VIDOFLUDIMUS SHOWS A SUPERIOR PROFILE COMPARED TO CYCLOPHOSPHAMIDE AND MMF IN AN EXPERIMENTAL SYSTEMIC LUPUS ERYTHEMATOSUS MODEL

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Introduction
Systemic lupus erythematosus (SLE) is a systemic autoimmune disease caused by multiple genetic polymorphisms and immunostimulatory environmental factors, which commonly affects young females. Mild disease manifestations such as fatigue, skin rashes, arthralgia, or fever can usually be controlled by low dose steroids and antiinflammatories. In many patients, however, autoimmune inflammation of solid organs holds the risk of progressive tissue remodeling and irreversible organ damage, which requires treatment with potent immunosuppressive drugs. For example, high dose cyclophosphamide (Cyc) or mycophenolate mofetil (MMF) has proven to be effective to control diffuse proliferative lupus nephritis in up to 60% to 80% of patients, and similar protocols have been applied in SLE patients with other types of severe immunopathologies. However, controlled trials revealed that immunosuppressive treatments are associated with significant morbidity and mortality in SLE. For example, in the Aspreva Lupus Management Study, MMF caused serious adverse effects in 27.7% of patients and treatment-related death in 4.9% of patients; Cyc caused serious adverse effects in 22.8% of patients and treatment-related death in 2.8% of patients. Most of the adverse effects and deaths were related to serious infections caused by the immunosuppressive and unspecific antiproliferative effects of Cyc and mycophenolate mofetil, evident by myelosuppression and leukopenia.

Vidofludimus (4SC-101) is a novel oral inhibitor of interleukin-17 (IL-17A and IL-17F) release and DHODH in clinical development for rheumatoid arthritis and inflammatory bowel disease. Vidofludimus has been demonstrated to be highly active in preclinical models of further autoimmune diseases such as multiple sclerosis, systemic lupus erythematosus (SLE), psoriasis, and transplant rejection. The primary objective of the study was to investigate the anti-inflammatory and immunosuppressive activity of vidofludimus in an experimental animal model of SLE (MRL/lpr/lpr) as compared with animals receiving mycophenolate mofetil (MMF) and cyclophosphamide (Cyc).

Methods
12 weeks old female MRL/lpr/lpr mice received vidofludimus (300mg/kg), MMF (100mg/kg) and placebo, administered as oral gavages every day for 6 weeks. Cyc (30mg/kg) group received intraperitoneal injections once every week. At 18 weeks of age animals were sacrificed to obtain samples for the analysis of renal parameters, tissue histology of lung and other organs, production of auto-antibodies, and bone marrow toxicity.

Results
A. Renal Function

B. Renal histology

C. Lung histology

D. Splenomegaly and lymphadenopathy

E. Serum Parameters

F. FACS

Conclusion
These data provide evidence that delayed onset of therapy with vidofludimus is effective in suppressing immunopathology and autoimmune tissue injury of MRL/lpr/lpr mice. The efficacy was comparable to Cyc with respect to suppression of experimental SLE. However, vidofludimus did not cause myelosuppression like the unspecific cell proliferation inhibitor Cyc which may relate to the more specific mode of action of vidofludimus. Vidofludimus had a superior activity profile than MMF in this mouse model of SLE. Thus, vidofludimus might represent a novel drug that could control active SLE like Cyc but avoid Cyc toxicity and could, therefore, be considered for induction and maintenance therapy of SLE.

Acknowledgement - The expert technical assistance of Dan Dragomirovic and Ewa Radomska is gratefully acknowledged.