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How will Bruton's tyrosine kinase inhibitors affect rheumatoid arthritis?:

Reply to: Bruton's tyrosine kinase inhibitors could induce rheumatoid arthritis-like manifestations

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Reply

To the editor

We thank Dr. Bernal and colleagues for their interest in our article and for their report regarding arthritis in a patient treated with ibrutinib. In thinking about potential mechanisms, we turn first to the possibility that a Bruton's tyrosine kinase inhibitor could somehow support B cell contributions to autoimmune disease. Btk-deficiency in mice profoundly depletes autoreactive B cells, while normal B cells are less affected.[1,2] This contrasts human patients who lack BTK, in whom all B cell subsets are depleted. These patients have fewer than 1% normal numbers, with failure of humoral immunity known as X-linked agammaglobulinemia (XLA).[3] Interestingly, remaining B cells in these patients are more likely to have autoreactive specificities.[4] However, these cells do not usually cause autoimmune disease, as patients do not develop autoantibodies, and there have been only rare reports of rheumatoid arthritis.[5] Most patients do well as long as they are treated with exogenous immunoglobulins.[6,7] This correlates with murine studies regarding the role of Btk in autoimmunity, as we and others have shown that Btk-deficiency protects against multiple forms of autoimmune disease in pre-clinical models.[2,8–13] Further, we have not found evidence that Btk-deficiency might induce autoimmunity on its own, never having seen spontaneous arthritis either in Btk-deficient C57BL/6 mice, nor on the autoimmune-prone NOD background.

The effects of BTK-inhibitors, such as ibrutinib, on autoreactive B cells in patients is unknown. The effects cannot be assumed to mimic those found in XLA. For one thing, the inhibitors target only the kinase domain, leaving the adaptor domain of BTK intact. The adaptor function of BTK in mice can operate independently of the kinase function,[14] and

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while its role in human B cells is not well-known, it could conceivably allow better B cell survival than is seen in XLA patients. Second, human patients who are given inhibitors already have established B cell populations, including autoimmune-prone and normal subsets. Whether blocking the kinase domain of BTK reduces the number of autoreactive B cells, as Btk-deficiency does in mice, or increases their relative proportion as occurs in XLA patients, is an important question that deserves study. However, if Dr. Bernal's patient had autoimmune arthritis due to increased autoreactive B cells, she would likely have autoantibodies acting as triggers, which is not the case.

BTK is also expressed in myeloid cells, mast cells and neutrophils, which support inflammatory arthritis. The role of BTK in these cells is understudied. Some reports regarding BTK-deficient innate cells have shown decreased functions, while others have shown hyperactive qualities, indicating that BTK may sometimes have a regulatory role, supporting the authors' cautionary advice.[15–19] As our article showed, Btk-deficiency in innate cells did not protect against autoantibody-mediated arthritis in a preclinical, serum transfer model, but neither did it increase arthritis. In the patient presented by Bernal and colleagues, a non-autoimmune inflammatory process mediated by the innate immune system is a possibility that could be supported by our study. However, most inhibitors, including ibrutinib, have been shown to suppress innate cell mediated inflammation in pre-clinical models and *in vitro* cellular assays.[20–23] Ibrutinib is known to have significant side effects, however, including hemorrhage, neutropenia, atrial fibrillation, infection and diarrhea, that may be due to off-target effects on other kinases including ITK, BLK, BMX, TEC, JAK3, and EGFR, to name a few.[24,25] Of note, musculoskeletal pain is also common and 11% of patients have reported arthralgias, as noted on the package insert.

New BTK-inhibitors are in development, and several are in clinical trials for treatment of rheumatoid arthritis. Some of these small molecules may have fewer off-target effects than ibrutinib. Preclinical studies using these drugs mirror those using Btk-deficient mice in showing efficacy for autoimmune disease, and there is little evidence so far from either those data or human XLA patients that targeting BTK should in itself increase the chances of autoimmune disease. Data from these studies may provide new information regarding the role of BTK in human autoreactive B cells and innate cell populations, as well as clinical outcomes. In the meantime, it may be hoped that clinicians will continue to practice vigilance in noting and reporting potential side effects, as Bernal and colleagues have done.

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References

1. Bonami RH, Sullivan AM, Case JB, et al. Bruton's Tyrosine Kinase Promotes Persistence of Mature Anti-Insulin B Cells. J Immunol. Feb 15; 2014 192(4):1459–1470. [PubMed: 24453243]

2. Crofford LJ, Nyhoff LE, Sheehan JH, Kendall PL. The role of Bruton's tyrosine kinase in autoimmunity and implications for therapy. Expert review of clinical immunology. Jul; 2016 12(7): 763–773. [PubMed: 26864273]

3. Conley ME. B cells in patients with X-linked agammaglobulinemia. Journal of Immunology. May; 1985 134(5):3070–3074.

4. Ng YS, Wardemann H, Chelnis J, Cunningham-Rundles C, Meffre E. Bruton's tyrosine kinase is essential for human B cell tolerance. The Journal of experimental medicine. Oct 4; 2004 200(7): 927–934. [PubMed: 15466623]

5. Patiroglu T, Akar HH, Gunduz Z, Sisko S, Ng YY. X-linked agammaglobulinemia in two siblings with a novel mutation in the BTK gene who presented with polyarticular juvenile idiopathic arthritis. Scand J Rheumatol. 2015; 44(2):168–170. [PubMed: 25757060]

6. Winkelstein JA, Marino MC, Lederman HM, et al. X-linked agammaglobulinemia: report on a United States registry of 201 patients. Medicine (Baltimore). 2006; 85(4):193–202. [PubMed: 16862044]

7. Howard V, Greene JM, Pahwa S, et al. The health status and quality of life of adults with X-linked agammaglobulinemia. Clin Immunol. Feb-Mar;2006 118(2–3):201–208. [PubMed: 16377251]

8. Steinberg BJ, Smathers PA, Frederiksen K, Steinberg AD. Ability of the xid gene to prevent autoimmunity in (NZB × NZW)F1 mice during the course of their natural history, after polyclonal stimulation, or following immunization with DNA. J Clin Invest. 1982; 70(3):587–597. [PubMed: 6980900]

9. Kendall PL, Moore DJ, Hulbert C, Hoek KL, Khan WN, Thomas JW. Reduced diabetes in btk-deficient nonobese diabetic mice and restoration of diabetes with provision of an anti-insulin IgH chain transgene. Journal of immunology. Nov 15; 2009 183(10):6403–6412.

10. Halcomb KE, Musuka S, Gutierrez T, Wright HL, Satterthwaite AB. Btk regulates localization, in vivo activation, and class switching of anti-DNA B cells. Mol Immunol. 2008

11. Satterthwaite AB, Lowell CA, Khan WN, Sideras P, Alt FW, Witte ON. Independent and opposing roles for Btk and lyn in B and myeloid signaling pathways. J Exp Med. 1998; 188(5):833–844. [PubMed: 9730885]

12. Whyburn LR, Halcomb KE, Contreras CM, Lowell CA, Witte ON, Satterthwaite AB. Reduced dosage of Bruton's tyrosine kinase uncouples B cell hyperresponsiveness from autoimmunity in lyn−/− mice. J Immunol. Aug 15; 2003 171(4):1850–1858. [PubMed: 12902486]

13. Nyhoff LE, Barron BL, Johnson EM, et al. Bruton's Tyrosine Kinase Deficiency Inhibits Autoimmune Arthritis in Mice but Fails to Block Immune Complex-Mediated Inflammatory Arthritis. Arthritis & rheumatology. Aug; 2016 68(8):1856–1868. [PubMed: 26945549]

14. Middendorp S, Dingjan GM, Maas A, Dahlenborg K, Hendriks RW. Function of Bruton's tyrosine kinase during B cell development is partially independent of its catalytic activity. J Immunol. 2003; 171(11):5988–5996. [PubMed: 14634110]

15. Lougaris V, Baronio M, Vitali M, et al. Bruton tyrosine kinase mediates TLR9-dependent human dendritic cell activation. J Allergy Clin Immunol. Jun; 2014 133(6):1644–1650. e1644. [PubMed: 24612681]

16. Wang J, Lau KY, Jung J, Ravindran P, Barrat FJ. Bruton's tyrosine kinase regulates TLR9 but not TLR7 signaling in human plasmacytoid dendritic cells. Eur J Immunol. Apr; 2014 44(4):1130–1136. [PubMed: 24375473]

17. Mangla A, Khare A, Vineeth V, et al. Pleiotropic consequences of Bruton tyrosine kinase deficiency in myeloid lineages lead to poor inflammatory responses. Blood. Aug 15; 2004 104(4): 1191–1197. [PubMed: 15117762]

18. Gonzalez-Serrano ME, Estrada-Garcia I, Mogica-Martinez D, et al. Increased pro-inflammatory cytokine production after lipopolysaccharide stimulation in patients with X-linked agammaglobulinemia. J Clin Immunol. Oct; 2012 32(5):967–974. [PubMed: 22665224]

19. Liu X, Zhan Z, Li D, et al. Intracellular MHC class II molecules promote TLR-triggered innate immune responses by maintaining activation of the kinase Btk. Nat Immunol. May; 2011 12(5): 416–424. [PubMed: 21441935]

20. Di Paolo JA, Huang T, Balazs M, et al. Specific Btk inhibition suppresses B cell- and myeloid cell-mediated arthritis. Nature chemical biology. Jan; 2011 7(1):41–50. [PubMed: 21113169]

21. Chang BY, Huang MM, Francesco M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 ameliorates autoimmune arthritis by inhibition of multiple effector cells. Arthritis research & therapy. 2011; 13(4):R115. [PubMed: 21752263]

22. Lou Y, Han X, Kuglstatter A, et al. Structure-based drug design of RN486, a potent and selective Bruton's tyrosine kinase (BTK) inhibitor, for the treatment of rheumatoid arthritis. J Med Chem. Jan 8; 2015 58(1):512–516. [PubMed: 24712864]

23. Xu D, Kim Y, Postelnek J, et al. RN486, a selective Bruton's tyrosine kinase inhibitor, abrogates immune hypersensitivity responses and arthritis in rodents. The Journal of pharmacology and experimental therapeutics. Apr; 2012 341(1):90–103. [PubMed: 22228807]

24. Burger JA. Bruton's tyrosine kinase (BTK) inhibitors in clinical trials. Current hematologic malignancy reports. Mar; 2014 9(1):44–49. [PubMed: 24357428]

25. Dubovsky JA, Beckwith KA, Natarajan G, et al. Ibrutinib is an irreversible molecular inhibitor of ITK driving a Th1-selective pressure in T lymphocytes. Blood. Oct 10; 2013 122(15):2539–2549. [PubMed: 23886836]