antlers of sika deer and can be chemically synthesized from glycerol, palmitic acid, and linoleic acid. Research using LPS-induced acute lung injury murine model has reported that EC-18 stimulates a more rapid resolution of LPS-induced lung inflammation. In addition, it has been reported that in a murine model of collagen-induced arthritis, EC-18 treatment ameliorated arthritis, with down-regulation of IL-6 level by regulating the activity of STAT3 in the synovium. Curdlan-administered SKG mice develop ILD spontaneously followed by peripheral arthritis, which resembles RA-ILD.

Objectives: We evaluated the modulatory effect of the EC-18 on arthritis and ILD in autoimmune arthritis animal model.

Methods: Male SKG mice were obtained from Dr. S. Sakaguchi. We injected curdlan (3mg/mice) in 8-week-old SKG mice and identified the presence of ILD by histological analysis at 20 weeks post-injection. Arthritis score was measured every week for up to 20 weeks. EC-18 (250mg/kg body weight/day, Enzychem Lifesciences Co., Daejeon, Korea) was administered every day orally. At 20 weeks post-injection, lung sections were stained with H&E and Masson's trichrome. Using the Opal method, multiplexed immunofluorescent staining of lung tissue was performed. According to the scale by Ashcroft et al., fibrosis severity of lung sections was assessed by a system of eight grades. Analysis of serum cytokines by the luminex multiplex cytokine assay was performed at 20 weeks post-injection.

Results: Oral administration of EC-18 decreased arthritis score significantly until 8 weeks post-injection and remained unchanged thereafter. At 20 weeks post-injection, histological analysis showed severe pulmonary destruction, including bronchial alveolar tissue damage and massive leukocyte infiltration, and fibrosis in the curdlan-administered mice, which was attenuated in EC-18 treated mice. In particular, 67% of curdlan-administered mice showed ILD-like phenotype, whereas the incidence rate in EC-18-treated mice was 17%. Furthermore, immunofluorescent-staining showed both IL-17A and neutrophil accumulation in lung in curdlan-administered mice; these were decreased in EC-18-treated mice. Interestingly, at 20weeks post-injection, EC-18 treatment down-regulated serum levels of IL-6 and TNF- α and up-regulated sIL-7R α (anti-fibrotic molecule).

Conclusion: Taken together, EC-18 exerts an anti-arthritis effect in early phase, but a long-term effect was not indicated. We emphasize the effect on ILD prevention of EC-18 via up-regulation of sIL-7R α and inhibition of neutrophil accumulation, suggesting a therapeutic agent potentially for RA-ILD.

Disclosure of Interests: None declared

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SAT0010

ANTI-CD30 IMMUNOTHERAPY AMELIORATES BONE AND CARTILAGE DESTRUCTION IN EXPERIMENTAL MODEL OF RHEUMATOID ARTHRITIS IN MICE

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Background: CD30 is a member of the TNF-receptor family and commonly expressed on lymphocytes of Hodgkin lymphoma and anaplastic large cell lymphoma. It has been reported that levels of soluble CD30 in serum and joint fluid is significantly elevated in rheumatoid arthritis (RA). Although RA patients may develop lymphoproliferative disorders (LPD) as a result of immunosuppression by MTX or bDMARDs, safety medications after the regression of LPD for RA have not yet been established.

Objectives: To explore the potential of CD30 targeting therapy for RA.

Methods: (1) Immuno-histological staining of CD30 was performed for fresh synovial tissues of RA and osteoarthritis (OA). In addition, double immunofluorescence staining of CD30 with CD3, CD20, CD68, CD138 were performed on RA synovial tissue. (2) Brentuximab vedotin (BV) is an anti-CD30 antibody conjugated with monomethyl auristatin E, designed to induce apoptosis of CD30 expressing cells. A multiple myeloma cell line (RPMI8226) was used as a non-lymphoma cell line and plasma cell-like cell line. Immuno-cytological staining for CD30 was performed on RPMI8226. Cells were cultured and harvested on days 0, 1, and 3 to evaluate the effects of BV (50 μ l / ml per well). Cytospin specimens were stained by May-Grunwald-Giemsa (MGG) staining for cell counting and by FIFC-terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining for detection of apoptosis. (3) Collagen antibody induced arthritis (CAIA) was induced in DBA/1 mice by arthritogenic cocktail of monoclonal antibodies against type II collagen. BV was administered to the treatment groups (30mg/kg and 70mg/kg n=4 each) and evaluated clinical score, histological findings and levels of SAA, IL-6, and TNF α in serum by ELISA. Student's t-test (two-tailed) was used to determine statistical significance for analysis of synovial tissues and cell line assay. Two way ANOVA with Dunnett's post hoc analysis was used for multiple comparisons of mice model.

Results: (1) The number of CD30-positive cells was significantly higher in RA synovial tissue than in OA synovial tissue ($p<0.01$) (Fig. 1). CD30-positive cells were detected around the lymphoid follicles. Double immunofluorescence

showed CD30 and CD138 double-positive cells in the synovial tissue of RA, suggesting CD30 is predominantly expressed by plasma cells. (2) RPMI8226 cells expressed CD30. BV caused apoptosis of RPMI8226 cells, and the number of cells treated with BV decreased to 95% compared to controls. (3) All control mice (n=4) developed severe arthritis, and their scores reached a peak (score: 13.3) on day 10. In the mice of treatment group of 30mg/kg, paw swelling was slightly decreased, their clinical score reached a peak (score: 9.3) on day 10. In contrast, paw swelling was significantly reduced in the 70mg/kg treatment group. The peak of the clinical score was 4.3 on day 10 (Fig.2). Histological score evaluated synovitis with infiltration of inflammatory cells, pannus formation, and erosion of bone and cartilage. Histological score of hind paws were 3.0 ± 0.8 for the control group, 2.7 ± 1.0 for 30mg/kg group, and 0.7 ± 1.1 for 70mg/kg group ($p<0.01$), respectively. The serum levels of SAA and IL-6 of treatment group were lower than those of no treatment group ($p<0.01$).

Conclusion: We showed the expression of CD30 on synovial tissue of RA and the expression of CD30 on plasma cells. In addition, the current study provides the first evidence that BV depletion of CD30-positive cells suppressed arthritis and osteochondral destruction in CAIA mice. Our results may provide an important clue for the development of an effective treatment for RA with iatrogenic immunodeficiency-related LPD.

Fig. 1: Immuno-histological staining of CD 30 for fresh synovial tissues

Fig. 2: BV dose-dependently suppress paw swelling and the clinical score of CAIA

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SAT0011

COMBINED INHIBITION OF AUTOPHAGY AND GLUTAMINE METABOLISM SUPPRESSES CELL GROWTH OF RA SYNOVIOCYTES AND AMELIORATES ARTHRITIS IN SKG MICE

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Background: Immunometabolism is now recognized to be crucial in the pathogenesis of rheumatoid arthritis (RA). We have recently shown that the expression of glutaminase 1 (GLS1), a key enzyme in glutaminolysis, is upregulated in fibroblast-like synoviocytes from RA patients (RA-FLS) and that GLS1 inhibition