Restablishment of Immune Tolerance in ANCA-Associated Vasculitis: Defining a cohort with sustained ANCA negativity and drug free clinical remission

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Objectives

ANCA associated vasculitis is complicated by frequent disease relapses. However, a proportion of patients have re-established immunological tolerance, demonstrating sustained clinical and immunological remission, off therapy. We studied these patients to define a tolerant phenotype.

Methods

Patients at 6 international centres were identified as tolerant from clinic databases and records examined. Patients who became ANCA negative following treatment, and remained ANCA negative in remission and off immunosuppresive (IS) therapy for 2 years or more were defined as tolerant(TOL). Those with recent relapses were termed non-tolerant(NON-TOL). A subset of TOL patients were compared to NON-TOL, age matched healthy control(HC)s and patients prior to and following drug withdrawal(DW) to identify a tolerance signature.

Results

48 tolerant patients were identified. Baseline characteristics are in Table 1. Induction regimens included steroids (92% patients) and cyclophosphamide (88%). During maintenance, 67% received azathioprine. Only 14% had episodes of relapse (none > 1) prior to becoming TOL. Median time to ANCA negativity was 6 months and was similar in PR3-and MPO-ANCA (5 and 8 months respectively;p=0.50). The proportion ANCA negative at 6 months was similar to patients in the IMPROVE trial (P=0.67). Median time to stop therapy was 32 months and did not differ according to ANCA type. Median duration of persistent ANCA negativity was 71 months and median duration off IS 60 months. Analysis of PBMC in a subset of TOL patients(n=6) demonstrated higher proportion of CD24+CD38+ Breg compared to NON-TOL patients(n=3), and similar levels to HC (n=9). Proportions of Treg did not differ. Analysis of gene expression within leukocyte subsets (n=6 for TOL, NON-TOL, HC and n=2 for DW) demonstrated significant changes following drug withdrawal, and excluding these genes, over 40 genes remained differentially expressed in TOL compared with NON-TOL within CD4 compartment, with ongoing analysis of CD8, CD14 and CD19 subsets.

Conclusions

Reestablishment of tolerance occurs in both PR3- and MPO-ANCA subjects. TOL appear to have fewer relapses prior to IS withdrawal. Immunological differences are found between TOL and NON-TOL patients and these may allow a tolerance signature to be defined for customising therapy and use as end points in trial design.

Table 1

Tolerant patients	
Age current (median, range)	69 (29-87)years
Age at presentation (median, range)	57 (14-74) years
Gender	50% female
ANCA subtype	48% PR3-ANCA
Time to ANCA negativity (median, range)	6 months (0.5-120)
Duration ANCA negative	71 months (12-244)
Relapse rate	14% (none more than once)
Time to stop IS from induction	32 months (13-204)
Time off IS since stopping	20 months (22-264)