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Et tu, Brutinib? Demise of a kinase target in rheumatoid arthritis?

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The outlook for people presenting with a diagnosis of rheumatoid arthritis (RA) has been transformed by the advent of "targeted" therapies comprising parenterally administered biologic drugs and more recently, orally available "small molecules". Despite different mechanisms of action, all these pharmacotherapeutics demonstrate similarly impressive efficacy in clinical trials. Nonetheless, few patients achieve and sustain long term remission, subjective symptoms of disease often persist, and many patients rank oral administration as their preferred mode of treatment.[1] Therefore, there has been interest in investigating alternative kinase targets that might widen the choice of oral medication and address contemporary unmet need.

The efficacy of biologic B-cell-depletion, particularly in seropositive RA, and the known pathogenic involvement of autoreactive B cells, has encouraged development of small-molecule inhibitors of B cell receptor (BCR) signaling for which Bruton's tyrosine kinase (BTK) is an attractive target. BTK is a member of the Tec family of non-receptor tyrosine kinases functioning as a key signaling protein, directly linking BCR activation to B cell proliferation and survival. BTK is expressed by B cells and most haematopoietic cells and participates in many other key immune pathways, including B-cell-activating factor receptor, Toll like receptor, chemokine receptor, and Fc receptor signaling.[2]

The first BTK inhibitor was ibrutinib, approved for the treatment of mantle cell lymphoma and subsequently for chronic lymphocytic leukaemia (CLL) although efficacy of ibrutinib in CLL may not be attributable to BTK inhibition alone, as off-target kinase inhibitory activity might contribute, for example, by promoting an tumour-killing Th1 phenotype. In the context of RA, there are safety concerns about off-target kinase effects and therefore several approaches to the pharmacological inhibition of BTK have been developed. Early generation BTK inhibitors, such as ibrutinib, form an irreversible covalent bond to a cysteine residue (Cys481) in the ATP binding site of BTK. Other compounds achieve reversible inhibition by formation of a weak, reversible hydrogen bond or a hydrophobic interaction. Attempts to generate more selective BTK inhibitors have combined properties of covalent and non-covalent inhibitors in compounds able to establish reversible covalent bonds with the Cys481 residue and temporarily inactivate the enzyme.[3]

No BTK inhibitor has yet reached phase III trials in RA and overall, the data from phase II studies has been discouraging. Clinical trials with BTK inhibitors including spebrutinib,[4] poseltinib[5] tirabrutinib,[6] acalabrutinib,[6] and evobrutinib,[7] failed to meet their primary endpoint. Against this collection of negative studies, strategy shifted to investigate dual kinase inhibition targeting a fixed-dose combination of the BTK inhibitor elsubrutinib and JAK inhibitor upadacitinib. However, this also failed to show benefit for elsubrutinib as a monotherapy and no additional benefit in combination with upadacitinib over JAK inhibition alone.[8]

Fenebrutinib, a highly selective non-covalent BTK inhibitor, is the only class member to deliver positive data to date. In seropositive RA patients with inadequate response to methotrexate, fenebrutinib increased the proportion of American College of Rheumatology (ACR)50 responses after 12 weeks of 150 mg daily compared to placebo, and reached effectiveness comparable to adalimumab with 200 mg bd.[9]

In this issue of *The Lancet Rheumatology*, Conaghan et al[10] report data for BMS986142, another non-covalent BTK inhibitor. However, unlike fenebrutinib, BMS986142 failed to reach statistical significance for co-primary endpoints and was tested in a mixed population, including seronegative individuals, and those with inadequate response to methotrexate or to up to two anti-TNFs. However, in a post-hoc analysis, only ACPA-positive patients receiving 200 mg achieved a statistically significant ACR20 response. Pharmacokinetic data for BMS-986142 was variable and inconsistent, raising questions about the completeness of target inhibition. This might be explained by inter-individual variability in CYP3A4/5, a major clearance pathway for BMS-986142, as well as enzyme autoinduction. BMS-986142 was associated with moderate dose-dependent reduction of CXCL13 although the effect could not be fully explored because the 350mg BMS-986142 dose was discontinued due to elevated liver enzymes and lack of benefit versus placebo. A novel aspect of the study design was the inclusion of RAMRIS assessments. Although these indicated modest

improvements in MRI synovitis scores, it is difficult to draw meaningful conclusions about other RAMRIS parameters after only 12 weeks of dosing.

The generally disappointing efficacy of small molecule BTK inhibitors in phase II RA clinical trials, including that of BMS-986142, was unanticipated. It may relate to pharmacologic issues concerning individual inhibitors. However, it may also be that we are yet to fully understand the pleiotropic implications of BTK inhibition on immunopathogenic processes in RA. Whatever the reasons, it seems unlikely that BTK inhibitors will be sufficiently competitive to join the existing therapeutic armamentarium of advanced therapies.

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