The presence of autoantibodies to multiple killer cell immunoglobulin-like receptors is associated with nephritis in SLE patients

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Purpose Natural killer cell cytotoxicity is regulated by inhibitory receptors recognising HLA. These include the CD94/NKG2A and the killer cell immunoglobulin-like receptors (KIR). Previously we described functional autoantibodies to CD94/NKG2A, in patients with systemic lupus erythematosus (SLE). Here we investigated whether patients with SLE, primary Sjögren’s syndrome (pSS) or systemic sclerosis (SSc) have autoantibodies to KIR-receptors and whether presence of such autoantibodies correlates to clinical manifestations.

Method HEK293-transfectants expressing KIR2DL1, KIR2DL2, KIR2DL3, KIR3DL1, KIR3DL2, KIR2DL4, KIR2DS2 or KIR2DS4 were incubated with serum from 191 SLE, 121 pSS, 48 SSc patients and 100 healthy donors. Binding of human IgG to each transfectant was determined using flow-cytometry and the median fluorescence intensity (MFI) was divided by the MFI of untransfected cells. The cut-off for autoantibody-positivity was set at the mean +4 standard deviations of healthy donors. Clinical data were tested for association to the presence of anti-KIR autoantibodies using Fischer’s exact test.

Results Autoantibodies to KIR-receptors were identified in 23.0% of SLE, 10.7% of pSS and 12.5% of SSc patients compared to 4.0% of healthy individuals. Anti-KIR antibodies to all eight receptors studied were detected in SLE and pSS sera, whereas SSc sera reacted with four of the receptors. The highest titers of anti-KIR antibodies were found in SLE sera. All KIR-positive healthy donor sera and the majority of KIR-positive pSS (76.9%) and SSc (50.0%) sera reacted with 1 KIR-receptor. In contrast, 36.3% and 22.6% of the anti-KIR-positive SLE sera reacted with 2–3 and >3 KIR-receptors, respectively. Autoantibodies to >3 KIRs were associated with an increased risk for lupus nephritis (80.0% vs 27.2%, p=0.001), an increased number of ACR criteria fulfilled (7 vs 6, p=0.02), presence of anti-Sm (50.0% vs 13.6%, p=0.01) and anti-RNP (70.0% vs 23.1%, p=0.003) antibodies compared to patients without anti-KIR antibodies. Age at disease onset (21 vs 30, p=0.74), SLICC damage index (1.5 vs 1.0, p=0.31) or presence of anti-dsDNA (70.0% vs 60.5%) were not significantly different.

Conclusion Autoantibodies to KIR-receptors are found in patients with SLE, pSS and SSc. Given the association with lupus nephritis such autoantibodies may have a clinical importance.

Echocardiography for the assessment of cardiovascular burden in lupus: a single centre cohort study

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Despite major achievements in understanding the pathobiology and management of Systemic Lupus Erythematosus (SLE), cardiovascular burden remains a complex challenge in routine practice. Echocardiography emerges as a valuable non-invasive technique widely recommended for the screening, evaluation and monitoring of cardiac involvement in different SLE settings.

Objectives to evaluate the prevalence and nature of the clinical and subclinical cardiac involvement in SLE, and to identify potential relationship with several disease-related parameters.

Design and methods Retrospective observational study in 120 consecutive SLE (fulfilling either 1987 ACR or new 2012 SLICC/ACR criteria), mean age 36.9±15.2 years and mean disease duration 9.2±8.5 years, attending the outpatient rheumatology department at least once. Demographic, clinical, immunologic profile, disease activity (SLICC/ACR), organ damage (SLICC/ACR) data were collected.

Patients were assessed according to a standardised protocol focused on clinical, immunologic profile, disease activity (SLICC/ACR), severity and organ damage (SLICC/ACR); cardiac involvement (valve damage, systolic and diastolic dysfunction, pericardial...
Biological drugs (bDMARDS) have changed landscape and outcomes in various rheumatic conditions. Increased risk for infections, paradoxical reactions, autoimmunogenicity are widely acknowledged and may be responsible for treatment failure and switching among biologics.

Objective To assess drug-induced autoimmunity (serology, clinical significance) in patients with rheumatoid arthritis (RA) treated with bDMARDS.

Patients and methods Longitudinal observational study in 246 bionaive RA receiving their first bDMARD, anti-tumour necrosis factor (TNF) or non-TNF drugs, according to local treatment guidelines.

Disease activity, therapeutic response and serial autoantibody profiles (antineural (ANA), anti-dsDNA) were systematically assessed at baseline and every six months. Prevalence, clinical significance and therapeutic implications of ANA/anti-dsDNA specificities were further analysed (SPSS-19, p<0.05).

Results 214 RA received TNF inhibitors (56 infliximab, 65 adalimumab, 8 golimumab, 18 certolizumab, 67 etanercept) as first bDMADs and 32 different mechanism of action (10 rituximab, 7 mab, 8 golimumab, 18 certolizumab, 67 etanercept) as first bDMARD. Anti-dsDNA positivity was found in 10 infliximab (17.85%), 4 adalimumab (12.30%), 3 etanercept (4.47%) and one tocilizumab (6.66%), within an average of 36.5 (2-67) months.

Conclusions Development of ANA with or without anti-dsDNA specificity is typically associated with loss of response to bDMARD in RA and infrequently responsible for drug-induced lupus. Systematic evaluation of ANA/dsDNA is not recommended in routine practice, but essential in certain specific clinical settings (secondary non-responders or lupus-like symptoms).

Significantly higher rates of ANA were reported in infliximab-treated RA (30.53%) as compared to adalimumab (18.46%), etanercept (7.46%) and tocilizumab (6.66) (p<0.05); anti-dsDNA positivity was found in 10 infliximab (17.85%), 4 adalimumab (12.30%), 3 etanercept (4.47%) and one tocilizumab (6.66%), within an average of 36.5 (2-67) months.

ANA/anti-dsDNA positive status correlated with RA activity (DAS28-ESR) and loss of therapeutic response, concomitant DMARDS (leflunomide) and corticosteroids, administration adverse reactions (p<0.05).

Only four patients (1.62%; 4/246) were classified as drug-induced lupus. Three of them (infliximab, adalimumab, tocilizumab –induced) developed mild to moderate disease, with characteristic malar rash, serositis, haematological, elevated ANA and anti-dsDNA that normalised six months after bDMARD discontinuation; the fourth patient had adalimumab-induced lupus two months after drug initiation, with severe course (subacute extensive skin lesions, cytopenia, serositis) and fatal outcome.

Conclusions Development of ANA with or without anti-dsDNA specificity is typically associated with loss of response to bDMARD in RA and infrequently responsible for drug-induced lupus. Systematic evaluation of ANA/dsDNA is not recommended in routine practice, but essential in certain specific clinical settings (secondary non-responders or lupus-like symptoms).