AUTOIMMUNE CONNECTIVE TISSUE DISEASES

NEW ORAL SMALL MOLECULES FOR LUPUS AND RELATED DISEASES

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Current treatment regimens for cutaneous and systemic lupus erythematosus (SLE) typically comprise some combination of glucocorticoids, antimalarials, immune-suppressive drugs, and cytotoxic agents in severe cases. To date, belimumab (anti-BLyS) is the only FDA approved biologic for treating SLE.
However, as our understanding of the pathogenesis of autoimmune diseases is growing, new therapies have being developed to target disease-specific pathways. Many small molecules have shown various degrees of efficacy in preclinical models, and many clinical trials are under evaluation.
Ruxolitinib, a JAK1/2 inhibitor, has been found to be effective in CLE skin lesions. Baricitinib,
another JAK1/2 inhibitor, has recently finished a phase 2 trial, revealing a significant improvement of skin rash in SLE patients. Tofacitinib, a JAK1/JAK3 inhibitor is now examined in SLE as well as in discoid lupus with or without concurrent SLE. At the moment, JAK-1 inhibitors filgotinib is under investigation in clinical trials.
The topical spleen tyrosine kinase (Syk) inhibitor, a highly conserved tyrosine kinase which mediates several biological functions including the regulation of immune responses, is currently under study in patients with subacute and chronic cutaneous LE.
The mTOR inhibitor rapamycin was efficacious and well tolerated in a small open label study in SLE patients but results from the ongoing phase II study and a study of idiopathic and lupus membranous nephropathy will better define its role in the treatment of SLE.
Among calcineurin inhibitors (CNI), tacrolimus was studied as induction and maintenance therapy in Asian patients with lupus nephritis (LN) and in those with refractory disease. A phase II study of fixed low dose voclosporin, a next-generation CNI, in LN is ongoing.
In regards to the new quinolone-3-carboxamide derivatives, paquinimod was safe and tolerated in both phase I and phase II studies and gave positive initial results. In addition, a phase II study on laquinimod for lupus arthritis and LN has been initiated.
Bortezomib, a nonselective proteosome inhibitor approved for multiple myeloma and mantle cell lymphoma, has been examined in cases of refractory lupus.
Some other small molecules, such as Bruton's tyrosine kinase (Btk) inhibition (ibrutinib), Rho kinase (ROCK) inhibition (Fasudil), Phosphatidylinositol-3 kinases (PI3K) inhibition, have shown successfully results in mice. Concerning dermatomyositis (DM), actually more than 80 clinical trials studies are under evaluation. Among them, a phase 4 study is

assessing the safety and efficacy of subcutaneous abatacept in 10 patients seven years of age and older with refractory juvanile DM. A phase 2 study on apremilast, a phosphodiesterase-4 (PDE-4) inhibitor, is evaluating the safety and efficacy of this drug in the treatment of cutaneous disease in patients with recalcitrant DM. A Phase 3 multicenter study is trying to assess the efficacy and safety of lenabasum, a small-molecule that selectively binds as an agonist the cannabinoid receptor type 2 (CB2), for the treatment of DM. A phase 1 study regarding the safety and efficacy of Janus kinase (JAK) inhibitor, tofacitinib, in adults with active, treatment-refractory dermatomyositis is ongoing.