apoptosis and autophagy. Reduced cathepsin B and D with increased cathepsin L is a phenotype suggesting reduced autophagy. Dysregulation of autophagy may be important in the pathogenesis of APS. Therefore, we aimed to determine the effect of αPL on monocyte cathepsin balance and autophagy.

Methods Healthy control (HC) monocytes were treated with 200 μg/ml of IgG purified from (n=9) patients with APS-IgG or (n=9) HC-IgG for 6 hour. Cathepsin B and D expression were measured by western blot. Cathepsin D, B, and L activity were measured using fluorescence-based assays. Intracellular proteolytic activity was determined using DQ-BSA.

Results Consistent with our previous proteomic analysis, western blots confirmed that cathepsin B and cathepsin D were down-regulated in monocytes treated with APS-IgG compared to HC-IgG. Similarly, cathepsin B and D activities were significantly reduced in monocytes treated with APS-IgG (p=0.0188 for B, 0.0323 for D). In contrast, cathepsin L activity was increased in monocytes treated with APS-IgG (p=0.0106). We then examined cathepsin activity in monocytes from patients with APS. Cathepsin L activity was increased significantly when these monocytes were treated with APS-IgG compared to HC-IgG (p=0.0257).

Lysosomal proteolysis is a key process in the late phase of autophagy. We therefore exposed HC monocytes to IgG, treated them with GM-CSF overnight and tested their intracellular proteolytic activity. APS-IgG reduced the lysosomal activity of GM-CSF-treated monocytes whereas HC-IgG had no effect.

Conclusions We found that APS-IgG regulate the expression and activity of lysosomal proteases cathepsins B/D and cathepsin L in opposite directions. Consistent with this finding, APS-IgG reduced lysosomal proteolysis in monocytes. Additional experiments are now underway to increase our understanding of how modulation of cathepsin activity and autophagy may be important in the pathogenesis of APS and to provide new therapeutic targets.

Systemic lupus erythematosus (SLE) is an autoimmune disease characterised by a loss of immunologic tolerance, production of auto-antibodies and inflammatory damage in multiple organs. We have tested the effect of a novel anti-inflammatory peptide, a fragment of alpha-1-antitrypsin, termed UBE on two animal models of SLE, MRL/lpr and NZBW/F1 mice. Treatment of MRL/lpr mice with low dose of UBE (1 microgram/kg) at early stage of disease namely, 12 weeks old mice, caused significant reduction in serum anti-dsDNA antibodies and in kidney and lung damage as determined in histopathological examination. Furthermore, a significant reduction in serum IL17, IL12 and anti dsDNA antibodies was observed in the UBE-treated mice. Isolated CD4 cells incubated with the peptide showed similar cytokine profile. Decreased levels of double negative CD4-CD8- and B220- cells were determined in lymph organs of UBE-treated animals. Similar effects were observed with NZBW/F1 mice, namely, the peptide (0.3 microgram/kg) caused significant reduction in proteinuria and, kidney and lung damage as determined in histopathological examination. The highly important SLE serum factor B-lymphotactin, a marine sponge, in a lupus preclinical model. Translation initiation via the eIF4E complex is a key step in cytokine and antibody production, and its inhibition has been successful in cancer models. Pateamine A has anti-proliferative and immunosuppressive effects. In the BXXB.Yaa strain, we tested the efficiency of Pateamine A in controlling lupus autoimmune symptoms and neurological complications. Animal treatment started when first signs of disease were present (12 weeks) and finished at the time in which the strain has a mortality rate of 50% (5 months). Our data shows that Pat A treatment reduces circulating levels of proinflammatory cytokines and autoantibodies increasing survival. An improvement in cognitive functions in treated animals was also observed with neural behaviour tests (learning/memory, and depression) together with a reduction of proinflammatory cytokines in the hippocampus. We did not observe any side effects of the treatment. Altogether our data suggests that inhibition of translation initiation has an effect in controlling disease activity at the immunological and neurological levels and open a new line of research for strategies to treat lupus and other autoimmune diseases based on the inhibition of translation at early stages.
REDUCTION OF SYSTEMIC LUPUS FLARES BY ATACICEPT IN A RANDOMISED, PLACEBO-CONTROLLED, PHASE IIb STUDY (ADDRESS II) AND ITS EXTENSION STUDY

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Purpose

Atacicept targets the B-cell stimulating factors, BLyS and APRIL, and has shown evidence of clinical response in patients with SLE. The 24 week Phase II ADDRESS II (NCT01972568) Study and its long-term extension (LTE; NCT02070978) provided data on disease activity with up to 48 weeks of atacicept treatment.

Methods

In ADDRESS II, patients were randomised (1:1:1) to receive weekly atacicept (75 or 150 mg SC injection) or placebo (PBO) for 24 weeks. Those who completed treatment were eligible to enter the LTE, to either continue on the same atacicept dose (atacicept groups), or switch from PBO to atacicept 150 mg (PBO/150 mg). The SLE flare analysis from both studies are reported here.