Anti-inflammatory and remyelinating effects of AZD4547 in experimental multiple sclerosis

Fynn Gurski¹, Kian Shirvanchi¹, Vinothkumar Rajendran¹, Ranjithkumar Rajendran¹, Fevronia-Foivi Megalofonou¹, Gregor Böttiger¹, Christine Stadelmann², Sudhanshu Bhushan³, Süleyman Ergün⁴, Srikanth Karnati⁴, and Martin Berghoff¹

¹Justus-Liebig-Universität Giessen
²Georg-August-Universität Göttingen Medizinische Fakultät
³Justus Liebig University Giessen Faculty of Medicine
⁴Julius-Maximilians-Universität Würzburg

June 10, 2024

Abstract

Background and Purpose: Fibroblast Growth Factor (FGF), VEGFR2, and CSF1R signalling pathways play a key role in the pathogenesis of multiple sclerosis (MS). Selective inhibition of FGFR by infigratinib in MOG35-55-induced EAE prevented severe first clinical episodes by 40%; inflammation and neurodegeneration were reduced, and remyelination was enhanced. Multi-kinase inhibition of FGFR1-3, CSF1R and VEGFR2 by AZD4547 may be more efficient in reducing inflammation, neurodegeneration and regeneration in the disease model. Experimental Approach: Female C57BL/6J mice were treated with AZD4547 (6.25 mg kg⁻¹ or 12.5 mg kg⁻¹) orally or placebo over 10 days either from time of EAE induction (prevention experiment) or onset of symptoms (suppression experiment). Effects on inflammation, neurodegeneration and remyelination were assessed at the peak of the disease (day 18/20 p.i.) and the chronic phase of EAE (day 41/42 p.i.). Key Results: In the prevention experiment, treatment with AZD4547 prevented severe first clinical episodes by 66.7 or 84.6% respectively. Mice treated with 12.5 mg kg⁻¹ of AZD4547 hardly showed any symptoms in the chronic phase of EAE. In the suppression experiment, treatment with AZD4547 resulted in a long-lasting reduction of severe symptoms by 91 or 100%. Inflammation and demyelination were reduced, and axonal density, numbers of oligodendrocytes and their precursor cells, and remyelinated axons were increased in both experimental approaches. Conclusion and Implications: Multi-kinase inhibition by AZD4547 in a well-tolerated dose of 1 mg kg⁻¹ in humans may be a promising approach to reduce inflammation and neurodegeneration, to slow down disease progression and support remyelination in patients.

Hosted file
