Extended Abstract

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Bruton's Tyrosine Kinase (Btk) Inhibitor Tirabrutinib Prevents the Development of Murine Lupus

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Abstract

Systemic Lupus Erythematosus (SLE) is a complex and heterogeneous autoimmune disease associated with the over production of high affinity autoantibodies. Over- activity of B-cell responsiveness to immune stimulation and direct activation of circulating FcR bearing cells are sufficient to initiate inflammatory responses, which may be an essential feature of SLE pathogenesis. Here, we examined the potential efficacy of tirabrutinib using NZB/WF1 and MRL/lpr mice within the model of spontaneous SLE. Tirabrutinib inhibited the assembly of anti-dsDNA in serum, and therefore the onset of proteinuria resulted in markedly lower in both lupus-prone mice. Furthermore, the treatment with tirabrutinib resulted in 100% survival, while 70% survival was observed in untreated mice. Significant reductions in the numbers of total IgG and anti-dsDNA- secreting B-cells were apparent in spleens from tirabrutinib treated mice.

Introduction

Systemic Lupus Erythematosus (SLE) is an autoimmune disease that is characterized by autoantibody production and tissue damage caused by immune complex [1,2]. Preclinical and clinical data suggest that pathogenic B-cells contribute to SLE pathogenesis by autoantibody production, antigen presentation, and cytokine generation. Pathogenic autoantibodies have been shown to play a central role in the manifestations of SLE and the titres of anti-dsDNA antibodies rise during flares of SLE disease activity, particularly lupus nephritis. Lupus nephritis is a severe manifestation of SLE with significant morbidity and mortality. and reported to affect approximately 60% of SLE patients [3]. Several biological agents targeting B-cells, such as anti-BAFF [4], anti-CD20 mAb [5,6], anti-CD22 mAb [7,8] have been developed at forefront therapy in SLE. Belimumab, anti-BAFF, has been approved by the FDA, however, clinical trials were not designed to evaluate the efficacy for the treatment of lupus nephritis. Therefore, there is a high unmet need in lupus nephritis. . Tirabrutinib is an irreversible second-generation Btk inhibitor with excellent efficacy and tolerability in R/R B-cell malignancies [12,13]. Tirabrutinib forms a covalent bond with Cys481 of Btk and, irreversibly inhibits the kinase activity of Btk. Besides an increase in the therapeutic options for B-cell lymphoma, Btk inhibition is also expected to develop in inflammatory disease due to its pleiotropic anti-inflammatory effects. BTK plays critical roles in activation mediated by Fc receptor (FcR), Toll-like receptor in myeloid cells.

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Keywords

Systemic lupus erythematosus; Lupus nephritis; Bruton's tyrosine kinase

Discussion and Conclusion

NZB/W F1 and MRL/lpr models have been extensively used to investigate many drugs [21]. It has been reported that B-cell- targeted therapies, such as anti-BAFF or anti-CD20 mAb show efficacy in both models, although rituximab did not meet the clinical endpoints in a human SLE study [22]. Of note, anti-CD20 mAb treatment in NZB/W F1 mice delayed the onset of the disease without decreasing anti-dsDNA antibodies. Furthermore, prevention of autoantibodies production and renal injury were achieved only after early initiation of the treatment of anti-CD20 mAb [23,24]. Our data show that. However, both were suppressed completely after early treatment with tirabrutinib in MRL/lpr mice. Since long-lived plasma cells which have lost CD20 and Btk expression contribute to the production of autoantibodies, these are not affected by B-cell depletion and tirabrutinib. It is intriguing that NZB/W F1 shows an immunological characteristic of persistent long-lived plasma cells. Together, our data are consistent with those of anti-CD20 mAb lupus studies, which demonstrated, Germinal centers are central to the development of long-lived plasma B cells and their clonal expansion to produce autoantibodies. Disease progression of lupus nephritis is associated with an increase in the number and size of germinal centers. Tfh cells are essential for formation of germinal centers and have been reported to contribute to lupus pathogenesis.

References

1. Nashi E, Wang Y, Diamond B (2010) The role of b cells in lupus pathogenesis. Int J Biochem Cell Biol 42: 543-550.

2. Hostmann A, Jacobi AM, Mei H, Hiepe F, Dorner T (2008) Peripheral B cell abnormalities and disease activity in systemic lupus erythematosus. Lupus 17: 1064-1069.

3. Cheng Lay (2018) The Causes and predictors of mortality in biopsy- proven lupus nephritis: the Sarawak experience. Clin Kidney J 11: 56-61.

4.Carter LM, Isenberg DA, Ehrenstein MR (2013) Elevated serum BAFF levels are associated with rising anti-double-stranded DNA antibody levels and disease flare following B cell depletion therapy in systemic lupus erythematosus. Arthritis Rheum 65: 2672-2679.

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