Longitudinal ANA titers

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BACKGROUND

Autoantibodies to cellular antigens, commonly referred to as antinuclear or anticellular antibodies (ANAs), are a hallmark of systemic lupus erythematosus (SLE), with greater than 95% of SLE patients ANA+. ANAs are also a marker of subclinical autoimmunity, with ~13% of the general adult population (18% of females and 10% of males) ANA+. Risk factors for developing subclinical autoimmunity and predictors for progression to clinical autoimmune phenotypes are poorly understood. An important step is to understand trajectories of ANA positivity and titers within individuals over time, and factors associated with these changes. We performed an exploratory analysis of electronic health record (EHR) data to assess intraindividual variation in ANAs longitudinally.

METHODS

Utilizing our academic health center's EHR with records dating from 1999, we extracted ANA (by immunofluorescence, IFA) and basic demographic data for all patients with at least one ANA. We also extracted ANA data for a subset of patients with validated SLE (by SLICC or ACR criteria).

- A titer of ≥1:80 was considered "positive", and a titer of < 1:80 was considered "negative".
- We investigated the overall trend in ANA titer between each patient's first and last observation by summarizing the number (and percentage) of SLE and control patients with a "titer decrease", "titer increase", or "stable titer". "
- Evaluated changes in ANA titer over time using a baseline category logit mixed model with a patient-level random intercept. A separate fixed parameter for time for each comparison of a non-negative titer relative to a negative titer was obtained.
- Estimated the odds of having a decreased titer value relative to a stable/increased titer at the next successive draw for various covariates using a generalized linear model.

RESULTS

6546 unique patients had at least two valid ANA-IFA results. A subset of 52 of these patients had validated SLE, the remaining were considered "controls". The majority of total patients were female (85%) and not Hispanic (90%) with a median age of 50 years. The mean number of valid ANA titers per patient was 2.6 (SD = 1.4), with a range of 2 to 20.

- Longitudinally, ANA titer strength varied (p<0.001).
- With the exception of a higher average odds of having a positive titer with each successive year [OR 1.84 (95% CI 1.62, 2.09)], no clear pattern of change between titers was identified.

***Table 1*. Summary changes for ANA titer from first to last observation over time.**

	Controls	SLE	Total
Titer Increase	2181 (33%)	11 (21%)	2192 (33%)
No Change	2129 (33%)	23 (44%)	2152 (33%)
Titer Decrease	2184 (34%)	18 (35%)	2202 (34%)
	6494	*52*	*6546*

***Table 2*. Summary statistics of number of days between first and last ANA observations for the patients with at least two valid draws:**

	Controls	SLE	Total
Mean (SD)	1359 (1453)	1434 (1478)	1359 (1453)
Median (Q3-Q1)	825 (246-1984)	820 (244-2296)	825 (246-1990)
Min, Max	[1-7198]	[22-5337]	[1, 7198]
	6494	*52*	*6546*

The majority of both controls and SLE had no change or a decrease in ANA from first to last observation; Figure 1 displays spaghetti plots for a random sample of patients.

***Figure 1*. ANA titers over time for 9 randomly selected patients per panel**

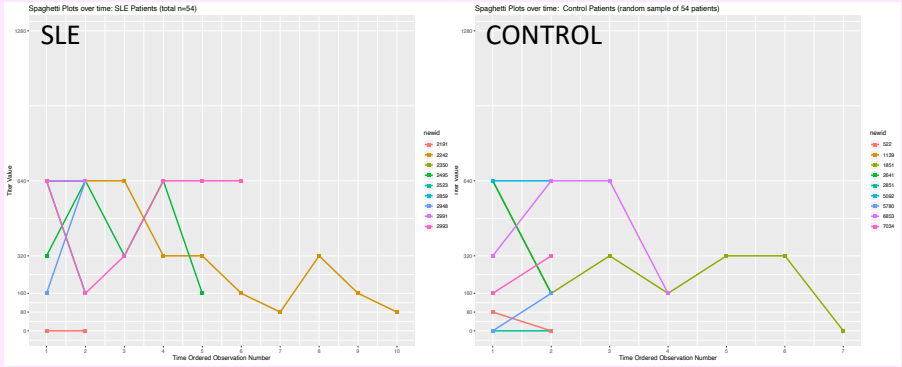
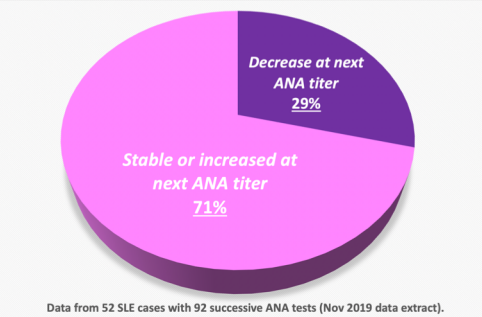


***Figure 2*. Proportion of SLE patients with changes in successive ANA titers relative to the prior titer.**



RESULTS (Cont.)

- 32% of successive ANA draws had a decreased titer relative to the preceding titer.
- Among persons who were ANA-positive at baseline, 1118 (22%) of controls and 2 (4%) of SLE subsequently had a negative ANA.
- 29% of successive draws among the SLE cases decreased (Fig 2).
- Controlling for basic demographic characteristics, being male increased the odds of having a decreased titer at the next successive draw (OR: 1.24, 95% CI: 1.11 – 1.40) .
- Each successive year between ANA titers increases the odds of having a decreased titer (OR: 1.02, 95% CI: 1.01-1.04).

CONCLUSIONS

Although based on prior series of cross-sectional data it has been observed that ANAs tend to increase with age, longitudinal data of intra-individual patterns are lacking. Our data provide initial evidence of intra-individual variability. What is most novel about our findings is the high degree of variability in ANA titers within the same individual, including decreases in titer value over time. Common clinical perception is that in SLE ANAs remain positive once antibodies are accrued, and that repeat testing would not influence management or alter a clinical diagnosis. **Our data suggest that ANA titers may be more dynamic than previously accepted.**

We will further investigate demographic and other covariates to evaluate associations and further discern titers in different clinical phenotypes over time.