Dapirolizumab pegol: A novel treatment of patients with SLE by inhibiting CD40L

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Abstract

CD40 ligand (CD40L) has been described as one of the key players in regulating T cell, B cell and antigen-presenting cell activity. Pre-clinical evidence and phase 1 and 2 clinical studies with anti-CD40L antibodies, such as ruplizumab and toralizuamb suggest that CD40L blockade may be efficacious in the treatment of inflammatory and autoimmune conditions. However, clinical development of these antibodies was discontinued because of significant thromboembolic events, due to Fcmediated cross linking, resulting in platelet activation. UCB and Biogen have developed Dapirolizumab pegol (DZP) which comprises of Fab fragments with a high affinity for CD40L, conjugated to polyethylene glycol (PEG) scaffolding to deliver desired pharmacokinetic characteristics. Lacking any Fc moiety, DZP has been engineered to minimise the risk of platelet activation through Fc-mediated cross-linking. To date UCB and Biogen have completed two clinical studies with DZP. The first in human study (SL0013) demonstrated a dose-proportional pharmacokinetics of DZP. The second clinical study was a Phase Ib multiple dose study (SL0014) in patients with mild to moderate SLE. Whole blood transcriptomic profiling demonstrated a reduction in B cell transcript levels on active treatment supporting the proposed mode of action for DZP. Lupus response rates were notable: 5/12 SRI4 and 5/11 BICLA responders in the CDP7657 arm, in comparison with 1/7 in the placebo arm. DZP was well tolerated with no changes in coagulation parameters or serious treatment emergent adverse events. The failure of many new, mostly biologic, drugs to meet their primary end points in double-blind clinical trials in patients with systemic lupus erythematosus (SLE) has caused a profound sense of disappointment among both physicians and patients. Arguably, the success of B cell depletion with rituximab in open-label studies and in patients with lupus nephritis in the USA and in difficult-to-treat patients with SLE in the UK, together with the approval of belimumab (which blocks B cell-activating factor (BAFF)) for use in patients with SLE and the recognition that clinical trial design can be improved, have given some cause for hope. However, changes to therapies in current use and the development of new approaches are urgently needed. The results of the latest studies investigating the use of several new approaches to treating SLE are discussed in this Review, including: fully humanized anti-CD20 and anti-CD19 monoclonal antibodies; inhibition of tyrosine-protein kinase BTK; CD40 ligand blockade; interfering with the presentation of antigen to autoreactive T cells using a peptide approach; a receptor decoy approach using an analogue of Fcγ receptor IIB; dual blockade of IL-12 and IL-23; and inhibition of Janus kinases.

Biography:

Farnaz Fallah-Arani is currently a Senior Group Leader in the therapeutic area of immunology at UCB Celltech in Slough and has experience in pre-clinical research and drug discovery of biologics and small molecules. She is an Immunologist by training and has a strong interest in the biology of autoimmune disease and transplantation.

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