Evaluating Transitions from Pre-Rheumatoid Arthritis to Clinically-Apparent Inflammatory Arthritis

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INTRODUCTION:

- Pre-Rheumatoid Arthritis (RA) is a period of elevations of antibodies to citrullinated protein antibodies (ACPA) before clinically-apparent inflammatory arthritis (IA).
- Gaps in understanding Pre-RA include:
  - How symptoms evolve in transition to IA
  - Progression to IA in ACPA+ asymptomatic individuals
  - How ACPA+ individuals who are prospectively followed to IA compare to those with new RA found through standard rheumatology referrals.

METHODS:

Participants, no IA at baseline:

- ACPA (+) (CCP3, Inova) with no history or examination evidence of IA
- Recruited from clinics, health fairs, and screening of relatives of patients with RA
- Followed prospectively for IA development

Participants, EarlyRA:

- CCP3+ patients with a baseline study visit <30 days since RA diagnosis

Data Collection:

- Questionnaires capturing pain, stiffness and swelling in 68 joints
- Physical examination
- Disease activity (DAS28CRP)
- Autoantibody levels

Statistical Analysis:

- Independent samples t-test
- Chi Square

RESULTS:

- 19/84 (22%) of CCP3+ participants developed IA ('converters') at a median of 509 days of follow up. 79% of them met 2010 ACR/EULAR criteria at time of IA identification.
- At baseline, converters reported longer duration of morning stiffness and had higher levels of CCP3 and RFIgM compared to non-converters.
- Converters had 2 trajectories of symptoms prior to IA: 1) waxing and waning or 2) period of minimal symptoms followed by steady worsening of symptoms.
- Converters with no joint symptoms at baseline (n=5) trended towards a longer duration to developing IA compared to those with baseline symptoms (median 686 days vs 363 days, p~0.09).
- At the time of diagnosis of IA, converters had lower levels of symptoms, DAS28CRP and CCP3 than patients with EarlyRA identified through standard clinic referrals

Table 1. Baseline characteristics of CCP+ subjects who did/did not develop IA

	CCP+ Non-Converter to IA (n=65)	CCP+ Converter to IA (n=19)	p-values*
Age, mean (SD)	58 (16)	57 (9)	0.91
% Female	64%	74%	0.83
% NHW	85%	68%	0.26
Any swollen joint (self-report)	7%	26%	0.06
Any painful joint (self-report)	58%	63%	0.44
Any stiff joint (self-report)	29%	37%	0.51
Any joint symptoms (self-report)	61%	74%	0.12
# of painful joints, mean (SD) [self-report]	2 (5)	4 (5)	0.43
# of stiff joints, mean (SD) [self-report]	1 (5)	4 (9)	0.12
# of swollen joints, mean (SD) [self-report]	1 (1)	1 (1)	0.39
# of minutes of morning stiffness, mean (SD)	**9 (23)**	**28 (58)**	**<0.01**
Pain level on VAS, mean (SD)	2 (2)	2 (2)	0.18
Fatigue level on VAS, mean (SD)	2 (2)	3 (3.0)	0.21
Overall well-being on VAS, mean (SD)	1 (2)	2 (2)	0.34
DAS28CRP	1.6 (0.5)	1.6 (0.5)	0.89
CCP3 level	**72 (73)**	**129 (106)**	**<0.01**
RF level	**10 (23)**	**33 (46)**	**<0.01**

Abbreviations: CCP=cyclic citrullinated peptide antibody; SD=standard deviation; NHW=non-Hispanic white; VAS=visual analog scale; DAS28CRP=Disease Activity Score 28 Joints C-Reactive Protein; RF=rheumatoid factor

Table 2. Comparison of disease activity in individuals 'converting' to IA during prospective follow-up with individuals presenting with EarlyRA through standard referrals to rheumatology clinics

	Converters at IA identification (n=19)	EarlyRA* (n=57)	p-value
Age, mean (SD)	58 (8)	53 (12)	0.09
% Female	71%	66%	0.76
% NHW	79%	67%	0.53
# of painful joints, mean (SD)	**8 (8)**	**24 (14)**	**<0.01**
# of stiff joints, mean (SD)	**5 (6)**	**23 (17)**	**<0.01**
# of swollen joints, mean (SD)	**3 (4)**	**16 (12)**	**<0.01**
Morning stiffness (minutes), mean (SD)	**22 (48)**	**59 (57)**	**0.03**
DAS28CRP	**2.8 (0.9)**	**3.9 (1.2)**	**<0.01**
CCP3 level	**145 (99)**	**213 (82)**	**0.01**
RF level	49 (52)	67 (46)	0.20

***EarlyRA defined as subject being within 30 days of initial identification of IA by a rheumatologist** Abbreviations: IA=inflammatory arthritis; CCP=cyclic citrullinated peptide antibody; SD=standard deviation; DAS28CRP=Disease Activity Score 28 Joints C-Reactive Protein; RF=rheumatoid factor

CONCLUSIONS:

- **For ACPA-positive individuals without IA at baseline, self-reported morning stiffness and high levels of CCP3 and RFIgM are associated with developing inflammatory arthritis.**
- These findings contribute to understanding the natural history of RA and building prediction models for future disease as well as to correlate biomarker changes with symptoms.
- Lower disease activity in 'converters' to IA compared to EarlyRA could indicate that prospective follow-up of ACPA+ individuals can identify IA at a time point where disease activity and CCP3 levels are less than in standard referral patterns, perhaps indicating a stage of disease more responsive to therapy.

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