Kv1.3 Channel Blocker Dalazatide (ShK-186): A Potential Novel Immunomodulating Therapeutic for ANCA Vasculitis and Lupus Nephritis


1. Dalazatide Targets Kv1.3 Channels on Autoimmune Effector Memory T Cells, Evidence of Kv1.3 in Autoimmune Disease

- **Effector memory T cells (TEM)** cause autoimmune disease
- Kv1.3+ autoreactive TEM cells identified in multiple autoimmune diseases
- TEM cells depend on the Kv1.3 channel for function
- Blockade of Kv1.3 suppresses inflammation
- Dalazatide is a highly specific and potent peptide inhibitor of Kv1.3

2. Safety and Phase I Trial Results

- **Dalazatide Clinical Activity – 30 mcg Dose**
  - Significant improvement in select lesions following 4 weeks of treatment
- **186-03 study of the safety, tolerability and pharmacodynamics of dalazatide in active plaque psoriasis**
  - Active plaque psoriasis with 3% BSA and multiple target lesions
  - Reduced twice-weekly subcutaneous injections at 2 dose levels (30 mcg or 60 mcg) for 4 weeks followed by 4-week follow-up
- **Safety & Tolerability**
  - Drug was well tolerated; all subjects completed all scheduled doses
  - Most AEs judged to be mild, consistent with previous trials
  - No subjects withdrew, reduced dose or missed a dose
- **Clinical Activity**
  - 50% of subjects in 60 mcg group achieved clinical improvement in target lesion
  - Improvement observed as early as day 15 and for up to 6 weeks following last dose (end of study)
  - 90% of subjects in 60 mcg group had reduction in PASI score

3. Case for Dalazatide in SLE and ANCA Vasculitis

Unmet needs in lupus and vasculitis
- Current therapies including steroids, cyclophosphamide, mycophenolate cause long term problems and do not prevent flares
- Current biologic therapies Rituxan and BALLY have incomplete efficacy

Opportunity for dalazatide therapy in systemic lupus erythematosus (SLE) patients
- During flares of disease, lupus nephritis patients show an increase of urinary (kidney) TEM cells
- Corticosteroid sparing and MOA complementary to B cell directed drugs
- Effector memory T cells (TEM) critically for diseases such as vasculitis and lupus nephritis.
- Kv1.3 channels / cell

Dalazatide reduces glomerular endothelial Kv1.3 expression in SLE patients.
- Kv1.3 expression is upregulated in TEM cells and that Kv1.3 was upregulated in TEM cells during the course of disease.
- Significant improvement in target lesions following 4 weeks of treatment
- Well tolerated with no serious adverse events reported.
- Pharmacokinetic analysis revealed that the doses and schedules were well tolerated in clinical studies.
- Dalazatide is currently in clinical trials for the treatment of SLE and vasculitis.

4. Kv1.3 Expression in SLE Effector Memory T Cells

Immunophenotypic analysis of PBMCs from SLE patients.
- Kv1.3 expression is elevated in blood of SLE patients during flares of disease.
- Kv1.3: A potential biomarker for treatment monitoring.

5. TEM+ Pathogenic in ANCA Vasculitis

TEM+ cells accumulate in the kidney during active disease and increase in blood during remission

6. Dalazatide suppresses proinflammatory Th17 cytokines in ANCA Vasculitis

Ex vivo analysis of ANCA vasculitis patient lymphocytes.
- Dalazatide suppresses IL-17A, TNFα, and IFNγ production by the activation of memory T cells

7. 3. Case for Dalazatide in SLE and ANCA Vasculitis

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