Objectives: To compare efficacy and safety of cyclosporine (CYA) with mycophenolate mofetil (MMF) and with azathioprine (AZA) in the long-term maintenance therapy of LN.

Methods: Ninety-six patients (pts) (93 females, mean age 31.98 ± 12.78 years) with SLE and biopsy proven LN (16 pts: class III; 64 pts: class IV; 16 pts: class V ISN/RPS). Fifty-six pts entered this study at diagnosis of LN and 40 during a course of a LN flare. Twenty-five pts (30%) had Glomerular Filtration Rate (eGFR) < 60 ml/min (MDRD) and proteinuria was 3.88 ± 2.89 gr/day. Induction therapy: 3 methylprednisolone pulses followed by oral prednisone in 92 pts and oral prednisone in 4 pts; cyclophosphamide in 74% of pts, MMF in 9.4%, AZA in 5.2%, and other immunosuppressors in 11.4%. After six months, 30 pts started maintenance therapy with CYA, 32 with MMF and 34 with AZA. At induction therapy there were not significant differences between the three groups in histological classes at renal biopsy, mean serum creatinine, eGFR and proteinuria, and type of induction therapy. The mean follow-up after the beginning of the study was 15.9 years for CYA, 10.5 for MMF, 14.1 AZA. Primary endpoint was renal response at 1, 5 and 10 years defined as complete renal response: eGFR > 60 ml/min and proteinuria < 0.5 g/die, partial response: eGFR > 60 ml/min and proteinuria ≥ 0.5 g/die, no response: eGFR < 60 ml/min. Secondary endpoint: incidence of flare and safety.

Results: At the beginning of maintenance therapy, the mean serum creatinine and eGFR were similar in the 3 groups (0.92 ± 0.26 mg/dl, eGFR 109.9 ± 49.5 ml/min in CYA, 0.86 ± 0.4 mg/dl, eGFR 119 ± 44.6 in MMF, 0.85 ± 0.3 mg/dl, eGFR 106.6 ± 43.9 ml/min in AZA). Proteinuria was higher in CYA group (CYA: 2.03 ± 1.7 g/day; MMF: 0.77 ± 0.8 g/day; AZA: 1.2 ± 1.1 g/day). At the beginning of maintenance therapy, complete, partial and no response were 26.6%, 60%, and 13.4% in CYA, 53.1%, 43.8% and 3.1% in MMF and 38.2%, 58.8% and 3% in AZA group (Fig 1). At 1 year, after 6 months of maintenance therapy, in CYA group the percentage of pts in complete remission increased to 73% (vs 65.6% in MMF and 40% in AZA), at 5 years it was 80% (vs 83% in AZA and in MMF) and 88% at 10 years vs 70% in MMF and 68% in AZA (Fig 2,3,4). The percentage of non-responsive pts was stable from 1 to 10 years in the CYA group (around 13%), it slightly increased in MMF group (from 3.1 to 13.5%) and in AZA group (from 15 to 24%). During the study, SLE flares occurred in 30% of CYA group, 41% in MMF and 32% of the AZA. The average time from the beginning of the study and the first flare was 3.95 ± 2.76 years in CYA, 3.62 ± 1.60 in MMF and 5.9 ± 2.37 in AZA. No side effects were reported in 90% of pts treated with CYA, in 81.3% with MMF and in 85.3% with AZA group.

Conclusion: This is the first study comparing these 3 drugs as maintenance therapy in the long term. After 10 years of observation, CYA, AZA and MMF have proven to be effective in consolidating and maintaining the remission of LN. Of interest are the results achieved in the CYA group. Despite worse clinical conditions at the beginning of maintenance therapy, CYA allowed a rapid achievement of LN remission in the great majority of pts compared to AZA and MMF. Remission persisted over 10 years of observation. The number and type of flares and of side effects were not different between groups.

Baseline

Figure 1

After 1 year

Figure 2

After 5 years

Figure 3

After 10 years

Figure 4

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Disclosure of Interests: Lorenza Maria Argolini: None declared, Elena Elefante: None declared, Francesca Saccon: None declared, Valentina Binda: None declared, Maria Gerosa: None declared, Luigi Sinigaglia Speakers bureau: Yes, I, ve been invited speaker by Amgen, Ely Lilly, UCB, Abbvie, Roche and BMS., Piergiorgio Messa: None declared, Andrea Doria: None declared, Marta Mosca Paid instructor for: GlaxoSmithKline, Lilly, UCB, Gabriella Moroni: None declared
DOI: 10.1136/annrheumdis-2019-eular.3393

WEDNESDAY, 12 JUNE 2019

Crystals

OP0047

A GENOME-WIDE ASSOCIATION STUDY IDENTIFIED NOVEL LOCI ASSOCIATED WITH THE PROGRESSION FROM ASYMPTOMATIC HYPERURICEMIA TO GOUT

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Background: Gout is one of the commonest forms of inflammatory arthritis induced by monosodium urate (MSU) crystals that result from elevated serum uric acid (SUA) level. Thus far, we and others have performed genome-wide association studies (GWASs) of gout by comparing the genetic differences between gout cases and normouricemia controls¹⁻³ and have identified gout risk loci such as *ABCG2* and *SLC2A9*: these are similar results to those from GWASs of SUA. Meanwhile, not all hyperuricemia cases develop gout: the reason, we consider, is that there are at least two steps (Figure 1) by which normouricemic individuals develop gout.

Objectives: The first ever GWAS of clinically defined gout cases and asymptomatic hyperuricemia (AHUA) controls was performed to identify novel gout loci that aggravate AHUA into gout, as distinct from loci causing SUA elevation.

Methods: We carried out a GWAS of 945 clinically-defined gout cases and 1,003 AHUA controls followed by two replication studies. In total, 2,860 gout cases and 3,279 AHUA controls (all Japanese males) were analyzed. And also, we compared the odds ratios (ORs) for each locus in the present GWAS (gout vs. AHUA) with those in the previous GWAS (gout vs. normouricemia). Furthermore, we investigated the effect of each locus on SUA using the results from our recent GWAS meta-analysis of SUA with a total of 121,745 Japanese subjects⁴.

Results: This new approach enabled us to identify two novel gout loci (rs7927466 of *CNTN5* and rs9952962 of *MIR302F*) and one suggestive locus (rs12980365 of *ZNF724*) at the genome-wide significance level ($P < 5.0 \times 10^{-8}$) (Figure 2). The present study also identified the loci of *ABCG2*, *ALDH2* and *SLC2A9*. One of them, rs671 of *ALDH2*, was identified as a gout locus by GWAS for the first time. Comparing ORs for each locus in the present vs. the previous GWAS revealed three "gout vs. AHUA GWAS" specific loci (*CNTN5*, *MIR302F* and *ZNF724*) to be clearly associated with mechanisms of gout development which distinctly differ from the known gout risk loci that basically elevate serum uric acid (SUA) level. The effect of each locus on SUA using the results from our recent GWAS meta-analysis of SUA are consistent with those of the present study.

Conclusion: This first discovery of "AHUA to Gout" loci using a new GWAS strategy will lead to elucidation of the molecular mechanism of the last step of gout development and to the prevention of gout attacks in high-risk AHUA individuals.

Figure 1. Two steps in the development of gout.

Figure 2. Manhattan plots of the present GWAS (Gout vs. AHUA).

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Disclosure of Interests: Yusuke Kawamura: None declared, Hirofumi Nakaoka: None declared, Akiyoshi Nakayama: None declared, Yukinori Okada: None declared, Ken Yamamoto: None declared, Hiroshi Ooyama: None declared, Blanka Stiburkova: None declared, Tony Merriman Grant/research support from: Ardeabiosciences, Ironwood Pharmaceuticals, Consultant for: Ardeabiosciences, Ironwood Pharmaceuticals, Masahiro Nakatochi: None declared, Kenji Wakai: None declared, Michiaki Kubo: None declared, Kimiyoshi Ichida: None declared, Nariyoshi Shinomiya: None declared, Hirotaka Matsuo: None declared

DOI: 10.1136/annrheumdis-2019-eular.4025

OP0048

GENOME-WIDE META-ANALYSIS REVEALED MULTIPLE NOVEL LOCI ASSOCIATED WITH SERUM URIC ACID LEVELS IN JAPANESE

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Background: Uric acid is an end metabolite of purines which is produced predominantly in the liver and is excreted by the kidneys and the intestine. Genes for urate transporters and proteins associated with cell metabolism might therefore be expected to be associated with serum uric acid (SUA). Indeed, urate transporter genes such as *SLC22A12* (also known as *URAT1*), *SLC2A9* (*GLUT9*), and *ABCG2* (*BCRP*) have been markedly associated with SUA^{1,2}, hyperuricemia, and gout³⁻⁵. To date, several genome-wide association studies (GWASs) of SUA have been performed with some populations including Japanese.

Objectives: We have investigated the genetic loci that influence SUA with more than 120,000 Japanese individuals with a genome-wide meta-analysis and have compared our findings with those of previous GWASs.

Methods: We performed a genome-wide meta-analysis based on three Japanese cohorts including those of the Japan Multi-institutional Collaborative Cohort (J-MICC) Study, the Kita-Nagoya Genomic Epidemiology (KING) Study, and the BioBank Japan (BBJ). We also performed the trans-ethnic meta-analysis across the present study and the Global Urate Genetics Consortium (GUGC)-based study to carry out fine-mapping analysis.

Results: We identified 8,948 variants at 36 genomic loci ($P < 5 \times 10^{-8}$) including eight novel loci (Figure 1). Of these, missense variants of *SESN2* and *PNPLA3* were predicted to be damaging to the function of these proteins; another five loci—*TMEM18*, *TM4SF4*, *MXD3-LMAN2*, *PSORS1C1-PSORS1C2*, *HNFA4*—are related to cell metabolism, proliferation, or oxidative stress; and the remaining locus, *LINC01578*, is unknown. We also identified 132 correlated genes whose expression levels are associated with SUA-increasing alleles. These genes are enriched for the UniProt transport term, suggesting the importance of transport-related genes in SUA regulation. Furthermore, trans-ethnic meta-analysis across our own meta-analysis and the GUGC has revealed 15 more novel loci associated with SUA (Figure 2).

Figure 1. Manhattan plot for the meta-analysis of SUA in Japanese.

Figure 2. Manhattan plot for the trans-ethnic meta-analysis of SUA.

Conclusion: Our findings thus provide important insight into SUA regulation and the pathogenesis of hyperuricemia and gout, and they provide a potential basis for the development of new treatments for these diseases.

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