CHEST Online Supplement

Functional Impact of a Spectrum of Interstitial Lung Abnormalities in Rheumatoid Arthritis

Tracy J. Doyle, MD, MPH; Paul F. Dellaripa, MD; Kerri Batra, MD; Michelle L. Frits, BA; Christine K. Iannaccone, MPH; Hiroto Hatabu, MD, PhD; Mizuki Nishino, MD; Michael E. Weinblatt, MD; Dana P. Ascherman, MD; George R. Washko, MD, MMSc; Gary M. Hunninghake, MD, MPH; Augustine M. K. Choi, MD; Nancy A. Shadick, MD, MPH; and Ivan O. Rosas, MD, FCCP

CHEST 2014; 146(1):41-50

e-Appendix 1.

Material and Methods

BRASS Registry: All BRASS subjects had a diagnosis of RA determined either by the 1987 American College of Rheumatology criteria (97.2%) or based on the opinion of their rheumatologist (2.8%). Physician questionnaires were filled out at baseline and annually thereafter. For past medical history, including pulmonary fibrosis, bronchiectasis, and bronchiolitis obliterans with organizing pneumonia, the questionnaire included the questions, "Has your patient **ever had the following manifestations related to RA**?" (baseline) and "Has your patient experienced the following manifestations related to RA in the PAST YEAR?" (follow-up). For asthma and COPD, the questionnaire included the questions, "**Since his/her diagnosis of RA**, has your patient developed any of the following **co-morbidities or drug-related toxicities?**" (baseline-COPD only) and "Has your patient developed any of the following co-morbidities or drug-related toxicities in the PAST YEAR?" (follow-up). These questionnaires also included a 28 joint count used to calculate the DAS-CRP3 score. Additional disease activity information was provided by the patient questionnaire with the RA Disease Activity Index (RADAI), which was calculated without joint stiffness due to that question inadvertently being absent from the initial questionnaire. Functional status was assessed with the MDHAQ.

Sequential Reading Method: In an unblinded manner, the first reader evaluated those CT scans with 1.0 mm and 5.0mm sections to assess concordance. There was a 95% concordance in reads and as such, subsequent readers used the 5.0mm sections (available for all CT scans). In brief, visual inspection of HRCTs was performed by three readers (2 radiologists and 1 pulmonologist). Radiologically severe ILA were defined as bilateral fibrosis in multiple lobes associated with honeycombing and traction bronchiectasis in a subpleural distribution. ILA were defined as changes affecting >5% of any lobar region including nondependent ground-glass or reticular abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, or traction bronchiectasis. Scans with focal or unilateral

 DOI: 10.1378/chest.13-1394

ground-glass attenuation, focal or unilateral reticulation, and patchy ground-glass abnormality (<5% of the lung) were considered indeterminate.

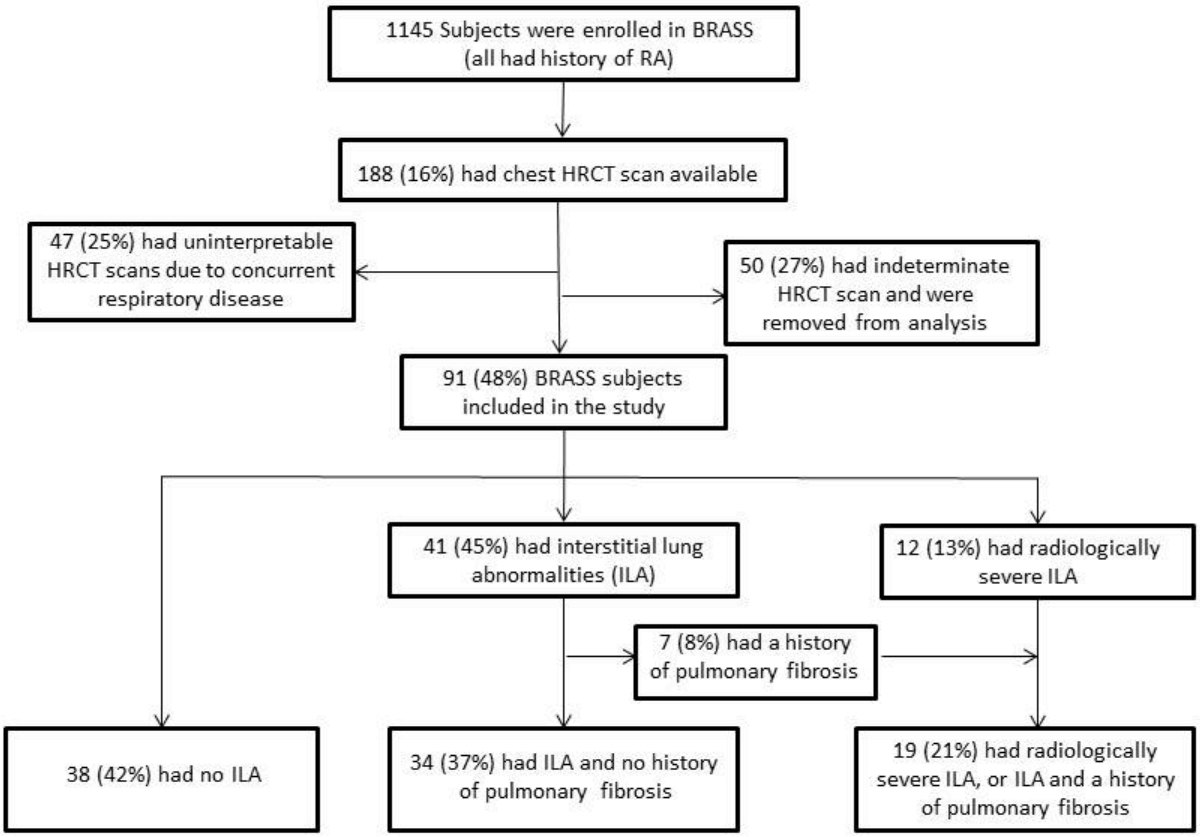
Results

Proximity of CT Scan and PFTs to BRASS Visit: In subjects with radiologically severe ILA, the average length of time between the CT scan and BRASS visit was 7.7 months (range 0 to 4.3 years) and between PFTs and BRASS visit was 10.3 months (range 0 to 4.4 years). In subjects with ILA, the average length of time between the CT scan and BRASS visit was 14.4 months (range 0 to 6.6 years) and between PFTs and BRASS visit was 6.8 months (range 0 to 2.4 years). A separate analysis was undertaken excluding individuals with a difference in time between CT scan or PFTs and BRASS visit of >2 years [no ILA (n=4), ILA (n=8), radiologically severe ILA (n=3)]. Between no ILA and radiologically severe ILA, there was a strengthening of the difference in pack years of smoking [9±16 vs. 27±23 (p=0.052)] and a weakening of the association with cough [21% vs. 56% (p=0.088)] and FEV1 [90±20 vs.75±15 (p=0.11)]. Between no ILA and ILA, there was a weakening of the difference in cough [21% vs. 46% (p=0.051)], dyspnea [24% vs. 50% (p=0.055)], FEV1% [90±20 vs. 78±24 (p=0.08)], and FVC% [90±17 vs. 82±19 (p=0.15)].

 DOI: 10.1378/chest.13-1394

CHEST™ Online Supplement

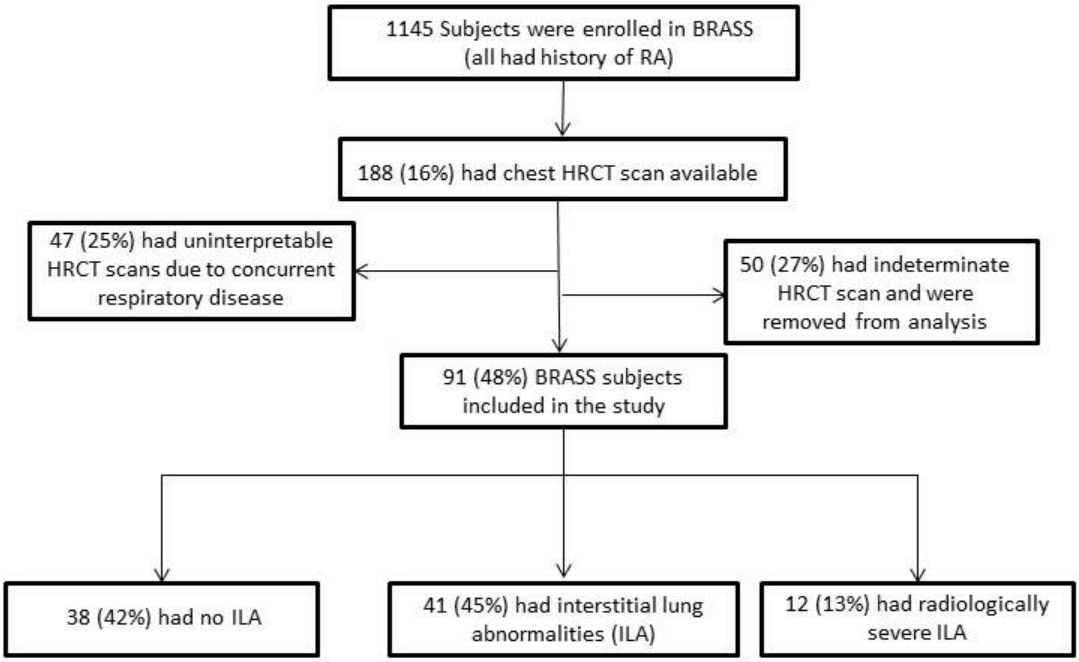
e-Figure 1: A flow diagram of study enrollment divides participants into three groups according to presence and subtype of subclinical interstitial lung abnormalities and a previous history of pulmonary fibrosis.



Abbreviations: BRASS = Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study; RA = rheumatoid arthritis; HRCT = high resolution computed tomography; ILA = interstitial lung abnormalities

 DOI: 10.1378/chest.13-1394

e-Figure 2: A flow diagram of study enrollment divides participants into three groups according to presence and subtype of subclinical interstitial lung abnormalities, independent of a history of pulmonary fibrosis.



Abbreviations: BRASS = Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study; RA = rheumatoid arthritis; HRCT = high resolution computed tomography; ILA = interstitial lung abnormalities

 DOI: 10.1378/chest.13-1394

CHEST™ Online Supplement

Tables

e-Table 1: Indication for exclusion of BRASS CT scans

Reason for Exclusion	Number
Pulmonary effusion	25 (53%)
Pneumonia	9 (19%)
Post-surgical changes (mass/cancer)	4 (9%)
Atelectasis	3 (6%)
Artifact	3 (6%)
Metastatic cancer	2 (4%)
Pulmonary embolism	1 (2%)
TOTAL	**47**

 DOI: 10.1378/chest.13-1394

e-Table 2: Indications for CT scans

Indication	No ILA (n=38)	ILA (n=34)	Radiologically severe ILA (n=12)
1. Chronic respiratory symptoms*	5 (13%)	10 (29%)	0 (0%)
2. Follow-up pulmonary fibrosis +/- symptoms (hypoxia, dyspnea)	1 (3%)	1 (3%)	12 (100%)
3. Acute infectious symptoms†	3 (8%)	2 (6%)	0 (0%)
4. Cancer staging and follow-up	7 (18%)	2 (6%)	0 (0%)
5. Lung nodule follow-up	10 (26%)	8 (24%)	0 (0%)
6. Assess for vascular or cardiac etiology‡	6 (16%)	1 (3%)	0 (0%)
7. Other**	6 (16%)	10 (29%)	0 (0%)

* Cough, shortness of breath, dyspnea on exertion

† Fever, weight loss, cough, shortness of breath, chest pain

‡ Pulmonary embolus, aortic dissection, aortic aneurysm, coronary artery disease

** Column 1: Bronchiectasis (n=1), lymphadenopathy (n=2), evaluate for pneumothorax (n=1), follow-up for methotrexate (n=1), polyarthralgias/rule-out sarcoid (n=1);
Column 2: MAI (n=1), COPD (n=1), Follow-up for methotrexate/rituximab (n=1), trauma (n=1); follow-up findings on previous imaging: PNA x 3, thoracic aortic aneurysm, r/o ILD, right apical scar (n=6).

Abbreviations: ILA = interstitial lung abnormalities; MAI = mycobacterium avium infection; COPD = chronic obstructive pulmonary disease; PNA = pneumonia

 DOI: 10.1378/chest.13-1394

e-Table 3: Baseline characteristics of BRASS subjects stratified by interstitial lung abnormalities (ILA), excluding subjects indeterminate for ILA (n=50) or unable to assess (n=47). Individuals with ILA and a history of pulmonary fibrosis (n=7) are included in the radiologically severe ILA group.

Variable*	Number (%) or Mean±Std Dev where appropriate		
	No ILA n=38 (67%)	**Radiologically severe ILA n=19 (33%)**	**P-value**
Demographic Parameters			
Age (years)	53±11	65±9	0.0012
Pack years of smoking	9±17	16±19	0.15
Respiratory Parameters			
Cough	8 (21%)	10 (53%)	0.032
Dyspnea	8 (21%)	10 (53%)	0.032
Spirometric Parameters	**n=14**	**n=14**	
FEV_1 (% of predicted) †	92±18	73±23	0.034
FVC (% of predicted) †	94±18	73±23	0.040
	n=8	**n=6**	
TLC (% of predicted) †	86±16	79±32	0.24
	n=8	**n=7**	
DLco (% of predicted) †	77±18	52±24	0.068
Exercise Capacity	**n=5**	**n=3**	
Six-minute walk distance	1715±206	1451±281	0.40

* Data missing: Pack years of smoking (n=10); † Forced expiratory volume at 1 second (FEV1). Forced vital capacity (FVC). Total lung capacity (TLC). Diffusion capacity of carbon monoxide (DLco). Pre-bronchodilator pulmonary function measurements presented.

 DOI: 10.1378/chest.13-1394

e-Table 4: Baseline characteristics of BRASS subjects without a history of pulmonary fibrosis, stratified by interstitial lung abnormalities (ILA), excluding subjects indeterminate for ILA (n=50) or unable to assess (n=47). Individuals with ILA and a history of pulmonary fibrosis (n=7) are included in the ILA group.

Variable*	Number (%) or Mean ± Std Dev where appropriate		
	No ILA n=38 (48%)	**ILA n=41 (52%)**	**P-value**
Demographic Parameters			
Age (years)	53±11	67±10	<0.0001
Pack years of smoking	9±17	21±34	0.035
Respiratory Parameters			
Cough	8 (21%)	18 (44%)	0.035
Dyspnea	8 (21%)	18 (44%)	0.035
Spirometric Parameters	**n=14**	**n=23**	
FEV_1 (% of predicted) †	92±18	68±27	0.0034
FVC (% of predicted) †	94±18	73±23	0.0064
	n=8	**n=7**	
TLC (% of predicted) †	86±16	78±15	0.34
	n=8	**n=7**	
DLco (% of predicted) †	77±18	69±13	0.40
Exercise Capacity	**n=5**	**n=3**	
Six-minute walk distance	1715±206	1382±388	0.40

*** Data missing:** Pack years of smoking (n=12); † Forced expiratory volume at 1 second (FEV1). Forced vital capacity (FVC). Total lung capacity (TLC). Diffusion capacity of carbon monoxide (DLco). Pre-bronchodilator pulmonary function measurements presented.

 DOI: 10.1378/chest.13-1394

e-Table 5: Characteristics of BRASS subjects stratified by interstitial lung abnormalities (ILA), excluding subjects unable to assess (n=47).

Variable	Number (%) or Mean ± Std Dev where appropriate			
	No ILA n=38 (28 %)	**Indeterminate ILA n=50 (37%)**	**ILA n=34 (25%)**	**Radiologically severe ILA n=12 (9%)**
Demographic Parameters				
Age (years)	53±11	65±10	68±10	65±7
Pack years of smoking	9±17	13±20	23±36	19±22
Rheumatoid Arthritis Parameters				
Rheumatoid Factor Level	90±165	146±320	319±638	415±731
Rheumatoid Factor Pos	21 (60%)	30 (63%)	26 (81%)	9 (82%)
Anti-CCP Level †	81±122	111±123	190±138	158±114
Anti_CCP Antibody Pos †	16 (43%)	28 (57%)	28 (88%)	9 (82%)
HLADR1 Shared Epitope	0.74±0.75	0.90±0.74	0.86±0.83	0.89±0.78
DAS28-CRP3 Score †	3.52±1.49	3.70±1.45	4.10±1.62	4.36±1.96
MDHAQ Score †	0.59±0.48	0.71±0.64	0.82±0.55	0.89±0.45
Modified RADAI †	3.28±1.89	3.40±2.13	3.54±2.19	4.45±1.76
Total Swollen Joints	6±7	5±7	7±6	11±8
Medication Use				
TNFα Inhibitor Use †	23 (61%)	28 (56%)	19 (56%)	10 (83%)
Methotrexate Use	30 (79%)	38 (76%)	5 (15%)	10 (83%)
Respiratory Parameters				
Cough	8 (21%)	16 (32%)	15 (44%)	7 (58%)
Dyspnea	8 (21%)	22 (44%)	16 (47%)	8 (67%)
Spirometric Parameters	**n=14**	**n=18**	**n=18**	**n=9**
FEV_1 (% of predicted) †	92±18	72±16	69±27	78±18
FVC (% of predicted) †	94±18	78±14	75±21	77±18
	n=8	**n=8**	**n=7**	**n=6**
TLC (% of predicted) †	86±16	80±12	78±15	79±32

 DOI: 10.1378/chest.13-1394

	n=8	n=6	n=7	n=7
DLco (% of predicted) †	77±18	78±22	69±13	52±24
Exercise Capacity	**n=5**	**n=3**	**n=3**	**n=3**
Six-minute walk distance	1715±206	1402±298	1382±388	1451±281

Data missing: Pack years of smoking (n=16), Rheumatoid factor (n=8), Anti-CCP (n=5), HLADR1 (n=40), DAS28 (n=3), MDHAQ (n=12), RADAI (n=12), Total swollen joints (n=1); †Anti-cyclic citrullinated peptide (anti-CCP). Disease Activity score-28 - c-reactive protein (3 variable) (DAS28-CRP3). Multi-Dimensional Health Assessment Questionnaire (MDHAQ). Modified Rhematoid Arthritis Disease Activity Index (RADAI without joint stiffness). Tumor necrosis factor alpha (TNFα). Forced expiratory volume at 1 second (FEV1). Forced vital capacity (FVC). Total lung capacity (TLC), Diffusion capacity of carbon monoxide (DLco). Pre-bronchodilator pulmonary function measurements presented.

 DOI: 10.1378/chest.13-1394