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OP0204

LUPUS COMPREHENSIVE DISEASE CONTROL IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS: APPLICATION OF A NEW INDEX

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Background: The main outcomes in SLE patients management are represented by the remission achievement and chronic damage prevention. Even though activity and damage are intimately connected, to date indices including both these outcomes are not available.

Objectives: In the present study, we aimed at assessing the application of a new index, the Lupus comprehensive disease control (LupusCDC), including disease activity and chronic damage progression.

Methods: We performed a longitudinal analysis, including SLE patients according to ACR 1997 criteria, followed-up in the period between January 2014 and December 2018, and with at least one visit per year. Disease activity was assessed by SLE Disease Activity Index 2000 (SLEDAI-2K) and three different remission levels were evaluated, as reported in Table 1 (1).

Table 1. Remission levels considered in the study (1).

Remission level	Definition
Complete Remission (CR)	No clinical and serological activity (SLEDAI-2K=0) in corticosteroid-free and immunosuppressant-free patients (antimalarials allowed)
Clinical remission off-corticosteroids (CIR-GCoff)	Serological activity with clinical quiescent disease according to SLEDAI-2K in corticosteroid-free patients (stable immunosuppressive therapy and antimalarials allowed)
Clinical remission on-corticosteroids (CIR-GCon)	Clinical quiescent disease according to SLEDAI-2K in patients on prednisone 1–5 mg/day (stable immunosuppressants and antimalarials allowed)

Chronic damage was registered according to SLICC damage index (SDI). All the patients were evaluated at baseline (T0) and every 12 months (T1, T2, T3, T4). At each time-point, we calculated the prevalence of LupusCDC, defined as remission achievement plus absence of chronic damage progression in the previous one year. We calculated this outcome including separately the different remission levels.

Results: According with inclusion criteria, 172 SLE patients were evaluated in the present analysis [M/F 16/156, median age 49 years (IQR 16.7), median disease duration 180 months (IQR 156)]. At first assessment, we observed a mean±SD SDI value of 0.7±1.1. In details, 56 patients (32.5%) showed damage in at least one organ/system and the presence of damage was significantly associated with age ($p<0.0001$, $r=0.3$) and disease duration ($p=0.0003$, $r=0.3$). During the follow-up, we observed a significant increase in SDI values compared with T0 (T1: mean±SD 0.8±1.3, $p<0.0001$; T2: 0.8±1.4, $p<0.0001$; T3: 0.9±1.4 $p=0.0001$; T4: 1.0±1.5 $p<0.0001$).

In figure 1A and 1B we reported the proportion of patients achieving the different levels of remission and LupusCDC, respectively. In particular, the LupusCDC definition including CR was the most frequently detected in all time-points evaluated (T1: 18.0%; T2: 31.9%; T3: 27.9%; T4: 24.4%), with a significant difference at T2 [LupusCDC(CR) versus LupusCDC(CIR-GCoff), $p=0.0002$; LupusCDC(CR) versus LupusCDC(CIR-GCon) $p=0.0002$], T3 [LupusCDC(CR) versus LupusCDC(CIR-GCoff), $p=0.03$; LupusCDC(CR) versus LupusCDC(CIR-GCon)

$p=0.006$], T4 [LupusCDC(CR) versus LupusCDC(CIR-GCon), $p=0.002$]. No significant differences were found when comparing the prevalence of different remission levels and the prevalence of LupusCDC including the corresponding remission.

Conclusion: In the present analysis we proposed for the first time a new index including disease activity and chronic damage, in order to evaluate the proportion of SLE patients reaching a comprehensive disease control. We found that CR is most frequently associated with the absence of damage progression.

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Figure 1. Proportion of patients achieving one of the three levels of remission (A), and of patients reaching LupusCDC according with different remission levels (B).

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OP0205

PHASE I STUDY OF D-0120, A NOVEL URAT1 INHIBITOR IN CLINICAL DEVELOPMENT FOR HYPERURICEMIA AND GOUT

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Background: D-0120 is a novel oral selective uric acid transporter (URAT1) inhibitor being developed for the treatment of hyperuricemia and gout by blocking the reabsorption of uric acid (UA) within the renal proximal tubule, thereby reducing serum uric acid concentrations. As a novel URAT1 inhibitor, D-0120 is anticipated to have more potent serum UA reducing effect than the approved URAT1 inhibitor lesinurad, but with less toxicity and wider therapeutic window. The pharmacological potential of D-0120 for the treatment of hyperuricemia and gout was demonstrated in preclinical studies. The results of the in vitro hURAT1 expressed CHO cell model showed that the inhibitory activity of D-0120 is 150-fold more potent than lesinurad and slightly more potent than verinurad.

Objectives: The purpose of this dose escalation study is to evaluate the safety and tolerability of D-0120 in multiple ascending doses in healthy volunteer, to characterize the pharmacokinetics (PK) of D-0120 and to assess pharmacodynamic (PD) effects and determine the drug-drug interaction (DDI) effect of febuxostat and D-0120 in healthy volunteers.

Methods: This is a randomized, double blind, multiple ascending doses Phase I study of D-0120 in healthy volunteers conducted at one site. Thirty-two healthy eligible volunteers with serum uric acid level ≥ 4.5 mg/dL but within normal range at screening were enrolled and dosed with D-0120 within 4 different single agent cohorts for a period of 7 days. Each cohort had 8 subjects randomized at 3:1 ratio for D-0120:placebo. A fifth cohort of 8 healthy eligible volunteers were enrolled and dosed with 5 mg of D-0120 in combination with 40 mg of febuxostat over a period of 9 days. Evaluation of safety, PK and PD was conducted at various timepoints while the patients were in

confinement. Further safety evaluation took place on Day 14. A Safety Review Committee reviewed safety, PK and PD data for each cohort of D-0120 dose level (2.5 mg, 5 mg, 10 mg, 20 mg) as well as when D-0120 5 mg was combined with 40 mg febuxostat. PK evaluation for multiple dose parameters included AUC_{0-τ}, C_{max}, C_{min}, T_{max} and FI.

Results: Dose escalation of D-0120 from 2.5 mg/day to 20 mg/day was completed without any dose limiting toxicities. Most AEs occurred during the study were mild to moderate in severity and did not require any treatment before resolution. There was no SAE and no dose reduction during the treatment period. The pharmacokinetic (PK) evaluation of ascending dose levels of D-0120 suggested a dose proportional increase in drug exposure and there was no significant change of PK profile between Day 1 and Day 7 of dosing. For pharmacodynamic (PD) evaluation, the serum uric acid (UA) levels before and after D-0120 dosing was evaluated on multiple days. The UA reduction effect achieved maximum at about 4-8 hours after dosing and the effect lasted for at least 24 hours. After the 7-day dosing period, the mean percentage of UA reduction from baseline showed an increasing trend as the dose level increased.

More detailed safety, PK and PD data from multiple D-0120 dose cohorts and D-0120/febuxostat combination cohort will be presented at the meeting.

Conclusion: The oral daily administration of a novel URAT1 inhibitor, D-0120, in healthy volunteers for 7 days was well tolerated at dose levels from 2.5 mg/day to 20 mg/day. The PK profile demonstrated a dose proportional increase. D-0120 administration for 7 days resulted in significant reduction of serum UA levels. Further evaluation of this novel agent in longer treatment period and in patients with hyperuricemia and/or gout is warranted.

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OP0206 ALLANTOIN - A BIOMARKER OF OXIDATIVE STRESS - IS HIGHER IN PATIENTS WITH GOUT THAN IN HEALTHY VOLUNTEERS, AND CORRESPONDS WITH SEVERITY OF DISEASE

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Background: Uric acid can be non-enzymatically oxidized into allantoin and other products by reactive oxygen species. Allantoin has emerged as a reliable biomarker for monitoring oxidative status both *in vitro* and *in vivo*¹. In gout patients, significantly increased plasma levels of allantoin have been found compared to healthy controls².

Objectives: The aim of this pilot study was to measure allantoin as a biomarker of oxidative stress in patients with gout using newly developed UHPLC-HILIC-MS/MS method³ and to investigate whether the allantoin levels are higher in patients with more severe disease (tophaceous gout).

Methods: We used clinical data and frozen serum (-80°C) from 10 patients with chronic tophaceous gout, 10 patients with chronic gout without tophi and 10 healthy controls. Allantoin was determined in serum with sensitive UHPLC-MS/MS method using an isotopically labeled internal standard as we described before³. In addition, the concentrations of serum CRP, creatinine and uric acid were measured. Data are summarized as medians with interquartile range [IQR]. Differences between two patient groups were evaluated using the Wilcoxon signed-rank test.

Results: The median concentrations of allantoin in the serum from patients with tophaceous gout were significantly higher than in patients with gout without tophi (4.2 [2.6] vs. 3.2 μM [1.5], $p = 0.0273$). There was no significant difference in other biochemical or demographic parameters (CRP, uric acid, creatinine, BMI, weight) between these two groups. Allantoin levels in healthy controls were significantly lower (0.5 vs. 4.2 [2.6], $p = 0.0020$, 0.5 vs. 3.2 [1.5], $p < 0.0001$) (Fig. 1).

Fig. 1. Box plots of allantoin concentration in patients with tophaceous gout with tophi, without tophi and in healthy controls.

Conclusion: We have observed significantly higher levels of serum allantoin in the patients with more advanced gout with tophi compared with the patients with chronic gout without tophi. We have found elevated values of allantoin in both groups in comparison with healthy controls. In our small cohort the level of allantoin correspond with the severity of disease presented by tophi. However, further studies in large cohorts are needed. We can speculate, whether higher level of oxidative stress may contribute to increased cardiovascular risk and mortality in patients with gout (and more so in severe gout)⁴.

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Cartilage - heal thyself!

OP0207 MECHANISM OF CHONDROPROTECTIVE EFFECTS OF 2-DEOXYGLUCOSE

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Background: We recently reported that the inhibitor of hyaluronan (HA) biosynthesis, 4-methylumbelliferone (4-MU) blocked IL-1β activation of MMP13 mRNA and protein expression in human osteoarthritic (OA), bovine as well as bovine or OA cartilage explants [1]. This was a somewhat counterintuitive observation