mofetil (MMF) are superior to micro-emulsion cyclosporine A and azathioprine respectively [6,7]. However, data regarding the use of TAC and MMF in EGPA is scarce.

**Conclusion.**— EGPA should not be a limitation to OHT, which can be performed with respect to the ISHLT guidelines. There is no optimal immunosuppressive strategy. Arrhythmia is a burden. Further data is needed.

**References**


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### A6 Cluster analysis to explore subclassification of eosinophilic granulomatosis with polyangiitis (Churg-Strauss)


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**Introduction.**— Results from descriptive studies of eosinophilic granulomatosis with polyangiitis (EGPA) suggest distinct clinical subclasses that may be determined by anti-neutrophil cytoplasmic antibody (ANCA) status. We used hierarchical cluster analysis to explore whether EGPA could be subclassified.

**Methods.**— We used standardized retrospective data for a cohort with clinical diagnoses of EGPA followed in four tertiary referral centers. Hierarchical cluster analysis involved the Ward method with 12 input variables assessed at diagnosis: constitutional symptoms; mucocutaneous, ophthalmologic, ear, nose and throat, cardiovascular, gastrointestinal, renal, and central nervous system involvement; peripheral neuropathy; non-fixed lung infiltrates; and ANCA positivity. The resulting clusters were described by their most prominent summary characteristics. The distribution of clinical variables was analyzed by ANCA status with chi-square test.

**Results.**— The dataset included 262 EGPA cases diagnosed between 1984 and 2012. ANCA were detected in 30.9% of cases. Cluster analysis revealed three clusters of 39 (cluster 1), 92 (cluster 2) and 131 subjects (cluster 3). Cluster 1 was characterized by renal involvement (84.6%) and high ANCA positivity (92.3%), cluster 2 by virtually absent renal involvement (3.3%) and ANCA positivity (4.3%) and cluster 3 by an intermediate phenotype with renal involvement (13%), ANCA positivity (31.3%) and frequent cardiovascular involvement (59.5% vs. 17.9% and 35.9% for clusters 1 and 2, respectively) and gastrointestinal involvement (42% vs. 15.4% and 12%, respectively). ANCA positivity was associated with renal disease (P < 0.0001), peripheral neuropathy (P = 0.005) and constitutional symptoms (P = 0.02).

**Conclusion.**— Cluster analysis of EGPA, although reinforcing the link between ANCA positivity and renal involvement in the disease, does not suggest that it is composed of clearly separated and mutually exclusive subclasses.

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### A7 Spleen tyrosine kinase (SYK) inhibition in experimental autoimmune glomerulonephritis (EAG)

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**Introduction.**— SYK has a critical role in immunoreceptor signalling. SYK inhibition with Fostamatinib (FOS) prevents immune-mediated injury in several animal models. The effect of SYK inhibition on autoantibody production, however, is not well defined. We aimed to address this question in EAG, an autoantibody dependent model of crescentic glomerulonephritis (CGN).

**Methods.**— In EAG, rats immunized with rat GBM antigen (α3) at day 0 develop autoantibodies to α3 and CGN by day 18, and have lung haemorrhage (LH) at day 36. In study 1, animals (n = 8/group) received either FOS 40 mg/kg or vehicle (VEH) by twice daily gavage from day 0–18, to study the effects of SYK inhibition on induction of autoimmunity. In study 2, animals received FOS 40 mg/kg or VEH from day 18–36, to study the effects of treatment on established disease. In both studies, animals were monitored until Day 36. Cytokine production by nephritic glomeruli was examined ex vivo. SYK expression in rat and human tissue was assessed by immunohistochemistry (IHC).

**Results.**— Results of studies 1 and 2 are summarised in figure 1. There was a 58% reduction in the number of α3-specific B cells in FOS treated rats (P < 0.01), as demonstrated by ELISpot assay.
Spontaneous MCP-1 production by nephritic glomeruli ex vivo was reduced following incubation with R406, the active metabolite of FOS, in a dose-dependent manner. IHC was positive for SYK in diseased rodent and human renal tissue (anti-GBM and AAV) but not in healthy controls.

Discussion.— SYK inhibition reverses CGN and prevents LH in EAG, by inhibiting both the induction of humoral autoimmunity and the effector immune response. We believe this is the first report that SYK inhibition reduces autoantibody production in a genuine model of autoimmunity. SYK is expressed in comparable human glomerular diseases.

Conclusion.— SYK inhibition may warrant further investigation as a treatment strategy in human autoimmune glomerular diseases, such as AAV and anti-GBM disease.

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A8 Serum biomarkers signature identifies patients with overt B-cell non-Hodgkin lymphoma associated with mixed cryoglobulinemia in chronic HCV infection

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Introduction.— Hepatitis C virus (HCV) is associated with B-cell disorders, including mixed cryoglobulinemia (MC) and B-cell non-Hodgkin lymphoma (B-NHL). Early diagnosis of B-NHL in HCV-infected patients is critical. We hypothesized that combination of serum biomarkers could be used to identify B-NHL associated with MC in patients with chronic HCV infection.

Methods.— One hundred and fifty-five HCV-infected patients have been exposed to drugs known to cause disease: 46 (33%) received methyldopa, 45 (32%) levamisole and cocaine, 33 (24%) PTU, 12 (9%) minocycline, two (1%) sulfasalazine and 1 (<1%) penicillamine (figure 1).


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Introduction.— The etiology of vasculitides associated with anti-neutrophil cytoplasmic autoantibodies (ANCA) remains largely unknown; however, drug-induced forms of disease exist. Reported culprits include hydralazine, minocycline, penicillamine, propylthiouracil (PTU), sulfasalazine and as recently described by our group, levamisole in the presence of cocaine. Our group has been the main clinical ANCA laboratory in New England and evaluation of positive patients is needed to identify exposures to known and potential culprit drugs.

Patients.— We conducted a systematic retrospective analysis of patients from 1989–2012 with an initial positive ANCA test by indirect capture ELISA directed against either MPO and/or PR3. For each new ANCA-positive patient, a limited discussion was held with the ordering clinician to review implications of the positive test and to identify exposure to any known culprit drugs (discussions noted in MGH ANCA test registry were used for initial data analyses).

Results.— A total of 2257 patients with positive ANCA tests were identified: 1428 (63%) were MPO-ANCA, 793 (35%) PR3-ANCA, and 38 (2%) dual MPO- and PR3-ANCA. 139 (6%) patients were exposed to drugs known to cause disease: 46 (33%) received hydralazine, 45 (32%) levamisole and cocaine, 33 (24%) PTU, 12 (9%) minocycline, two (1%) sulfasalazine and 1 (<1%) penicillamine (figure 1).