Title
Predicting autoimmune connective tissue diseases: three year follow up of an At Risk cohort identifies late progression and predicts need for therapy

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Background
Autoimmune connective tissue diseases (AI-CTD) are known to be preceded by a phase of asymptomatic ANA positivity for months to years. However, the vast majority of ANA-positive individuals never develop an autoimmune condition. Additionally, due to their complex nature, AI-CTD are often difficult for non-specialists to identify. This leads to large numbers of ANA positive individuals being referred to rheumatology, but most of these can be safely discharged. We previously recruited an At-Risk AI-CTD cohort of 150 patients with ANA and non-specific symptoms of less than 12 months duration. We previously reported that 17% of At Risk individuals met criteria for SLE or pSS after 12 months follow up and this was predicted by family history and an IFN Score. However, patients that we classified as “non-progressors” in that work may have included a diversity of clinical outcomes. Some may have progressed to meet classification criteria at later time points. Others may have had clinically significant features of autoimmunity despite not meeting classification criteria, and may have required immunosuppressant therapy for this.

Objectives
1. To present 3 year follow up data of the At Risk cohort, including more detailed analysis of the non-progressor group
2. To test the ability of baseline clinical features and biomarkers to predict these outcomes

Methods
Patients newly referred to rheumatology were recruited if they had: (i) ANA positive by any clinical assay; (ii) did not meet criteria for AI-CTD (SLE, pSS, IIM, Scleroderma); (iii) symptom duration less than 12 months. Diagnostic criteria for SLE, pSS, IIM and Scleroderma were assessed at first presentation (baseline) then 12-monthly for 3 years. Patients were given a helpline number to call for additional assessment if they had new symptoms between these visits. We categorised progression status as follows:

1. Absolute non-progressors (no clinical criteria at all time points, i.e. baseline, 12 months, 24 months, 36 months)
2. Undifferentiated CTD (U-CTD) (>=1 clinical criteria at baseline persisting at follow up but not meeting criteria)
3. Year 1 progressor (not meeting criteria for AI-CTD at baseline but meeting criteria for AI-CTD within 12 months)
4. Late progressor (not meeting criteria for AI-CTD at baseline but meeting criteria for AI-CTD later than 12 months)

We also documented whether patients had required treatment with anti-malarials (hydroxychloroquine) or immunosuppressants (methotrexate, azathioprine, biologic agent or any combination of these) at each visit. We compared clinical characteristics, routine immunology investigations and IFN Scores between these groups at baseline.

Results
3 year follow up data were available in 146/150 patients. Proportions of patients in the above categories were: Absolute non-progressors: 33/146 (23%); Undifferentiated CTD: 86/146 (59%); Year 1 progressors: 21/146 (14%); Late progressors (in years 1 – 2): 5/146 (3%). No patient progressed or required immunosuppression beyond 2 years of observation.Of patients with U-CTD, 6 were prescribed an immunosuppressant (all methotrexate). The present work therefore describes a larger group of 32/146 (22%) of At Risk individuals who developed clinically significant disease including 21 Year 1 progressors, 5 late progressors, and 6 who did not meet criteria but needed an immunosuppressant.

Clinical features had limited utility in predicting these outcomes. Of 31 patients with the least objective evidence of AI-CTD (no clinical criteria at baseline), although most remained well, outcomes were not wholly benign. 1 progressed to meet criteria within 1 year, 2 progressed at 1-2 years, 3 were prescribed hydroxychloroquine and 1 was prescribed an immunosuppressant (methotrexate). Nevertheless, the 108 patients with at least 1 criterion at baseline had the highest risk. Of these, 20 progressed to meet criteria within 1 year, 2 progressed at 1-2 years, the others all had U-CTD. 35 were prescribed hydroxychloroquine

and 13 were prescribed an immunosuppressant. No one criterion at baseline was more predictive of long-term outcomes. More objective criteria such as thrombocytopenia were not more predictive than the “softer” signs such as alopecia and mucosal ulcers. There was also no association between number of ENA or levels of C3 and C4 and progression to any of these outcomes.

As we previously reported, interferon scores were associated with progression to meet criteria within 12 months. These associations were stronger than our previous analysis comparing Year 1 progressors with absolute non-progressors. We therefore also tested whether IFN Score could also predict the other adverse outcomes of late progression and requirement for an immunosuppressant. Late progression was not predicted by baseline IFN Scores. However, within U-CTD, patients who required an immunosuppressant had higher expression of IFN Score A ($p=0.011$) and IFN Score B ($p<0.001$).

Conclusions

Among ANA-positive referrals, progression to AI-CTD usually occurred within 12 months but a substantial number progressed later. No clinical feature or routine laboratory test could eliminate the possibility of an adverse outcome. Of patients who never met criteria for an AI-CTD, a proportion still developed clinically significant symptoms with either persistent features of autoimmunity or need for long term therapy. IFN Scores had a unique value in predicting these outcomes.

At Risk individuals who ultimately developed clinically significant disease are therefore immunologically but not clinically distinctive. Future work will incorporate biomarkers into clinically applicable risk models to allow earlier exclusion of AI-CTD or trials of preventative treatment.