diagnosis of APS is suspected. Hydroxychloroquine could be a valid treatment in CNS manifestations in patients with APS.

Funding Source(s): None

67 THERAPEUTIC AND RENAL PROTECTIVE EFFECTS OF DZ2002, A REVERSIBLE SAHH INHIBITOR, ON LUPUS-PRONE NZB×NZW F1 MICE

1Shijun He*, 2Zemin Lin, 2Wei Tang, 1Jiangping Zuo. 1Shanghai Institute of Materia Medica, Chinese Academy of Sciences; 2Shanghai Institute of Materia Medica

Background Glomerulonephritis is one of the major complications and causes of death in systemic lupus erythematosus (SLE). DZ2002 is a reversible S-adenosyl-l-homocysteine hydrolase (SAHH) inhibitor with potent therapeutic activity against lupus nephritis in mice. However, the molecular events underlying the renal protective effects of DZ2002 remained unclear. This study is designed to uncover the molecular mechanisms of DZ2002 on glomerulonephritis of lupus-prone mice.

Methods Female NZB/W F1 mice were treated orally with DZ2002, and the proteinuria level and body weight were determined. After the mice were euthanized, serum biochemical parameters and renal damage were determined. Splenocytes of NZB/W F1 mice were isolated for ex vivo study. The LLCM-MS-based label-free quantitative (LFQ) proteomic approach was applied to analyze the kidney tissue samples from the NZB/W F1 mice treated with DZ2002 or vehicle. KEGG pathway enrichment and direct protein-protein interaction (PPI) network analyses were used to map the pathways in which the significantly changed proteins (SCPs) involved. The selected proteins from proteomic analysis were validated by Western blot analysis and immunohistochemistry in the kidney tissues.

Results Treatment of the mice with DZ2002 significantly attenuated the progression of glomerulonephritis and improved the overall health. The improvement was accompanied by decreased levels of nephritogenic anti-dsDNA antibodies, serum IL-17, IL-23p19 and TGF-. DZ2002 also significantly suppressed TLR agonists-stimulated up-regulation in IL-6 and IL-23p19 production in murine BMDCs, and prevented Th17 differentiation and suppressed IL-17 secretion by the T cells in a BMDC-T cell co-culture system. Pathway analysis of proteomic data revealed that 13 SCPs were involved in tight junction and focal adhesion process. Further protein expression validation demonstrated that DZ2002 treated NZB/W F1 mice exhibited down-regulation of -actinin-4 and integrin-linked kinase (ILK), as well as the restoration of 1-integrin activation in kidney tissues compared with vehicle treated ones.

Conclusions Our study demonstrated that DZ2002 effectively ameliorates lupus syndrome in NZB/W F1 mice by regulating TLR signaling-mediated antigen presenting cell (APC) responses. Alongside of attenuating glomerular immune complexes deposition and impeding pathologic lymphocytes polarization in SLE, the renal protective effects of DZ2002 may partly attributed to stabilization of the actin cytoskeleton and maintenance of podocyte numbers, in turn, are effective to improve proteinuria and kidney function in lupus nephritis.

Funding Source(s): The National Basic Research Program of China (973 Program) (grant number: 2014CB541906); and the National Nature Science foundation of China (grant number: 81402939)

68 ADMINISTRATION OF ARTEMISININ ANALOGUE SM934 AMELIORATES DISEASE MANIFESTATION IN LUPUS-PRONE MICE VIA RESTORING IMMUNE HOMEOSTASIS

1Zemin Lin*, 2Jiangping Zuo, 3Shijun He, 4Wei Tang. 3Shanghai Institute of Materia Medica, Chinese Academy of Sciences; 4Shanghai Institute of Materia Medica

Background Artemisinin and its derivatives were reported to possess strong regulatory effects on inflammation and autoimmune diseases. This study was designed to examine the therapeutic effects and underlying mechanisms of SM934, a water-soluble artemisinin analogue, on lupus-prone mice.

Methods For MRL/lpr mice: In vivo, the preventative or therapeutic effects of SM934 in MRL/lpr mice were investigated. Ex vivo, the mechanisms of treatment were explored according to the immunologic correlates of disease. Impacts of SM934 on Toll-like receptor (TLR)-triggered antigens presenting cell (APC) responses were evaluated. In vitro, the effects of SM934 on the activation and differentiation of CD4+ T cells were examined. For NZB/W F1 mice: In vivo, the lupus-prone mice were treated with SM934 for 3 or 6 months respectively to investigate the effect on clinical manifestations and immunological correlates. To further explore the mechanisms of SM934, ovalbumin (OVA)-immunized or interferon (IFN)–elicited C57BL/6 mice were used.

Results In vivo, SM934 treatment significantly prolonged the life-span of MRL/lpr mice, ameliorated the lymphadenopathy, decreased the levels of serum anti-nuclear antibodies (ANAs) and the pathogenic cytokines IFN-, IL-6, IL-10 and IL-21, and reduced the proportion of double negative T cells. Treatment with SM934 significantly delayed the progression of glomerulonephritis and improved the survival of NZB/W F1 mice. Clinical improvement was accompanied with decreased anti-dsDNA Abs and serum interleukin IL-17. In addition, SM934 treatment promoted the IL-10 production from macrophages of NZB/W F1 mice, OVA-immunized C57BL/6 mice and IFN-elicited C57BL/6 mice. Ex vivo, SM934 treatment elevated the percentage of Treg cells, inhibited the development of Th1 and Th17 cells. Moreover, SM934 suppressed the TLR-triggered activation and proliferation of B cells. In vitro, SM934 inhibited the differentiation of Th1 and Th17 cells as well as TLR-associated B-cell activation and plasma cell differentiation. SM934 enhanced IL-10 production from primary macrophages stimulated with IFN-.

Conclusions Taken together, these results demonstrated that the artemisinin analogue SM934 exerted significant therapeutic benefits in lupus-prone mice, by inhibiting both the pathogenic helper T cell development and responses, enhancing anti-inflammatory cytokine IL-10 production and suppressing plasma cell formation. These properties of SM934 might contributed to the restoration of the immune homeostasis in lupus-susceptible mice, and thus cast a light on a novel strategy for lupus treatment.

Funding Source(s): National Science Fair Committee (NSFC), China (No. 81273524, 81322049), National Science and
Technology Major Project New Drug Creation and Manufacturing Program, China (2014Z × 09101002) and National Key Basic Research Programme (973 Programme, 2014CB541906).

Artemisinin analogue SM934 treatment restore immune homeostasis in lupus-prone mice

LUPUS IMPACT TRACKER CAN DIFFERENTIATE AMONG TREAT 2 TARGET OUTCOMES IN LUPUS PATIENTS WITH AND WITHOUT CONCURRENT FIBROMYALGIA

Meenakshi Jolly, Herve Devilliers, Ivigo Rua Figueroa, Javier Narváez-García, Jaime Calvo Alen, María Galindo Izquierdo, Francisco Javier López-Longo, Antonio Fernandez Nebro, Eva Tomero Muriel, Esther Uriarte Isaelaya, Mercedes Freire González, Ricardo Blanco Alonso, Coral Moureño Rodríguez, José C. Rosas-Gómez de Salazar, Gema Bonilla-Hernán, Javier Narváez-García, Eva Salgado-Pérez, Lorena Expósito, Joel Block, Jose Maria Pejo Reigosa, Rush University Medical Center; 2University of Dijon; 3Hospital De Gran Canaria dr. Negrín; 4Hospital de Bellvitge; 5Hospital Universitario Araba; 6Hospital Universitario 12 De Octubre; 7Hospital General Universitario Gregorio Marañón; 8UGC de Reumatología, Instituto de Investigación Biomédica de Málaga (IBIMA) Hospital Regional Universitario de Málaga, Spain; 9Hospital De La Princesa; 10Hospital De Donostia; 11Hospital Juan Canalejo A Coruña (CHUAC); 12Hospital Marques de Valdecilla; 13Complejo hospitalario Universitario Vigo; 14Hospital De Marina Baixa; 15Hospital De La Paz; 16Bellvitge University Hospital, Barcelona; 17Complejo Hospitalario De Ourense; 18Hospital Universitario de Canarias

Background Remission and Low Disease activity state (LDAS) are the treat to target (T2T) outcomes used Systemic Lupus Erythematosus (SLE). Lupus Impact Tracker (LIT), a ten item unidimensional patient reported (PRO) tool with good psychometric properties and responsiveness including to composite response Index (SRI) and T2T outcomes. SLE patients often fibromyalgia (FM). We report discriminant validity of LIT to T2T outcomes in SLE patients stratified by FM from the largest European SLE registry-cohort.

Methods Observational, multi-center data from 1364 adult patients with SLE meeting 1997 ACR criteria were obtained. This included demographics, LIT, disease activity-DA (SLEDAI) and medications. Remission off therapy (ROFT) was defined as SLEDAI=0 without prednisone or Immunosuppressive/s. Remission on-therapy (RONT) was SLEDAI=0 and a prednisone dose 5 mg/day and/or Immunosuppressive/s. LDAS (modified) was SLEDAI 4, prednisone dose 5 mg/day and/or Immunosuppressive/s. LDAS (modified) was SLEDAI 4, prednisone dose 9 mg/day and/or Immunosuppressive/s. Non-optimal (NO) disease status was SLEDAI >4 and/or prednisone dose >9 mg/day and/or immunosuppressive/s in induction dose. LIT values were compared between T2T groups using mixed models among (a) all patients, (b) with and (c) without FM. For Model 1 : RONT and LDAS were combined (given relatively very low DA and lower prevalence of steroid use in LDAS) and compared with NO and ROFT. For model 2, all 4 T2T categories were used.

Results 1232/1364 (90%) were women, and 95% were Caucasian,76/1364 had FM. Median LIT (Q1, Q3) was 10 (4,6). LIT scores were significantly different among T2T categories (table 1). Significant relevant differences were not evident between RONT and LDAS groups: 1) RONT had greater medication use than LDAS (prednisone 5~10 mg/day use of 17.2% vs 8.3%). 2) In LDAS, mean SLEDAI was 2, which can occur without clinical DA. RONT thus fared slightly worse than LDAS in patients evaluation of SLE impact.