which have a dynamic structure, are key to homeostasis. However, the failure of these mechanisms to work synchronously can lead to morbidity complicating the course of many chronic diseases.

Objectives: To evaluate the effect of anti-atherosclerotic liquid (AAL), anti-inflammatory capsules (AIC) and anti-oxidant liquid (AOL) supplementation on the flow-mediated dilatation (FMD), inflammatory, oxidative stress and endothelial dysfunction markers in patients with selected chronic diseases

Methods: We analyzed data of 178 patients from cohorts with selected chronic diseases (Rheumatoid arthritis, familial Mediterranean fever, DM type-2, Hypertension, Multiple sclerosis, Chronic obstructive pulmonary disease, Alzheimer disease and Cancer) in this quasi-experimental study. Endothelial dysfunction was determined by FMD and serum asymmetric dimethylarginine (ADMA) levels. Serum ADMA, high sensitive C-reactive protein (hs-CRP), serum PTX3, malondialdehyde (MDA), Cu/Zn-superoxide dismutase (Cu/Zn-SOD), glutathione peroxidase (GSH-Px) levels and FMD were studied in baseline and after 12 weeks of Morinda citrifolia (AAL, 3ml once per day), omega-3 (AIC, 3 capsules once per day) and extract with Alaskan blueberry and 21 different red purple fruit vegetables (AOL, 30ml once per day). Stepwise multivariate regression analysis evaluated the association of FMD with clinical and serologic parameters.

Results: Serum ADMA, MDA, PTX3, hsCRP and albumin levels, and proteinuria were significantly decreased and CuZn-SOD, GSH-Px and FMD levels were significantly increased following AAL, AIC and AOL therapies. FMD was negatively correlated with serum ADMA, MDA, PTX3, hsCRP levels, SBP and DBP and positively correlated to CuZn-SOD and eGFR levels both at baseline and after the 12-weeks treatment period. Multivariate regression analysis revealed that ADMA and PTX3 levels were independently related to FMD both before and after AAL, AIC and AOL therapies (Table 1, Figure 1).

Conclusion: Our study shows that serum ADMA, MDA, PTX3 levels are associated with endothelial dysfunction in patients with selected chronic diseases. Short-term AAL, AIC and AOL therapies significantly improves FMD and normalizes ADMA, PTX3, hsCRP and MDA. This may have implications for adjunctive therapy in a number of chronic disorders.

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Table 1. Analysis of association between change (Δ) in FMD and relevant parameters by univariate and multivariate linear regression analysis.

	Univariate Rho (p)	Multivariate Beta (p)
Δ FMD (%) ($r^2=0.30$)		
Change		
ADMA ($\mu\text{mol/l}$)	-0.63 (<0.001)	-0.25 (0.01)
MDA (nmol/ml)	-0.58 (<0.001)	-0.18 (0.02)
SOD (U/ml)	0.48 (<0.001)	NS
GSH (U/ml)	0.02 (0.75)	NS
HOMA	-0.21 (0.001)	NS
eGFR (ml/min/ 1.73 m ²)	-0.03 (0.62)	NS
hsCRP (mg/l)	-0.45 (<0.001)	NS
PTX3 (ng/ml)	-0.49 (<0.001)	-0.21 (0.01)
SBP (mmHg)	-0.26 (<0.001)	NS
DBP (mmHg)	-0.11 (0.12)	NS
Hemoglobin (g/dl)	0.07 (0.32)	NS
Total Cholesterol (mg/dl)	-0.05 (0.49)	NS
Triglyceride (mg/dl)	-0.11 (0.12)	NS
LDL (mg/dl)	-0.12 (0.07)	NS
HDL (mg/dl)	0.02 (0.82)	NS
HbA1c (%)	-0.26 (<0.001)	NS

Figure 1. Scatter-plot graphs between FMD and ADMA, MDA, CuZn-SOD, PTX3.

and asymmetric dimethylarginine. *Am J Kidney Dis.* 2006;47(1):42-50. doi:10.1053/j.ajkd.2005.09.029.

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FRI0548

PREVALENCE AND THERAPY OF RHEUMATOLOGICAL ADVERSE EVENTS DUE TO IMMUNE CHECKPOINT INHIBITOR THERAPY

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Background: Immune checkpoint inhibitors (ICIs) have improved cancer therapy and especially clinical outcomes for patients with many malignancies [1]. ICIs lead to a higher immune system activity and subsequent attack of tumor cells. However, this effect can cause rheumatological immune related adverse events (rh-irAE), which have not yet been extensively studied.

Objectives: To determine the prevalence and type of rh-irAE in patients treated with ICIs. Additionally, our study focused on duration, severity and therapy of rh-irAE as well as the correlation between tumor response rate and patients with or without rh-irAE.

Methods: We analysed 437 patients between January 2014 and October 2019, treated with ipilimumab (anti-CTLA-4) and/ or nivolumab (anti-PD-1) or pembrolizumab (anti-PD-1) at the Department of Oncology, Hematology and Rheumatology at the University Hospital in Bonn, Germany.

Results: Of the 437 patients, 260 (60%) were males, 177 (40%) were females with a mean age of 64 years (SD $\pm$ 14) at the beginning of the ICI-therapy. 152 patients (34.8%) displayed at least one irAE.

We identified 20 patients (4.6%) with a minimum of one rh-irAE due to ICI-therapy, seven of those had a pre-existing rheumatological disease. Those 20 patients were initially treated for melanoma, lung cancer, head and neck tumor and gastrointestinal carcinoma. Rh-irAE occurred in one patient (2.6%) with ipilimumab, in nine patients (4.8%) with nivolumab, in nine patients (5.7%) with pembrolizumab and in one patient (1.9%) with a combination of ipilimumab and nivolumab.

Arthralgia developed most frequently in nine of the 20 patients (45%). Arthritis and myositis occurred with equal frequencies, in three cases each (3 patients, 15%). Furthermore, three of the 20 patients (15%) developed a psoriatic arthritis and one patient (5%) osteoarthritis. The time to the first rh-irAE after exposure to ICIs was in median 100 days (IQR 45 – 406 days). The first rh-irAE were classified as moderate severe (CTCAE [Common Terminology Criteria of Adverse Events] grade 2: 55%).

15 patients (75%) were treated with systemic corticosteroids. In three cases (15%) additional therapy with methotrexate and in one patient (5%) with tocilizumab was required. Other therapies including non-steroidal anti-inflammatory drugs and opioids were also used in eight patients. Even though patients benefited from ICI treatment, therapy had to be discontinued in nine of them (45%).

Interestingly, patients with rh-irAE had a significantly higher tumor response rate compared to patients without any irAE (95% vs. 33%; $p < 0.0001$).

Conclusion: Our results show, that rh-irAE occur under ICI-therapy and in patients with higher tumor response. However, they are not the most frequent irAE after ICI exposure: 10.2% of all irAE were rheumatological (22 rh-irAE cases in 20 patients of a total of 216 irAE cases in 152 patients). As the use of ICIs is increasing for different malignancies the incidence of rh-irAE can be expected to increase.

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FRI0549

RISK OF INVASIVE FUNGAL INFECTION IN SYSTEMIC LUPUS ERYTHEMATOSUS: A NATIONWIDE POPULATION-BASED STUDY IN TAIWAN

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Background: Infectious disease is one of the leading causes of mortality in systemic lupus erythematosus (SLE). Among these infections, invasive fungal infection (IFI) carries high mortality rate (25-70%), but the literature of IFI in SLE is limited.

Table 1. Independent risk factors of IFI in patients with SLE^a

	Candidiasis		Cryptococcosis		Aspergillosis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age>50	1.77 (1.27-2.47)	<0.001				
Diabetes mellitus	1.65 (1.16-2.35)	0.006				
End-stage renal disease	1.76 (1.29-2.41)	<0.001				
Stroke	1.77 (1.26-2.47)	<0.001	1.96 (1.09-3.53)	0.024		
Mycophenolate mofetil	2.72 (1.60-4.61)	<0.001			4.02 (1.32-12.26)	0.015
Cyclosporin					4.94 (1.61-15.10)	0.005
Cyclophosphamide	1.50 (1.07-2.10)	0.019				
Intravenous steroid	28.19 (21.17-37.52)	<0.001	63.51 (36.10-111.71)	<0.001	34.80 (15.09-80.24)	<0.001

^a All factors with $P < 0.05$ in univariate analysis were selected for Cox multivariate analysis. CI, confidence interval; HR, hazard ratio.

Figure 1. Incidence rate and incidence rate ratio of invasive fungal infection

Figure 2. Kaplan-Meier curve of invasive fungal infection-free status in SLE versus non-SLE group.

Objectives: To investigate the epidemiology and risk factors of invasive fungal infection and its subtypes, including candidiasis, aspergillosis, and cryptococcosis, in SLE patients.

Methods: All patients with newly diagnosed SLE between 1997-2012 were enrolled from Taiwan National Health Insurance Research Database, with an age- and sex-matched non-SLE control group in a ratio of 1:10. IFI was identified by ICD9 codes¹ from discharge record and validated by use of systemic anti-fungal agents. The incidence rate (IR), incidence rate ratio (IRR), cause mortality rate of IFI and its subtypes were compared. A Cox multivariate model with time-dependent covariates was applied to analyse the independent risk factors of IFI.

Results: A total of 269 951 subjects (24 541 SLE and 245 410 control) were included. There were 445 episodes of IFI in SLE group. Candida was the most common pathogen (52.8%), followed by cryptococcus and aspergillus. The IR of IFI in SLE was 20.83 per 10,000 person-years with an IRR of 11.1 (95% CI 9.8-12.6) compared to the control (figure 1). Kaplan-Meier curve also disclosed a lower IFI-free survival in SLE (figure 2). The all-cause mortality rate was similar between SLE and the control (26.7 vs 25.7%). In SLE, treatment with mycophenolate mofetil (HR=2.24, 95% CI 1.48-3.37), cyclosporin (HR=1.65, 95% CI 1.10-1.75), cyclophosphamide (HR=1.37, 95% CI 1.07-1.75), oral daily dose of steroid>5 mg prednisolone (HR=1.26, 95% CI 1.01-1.58), and intravenous steroid therapy (HR=29.11, 95% CI 23.30-36.37) were identified as independent risk factors of IFI. Similar analyses were performed for subtypes of IFI. Distinctive risk factors were found between different subtypes of IFI (table 1).

Conclusion: SLE patients have a higher risk of IFI. Intravenous steroid therapy is the most important risk factor of IFI. This study provides crucial information for risk stratification of IFI in SLE.

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FRI0550 CAN CYTOKINE GENE POLYMORPHISMS BE USEFUL FOR THE THERAPEUTIC CHOICE IN JAPANESE PATIENTS WITH RHEUMATOID ARTHRITIS?

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Background: Rheumatoid arthritis (RA) is a common autoimmune disease. It is characterized by systemic synovitis with bone erosion and joint cartilage degradation(1). Production of autoantibody is important for autoimmune disease. Cytokines play crucial roles in its pathogenesis(2). SNP distribution varies between races. Few studies have examined SNP targeted at Japanese patients. The analysis of cytokine gene polymorphisms is important factor of pathophysiology and treatment.

Objectives: This analysis was aimed to investigate the association between cytokine gene polymorphisms and autoantibody and therapeutic response in Japanese RA patients.

Methods: This study subjects consisted of 100 RA patients and 50 healthy controls. We extracted data on patient sex, age, disease duration, rheumatoid factor (RF), anti cyclic citrullinated peptide (anti-CCP) antibody and therapeutic response including methotrexate (MTX) and biological DMARDs. Genomic DNA was isolated from peripheral blood, these were genotyped for TNFα, TGFβ₁, IL-6, IL-10 and IFNγ polymorphisms. We analyzed these data using a chi-square test.

Results: IL-10 (-819 C/T and -592 C/A) revealed that there were significant decrease in the frequency of IL-10 (-819) CC genotype and (-592) CC genotype as compared to controls in RA patients. Genotyping of IL-10 showed that there was significant decrease ACC/ACC genotype (Table 1).

IFNγ (+874 A/T) revealed that there was significant decrease in the frequency of TT genotype as compared to controls (Table 1).

No significant differences in TNFα, TGFβ₁ and IL-6 genotypes and alleles frequency were observed between RA patients and control.

TGFβ₁ (+869 A/T) in patients with anti-CCP antibody positive revealed that there was significant decrease in the frequency of TT genotype as compared to patients with anti-CCP antibody negative (Table 2).

No significant association between RF and any cytokine gene polymorphism.

Analyzing cytokine gene polymorphisms could be useful for treatment with MTX and biological DMARDs.