Response to Comment on "Therapeutic Targeting of Syk in Autoimmune Diabetes"

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Letters to the Editor

Comment on “Therapeutic Targeting of Syk in Autoimmune Diabetes”

I read with great interest the recent article by Colonna et al. (1). The article was highly interesting and thought provoking. Interestingly, Syk inhibitors are rapidly emerging as an alternative therapeutic option in the management of multiple different diseases besides autoimmune diabetes.

For instance, C-61 is a novel new Syk inhibitor that attenuates cellular resistance to radiotherapy when administered to subjects with acute lymphoblastic leukemia (2). R406 is another similar Syk inhibitor that has a negative effect on the BCR signaling pathway and thereby attenuates therapeutic drug resistance to chemotherapeutic agents such as fludarabine in patients with chronic lymphocytic leukemia (3).

Similarly, R788 has benefits in renal pathologic conditions such as Ab-associated glomerulonephritis, as it decreases IL-1 levels as well as decreases renal proteinuria (4).

Interestingly, R788 has been shown to be of therapeutic benefit in rheumatoid arthritis, too (5).

Other recent studies also indicate that Syk inhibitors may decrease cellular destruction in tissues exposed to ischemia-reperfusion injury (6). The above examples clearly indicate the possible therapeutic role of Syk inhibitors in diseases ranging from glomerulonephritis to arthritis and the urgent need for further studies to fully elaborate their other potential benefits.

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Response to Comment on “Therapeutic Targeting of Syk in Autoimmune Diabetes”

In our recent publication (1) in The Journal of Immunology, Syk inhibition was shown to prevent progression of autoimmune diabetes. We are happy to reply to the letter from Dr. Kapoor regarding the possibility of additional indications for inhibitors of the Syk protein tyrosine kinase (PTK). Syk is critical for signaling of a growing list of innate and adaptive ITAM-mediated activating pathways, including the BCR, FcR, NK immunoreceptors, platelet activation receptors, pathogen pattern C-type lectin receptors, and the inflammasome. Thus, effective on-target inhibition of Syk catalytic activity could be therapeutically active in a broad arena of clinical autoimmune diseases triggered by immune activation pathways in innate or adaptive immunity. In rodent models, Syk inhibition has reduced inflammation in asthma, arthritis, experimental allergic encephalomyelitis, and lupus.

The first Syk inhibitor to be evaluated clinically is R788. Early studies noted proof-of-concept clinical activity in an Ab-mediated disease [immune thrombocytopenia (2)], but it is also active in rheumatoid arthritis (3). Furthermore, in lymphoid malignancies, Syk inhibitors are active in BCR-dependent B cell lymphomas (4) and in T cell lymphomas (5, 6), which aberrantly express syk. In treated patients and in rodents, B cell numbers are not dramatically lowered, implying that B cell development continues despite the fact that syk deficiency blocks B cell development at the pre-B cell stage (7). Taking a page from the oncology literature, it is possible that in autoimmunity, as in cancer, activated autoaggressive lymphoid cells may be addicted to sustained activatory signaling, rendering them more sensitive to pharmacologic modulation of these activation pathways than normal lymphoid cells.

Looking deeper, emerging evidence suggests that R788 efficacy may also be explained in part by off-target dose-dependent PTK inhibitory activities, as seen with imatinib (8, 9) and other multi-PTK inhibitors. For instance, we have shown that R788 also inhibits dendritic cell development in vivo through Flt3 inhibition, which could also contribute to anti-inflammatory effects of R788 irrespective of syk inhibition.

We agree that on-target inhibition of the PTK Syk represents a rational and promising approach to the treatment of autoimmunity, transplantation, and cancer. Should clinical studies continue to provide strong evidence for efficacy, R788 may prove to be a first-in-class Syk inhibitor (10, 11). Clinical development of these multikinase inhibitors will continue despite the potential for unexpected toxicities or serendipitous benefits due to off-target effects. For sick patients waiting for therapies today, the perfect should not be the enemy of the good (12). As long as multikinase inhibitors have reasonable

References


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toxicity profiles, promiscuous kinome inhibition may be an imperfect yet happy compromise with which to live.

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