although body weight decreased in the early stages of the disease, weights recovered while clinical scores continued to worsen, and overall, the mean clinical score and mean body weight were not correlated (Figure 1a and b;  $r = .1925$  and  $P = .3674$ ). Time on the rotarod had a significant negative correlation with mean body weight (Figure 1c and d;  $r = -.6410$  and  $P = .0007$ ) and mean clinical score (Figure 1e and f;  $r = -.7815$  and  $P < .0001$ ). Analysis of the clinical disease by rotarod provides a relevant measurement in subtle changes in mobility in an objective manner. However, determination of the clinical disease severity by rotarod becomes less sensitive once the animals begin displaying moderate to severe hind limb paralysis. Therefore, we focused on testing the effects of kynurenine on the clinical scoring scale in lieu of the rotarod and body weights.

### *Prophylactic kynurenine treatment decreases the disease severity in EAE induced mice*

We compared the effects of kynurenine with TCDD (each at 200 mg/kg intraperitoneally daily for 10 days) for their ability to limit EAE onset and progression. Treatments started at the time of EAE induction. Compared to animals treated with vehicle, mice given kynurenine or TCDD had delays in disease onset and reduced clinical scores, with comparable final clinical scores at the end of the experiment (Figure 2a). Importantly, the mean cumulative clinical score (AUC) was significantly decreased in the prophylactic kynurenine treated mice to a degree similar to mice treated with TCDD (Figure 2a and b;  $P < .0001$ ) versus vehicle treated mice.

### *Therapeutic kynurenine blocks EAE relapses*

In a second set of experiments, we examined how kynurenine influenced the clinical scores of mice treated at the peak of disease. Therapeutic kynurenine treatment did not significantly ( $P = .4463$ ) decrease the clinical scores up to 36 days post-inoculation (Figure 2c and d). However, in this group of mice the vehicle control group demonstrated a relapse beginning around day 36, reaching scores comparable to the initial peak of disease that was not observed in the kynurenine treated animals ( $P = .0309$ ), thus preventing disease relapse (Figure 2c and e;  $P = .0479$ ).

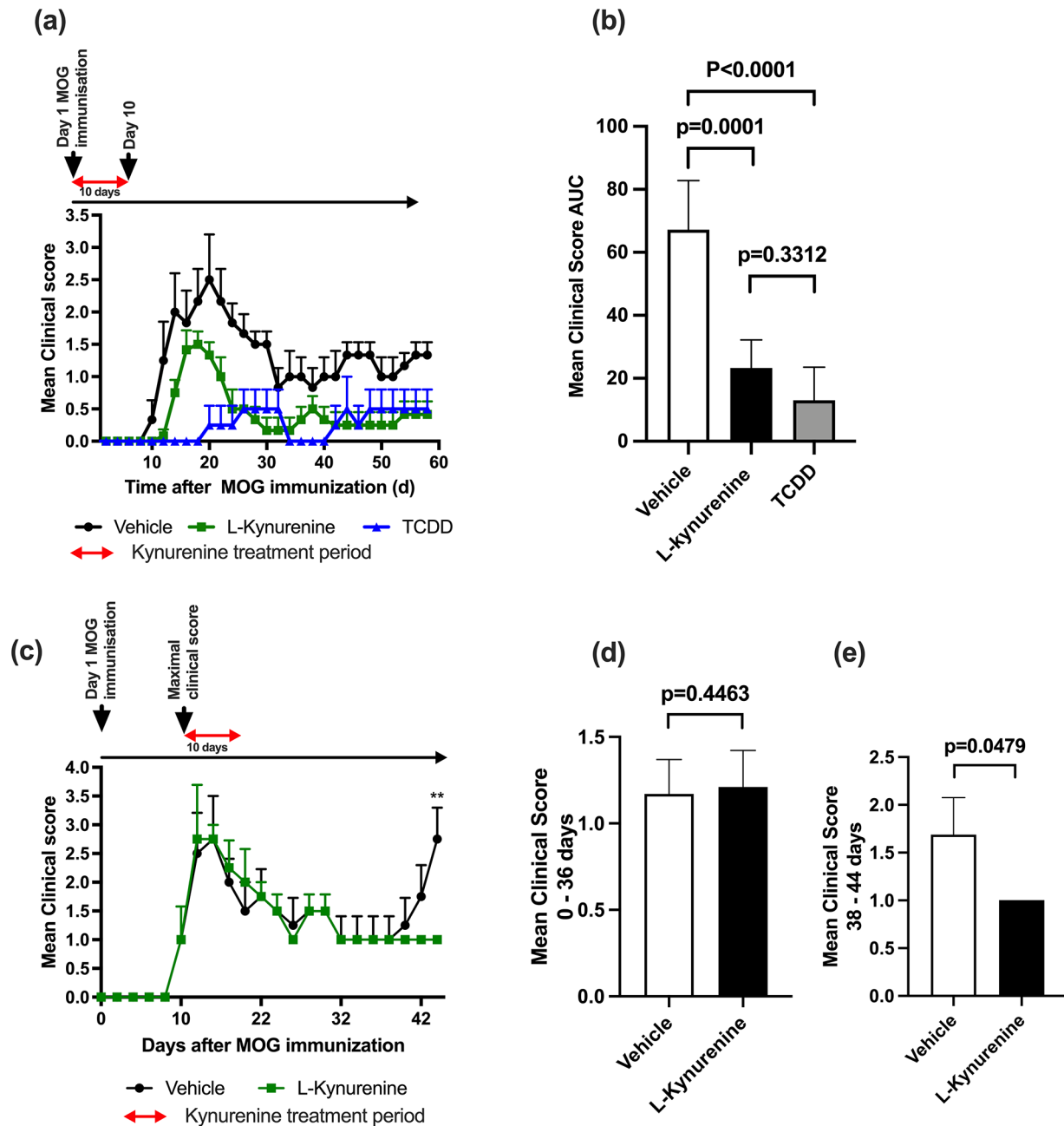
## Discussion

This study investigated both the prophylactic and therapeutic treatment effects of kynurenine on MOG-induced EAE mice. The prophylactic kynurenine treatment had a significant effect

in preventing the development of more severe disease course with reduced relapse and improved clinical outcomes. The therapeutic group significantly decreased the severity after 36 days by preventing the relapse completely.

Recently the Food and Drug Administration (FDA) approved disease-modifying therapies (DMTs) for different types of MS: ofatumumab (relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS)), ocrelizumab (RRMS and primary progressive MS (PPMS)), fingolimod (RRMS and paediatric MS), cladribine (RRMS and SPMS), siponimod (RRMS and SPMS), diroximel fumarate (RRMS and SPMS), and ozanimod (RRMS and SPMS). However, current treatments only help to modify the course of disease progression. There are mounting preclinical studies focused on molecular drug targets with the aim of developing better therapies to prevent MS attacks. Rituximab, an off-label drug for MS patients, was effective in decreasing the EAE disease severity administered preventatively compared to prophylactic and therapeutic administration. Another MS disease modifying drug, fingolimod significantly reduced the gravity of clinical symptoms in EAE mice both prophylactically<sup>20,21</sup> and therapeutically. In this regard, there are controversies present in the literature. de Bruin and colleagues observed no improvement in motor performance in EAE mice administered with fingolimod starting from the early stage of the disease, while social preference was normalised by late treatment. Nonetheless, myelin oligodendrocyte glycoprotein (MOG)-DNA,<sup>22</sup> proteolipid protein – bifunctional peptide inhibitor (BPI) and glutamic acid decarboxylase – BPI<sup>23</sup> reduced the clinical signs when administered in both prophylactic and therapeutic settings. In our study, prophylactic and therapeutic administration of kynurenine effectively decrease the clinical signs in mice with EAE. Our findings suggest that kynurenine should be explored as a novel therapy for MS.

Kynurenine is a recognised agonist of the AhR. We hypothesise that the activation of the KP during neuroinflammatory conditions could alter AhR signalling. Upregulation of IDO increased the accumulation of the KP metabolite, kynurenine, which could bind to and activates the AhR. Agonistic kynurenine appears to drive a definitive AhR-mediated immunoregulatory profile in both dendritic cells and CD4+ T cells. Given the important roles of the AhR in immunomodulation, studies focusing on neuroinflammation mediated kynurenine-AhR axis pathway point to a potential new therapeutic target for brain diseases. As such, Cuartero et al showed that L-kynurenine could activate the AhR pathway in the brains of a mouse model of stroke. A synthetic indole-containing compound, laquinimod, ameliorated EAE via AhR-dependent signalling in astrocytes. The mechanism(s) accounting for the beneficial effects of kynurenine in our EAE model still need to be characterised. There are several options: (1) kynurenine as an AhR endogenous ligand could stimulate the differentiation of CD4+ T-cells into FoxP3+ Tregs rather than pro-inflammatory Th17 cells<sup>24</sup> (Figure 3), (2) kynurenine administration could favour KYNA

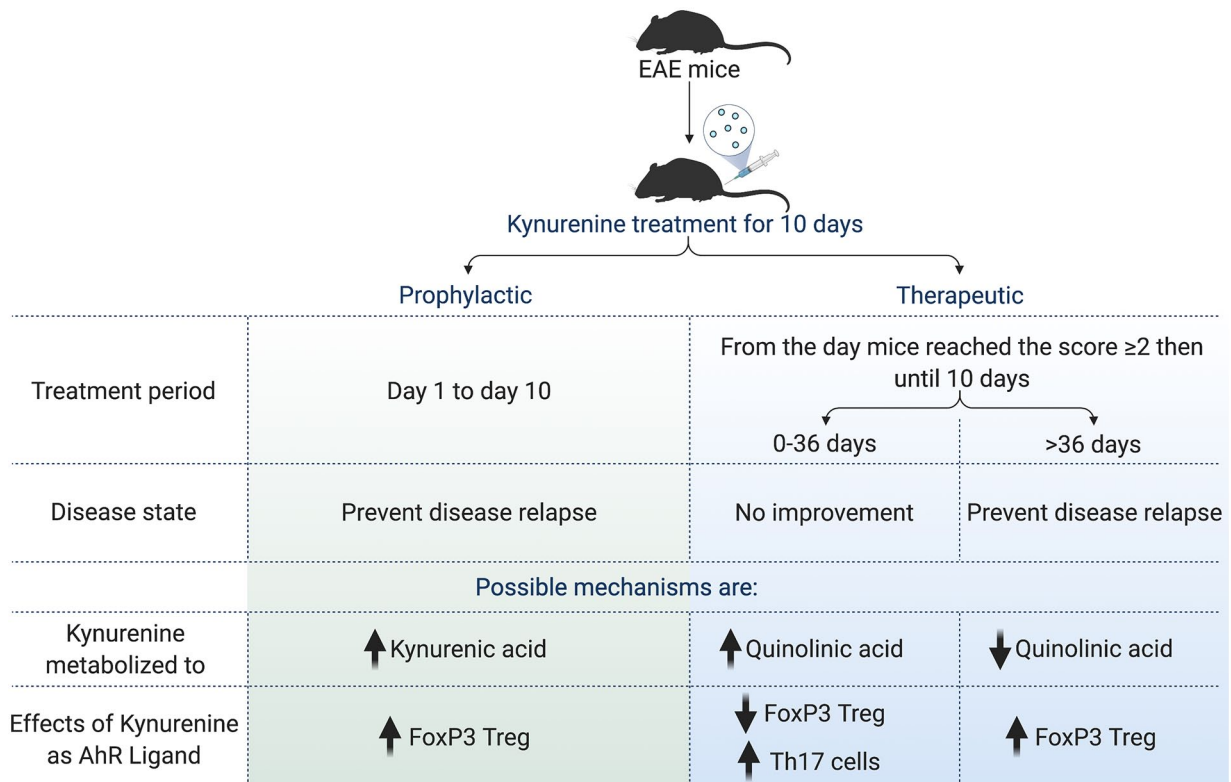


**Figure 2.** Kynurenine treatment decreases the disease severity in EAE induced mice. (a) Prophylactic treatment groups: Mean EAE disease scores in vehicle (n=6), L-kynurenine (KYN, 200mg/kg intraperitoneal daily for 10days, n=6), and TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin, 200mg/kg intraperitoneal daily for 10days, n=6) (Mean  $\pm$  SEM). Treatment was initiated from day 1 EAE induction until day 10 ( $\leftrightarrow$  Treatment days). (b) Area under curve (AUC) of mean EAE clinical score for vehicle (clear), KYN (black-filled) and TCDD group (grey-filled) (Mean  $\pm$  SEM). (c) Therapeutic treatment groups: Mean EAE disease scores in vehicle (n=6) and L-kynurenine (KYN, 200mg/kg intraperitoneal daily for 10days, n=6). Treatment was initiated once the clinical score reaches 2 and remain in the same score 2 consecutive days ( $\leftrightarrow$  Treatment days; Mean  $\pm$  SEM). (d) Mean EAE clinical score (0-36 days) for vehicle (clear) and KYN (black-filled) (Mean  $\pm$  SEM). (e) Mean EAE clinical score (38-44 days) for vehicle (clear) and KYN (black-filled) (Mean  $\pm$  SEM).

production, a neuroprotective compound, instead of production of the neurotoxin quinolinic acid (Figure 3). We have also shown in our recent publication that inhibition of kynurenine production by 1-methyl tryptophan (an IDO1 inhibitor) at later stages of the disease (EAE score  $\geq$ 2) significantly increased FoxP3 production<sup>17</sup> which indicates that kynurenine is essential for maintaining the T cell tolerance during inflammation. As shown in our previous study<sup>17</sup> in figure 6B KMO inhibition (increased

levels of kynurenine) was able to generate a much stronger and chronic (over 7 days) improvement of the EAE clinical score compared to IDO1 inhibition (figure 5B) that only lasted 2 days (temporary lack of kynurenine biosynthesis).

We also speculate that prophylactic kynurenine administration may have resulted in increased Treg cells and kynurenine acid production, which may have contributed to neuroprotection and decreases the disease severity. However, therapeutic



**Figure 3.** Timed administration of kynurenine in EAE induced mice.

administration until 36 days did not effectively reduce the disease symptoms, which might be due to increased metabolism of kynurenine to quinolinic acid (neurotoxic compound) and not enough kynurenine for Treg induction. But after 36 days, relapse was prevented in the kynurenine treated group, which might be due to compensated Treg induction and reduced quinolinic acid accumulation (Figure 3). It could be expected that increased kynurenine might also direct this pathway towards formation of neurotoxic compounds such as 3-hydroxykynurenine and quinolinic acid by monocytic cells. In our study, we treated the mice for only 10 days (both prophylactic and therapeutic). We hypothesise that this short-term kynurenine was able to act as an AhR ligand and decreased the clinical symptoms by increasing immunotolerance. Nevertheless, more research is needed to determine the mechanisms of action of kynurenine and assess the treatment over a longer period.

Finally, the 2 main limitations of this study are: (1) not all KP metabolites have been quantified and (2) we did not study the effects of KP metabolites, especially kynurenine and kynurenic acid in the present study. The therapeutic ability of kynurenine is currently being assessed in clinical trials to treat myalgic encephalomyelitis/chronic fatigue syndrome,<sup>25</sup> making kynurenine a potential drug candidate for MS given its known safety and efficacy profiles. In conclusion, this study provides a firm basis for human trials of kynurenine administration as part of MS therapy.

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### Author Contributions

All authors contributed to the experimental design. GS: analysed the data and wrote the manuscript; AB: designed and performed the experiment. ASP assisted with the design of Figure 3. DG, LS, BB and GG contributed to the proofreading of the manuscript. All authors contributed to the article and approved the submitted version.

### Data Availability Statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

### Ethics Approval and Consent to Participate

All animal studies were carried out under protocols approved by the Institutional Animal Care and Use Committee at University of Bordeaux.

### Consent for Publication

Not applicable

### Supplemental Material

Supplemental material for this article is available online.

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