DOI: 10.1002/eji.202470200

European Journal of Immunology Clinical-Basic-Translational

1405 – P3.06.21

Bruton's tyrosine kinase inhibitors tolebrutinib, evobrutinib and fenebrutinib affect neutrophil functions in vitro: implications for treatment of autoimmune disease

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Purpose: Multiple sclerosis (MS) is a neurodegenerative, autoimmune disease that is still incurable. Nowadays, a variety of new drugs are being developed to prevent excessive inflammation and halt neurodegeneration. Among these are the inhibitors of Bruton's tyrosine kinase (BTK). Being indispensable for B cells, this enzyme became an appealing therapeutic target for autoimmune disease. Recognizing the emerging importance of BTK in myeloid cells, we investigated the impact of upcoming BTK inhibitors on neutrophil functions. Although adaptive immunity in MS has been thoroughly studied, unanswered questions about the pathogenesis can be addressed by studying the effects of candidate MS drugs on innate immune cells such as neutrophils, previously overlooked in MS.
Methods & results: In this study, we used three BTK inhibitors (evobrutinib, fenebrutinib and tolebrutinib), and found that they reduce neutrophil activation by the bacterial peptide N-formylmethionyl-leucyl-phenylalanine and the chemokine interleukin 8/CXCL8. Furthermore, they diminished the production of reactive oxygen species and release of neutrophil extracellular traps. Additionally, the production of CXCL8 and interleukin-1β in response to inflammatory stimuli was decreased. Inhibitory effects of the drugs on neutrophil activation were not related to toxicity. Instead, BTK inhibitors prolonged neutrophil survival in an inflammatory environment. Finally, treatment with BTK inhibitors decreased neutrophil migration towards CXCL8 in a Boyden chamber assay but not in a transendothelial set-up. Also, in vivo CXCL1-induced migration was unaffected by BTK inhibitors.
Conclusion: Collectively, this study provides novel insights into the impact of BTK inhibitors on neutrophil functions. These findings might have important implications for patients' innate immune responses but can also impact excessive neutrophil activation in chronic inflammatory conditions, such as MS.

