

RA PULMONARY MANIFESTATION

Dr.Kooranifar-IUMS

- RA Produces Significant Disability And Shortens Survival (5-10 years).
- Relative Risk Of Cardio-Pulmonary Disease, Infection, Osteoporosis With Fractures & Lymphoma Increased Three Times Compare To The General Population.
- Lung Involvement Occurs In 60-80% Of RA Patients, Many Of Whom (29-68%) Are Asymptomatic.

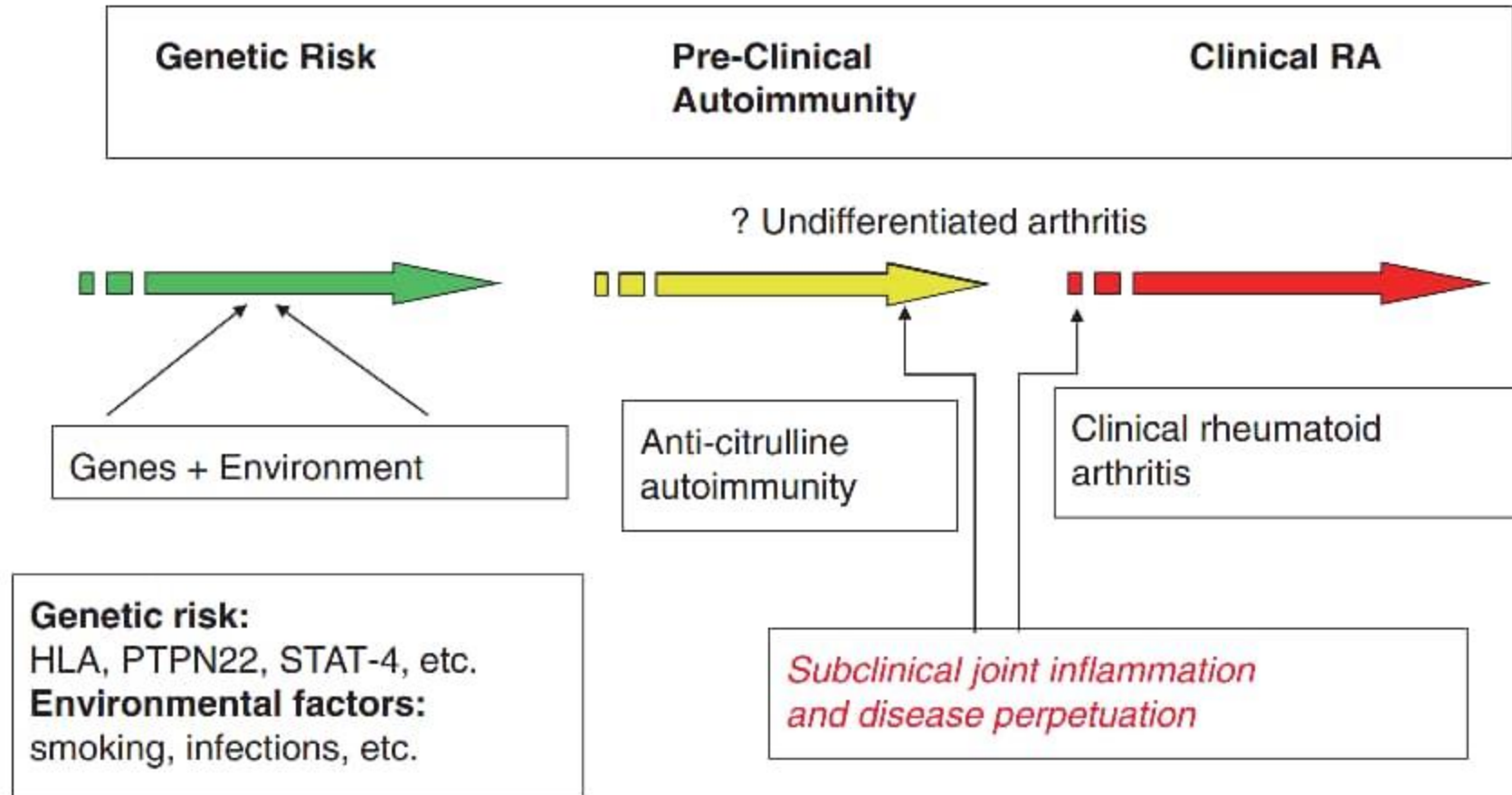
Initiation of RA-related autoimmunity in the lung: possible contributions of genes and environment (e.g. smoking, infection) to local inflammation (e.g. iBALT)



Persistence and expansion of autoimmunity; detectable in circulation as RA-related autoantibodies (*Preclinical RA*)



Development of articular disease that is classifiable as RA



- Has A Male Predominance
- Rheumatoid Nodule → Increase IPF
- High Titers of Rheumatic Factor → Increase IPF
- Smoking:

Increase IPF

Increase Anti CCP Titers

Possible risk factors for rheumatoid arthritis-associated interstitial lung disease

Stronger evidence

Smoking

Male sex

Advanced age

Rheumatoid arthritis disease score

Weaker evidence

Methotrexate

Anti-TNF agents

Anti-cyclic citrullinated antibodies

Genetics

TNF tumor necrosis factor

- Seropositive RA Actually Starts In Lung
- Early Diseases → Peribronchial Lymphocytic Infiltration
- Long Standing Disease → Fibrosis Predominance (Honeycombing)
- Both NSIP And UIP Are Present

- In RA UIP Is Associated With A Worse Outcome Than NSIP
- UIP Has A Worse Outcome In RA Than Other CTDs
- RA- Related UIP Was Better Than The Outcome In IPF
- Minor Pulmonary Fibrosis Was Seen In 60% Of Patient (Some Without Clinical Evidence Of ILD)

- Most Frequent Symptom/Sign :

- Exertional Dyspnea
- Bilateral Basal Crackles
- Tachypnea
- Cyanosis
- Right Heart Failure

- A Strong Predictor of Clinical Decline Is A Gas Transfer Less Than 55% of Predicted At Presentation

LUNG MANIFESTATIONS

Interstitial pulmonary fibrosis

Organizing pneumonia

Obliterative bronchiolitis

Follicular bronchiolitis

Bronchiectasis

Vasculitis

Nodules

Pleural disease

Lymphocytic interstitial pneumonia

Drug induced

Bronchiectasis without fibrosis^a

Findings of fibrosis (i.e., traction bronchiectasis and bronchiolectasis, intralobular interstitial thickening, irregular interlobular septal thickening, irregular interfaces)^a

Honeycombing

Ground-glass opacity^a

Peripheral and subpleural predominance of fibrosis or ground-glass opacity^{a,b}

Lower lung zone and posterior predominance^{a,b}

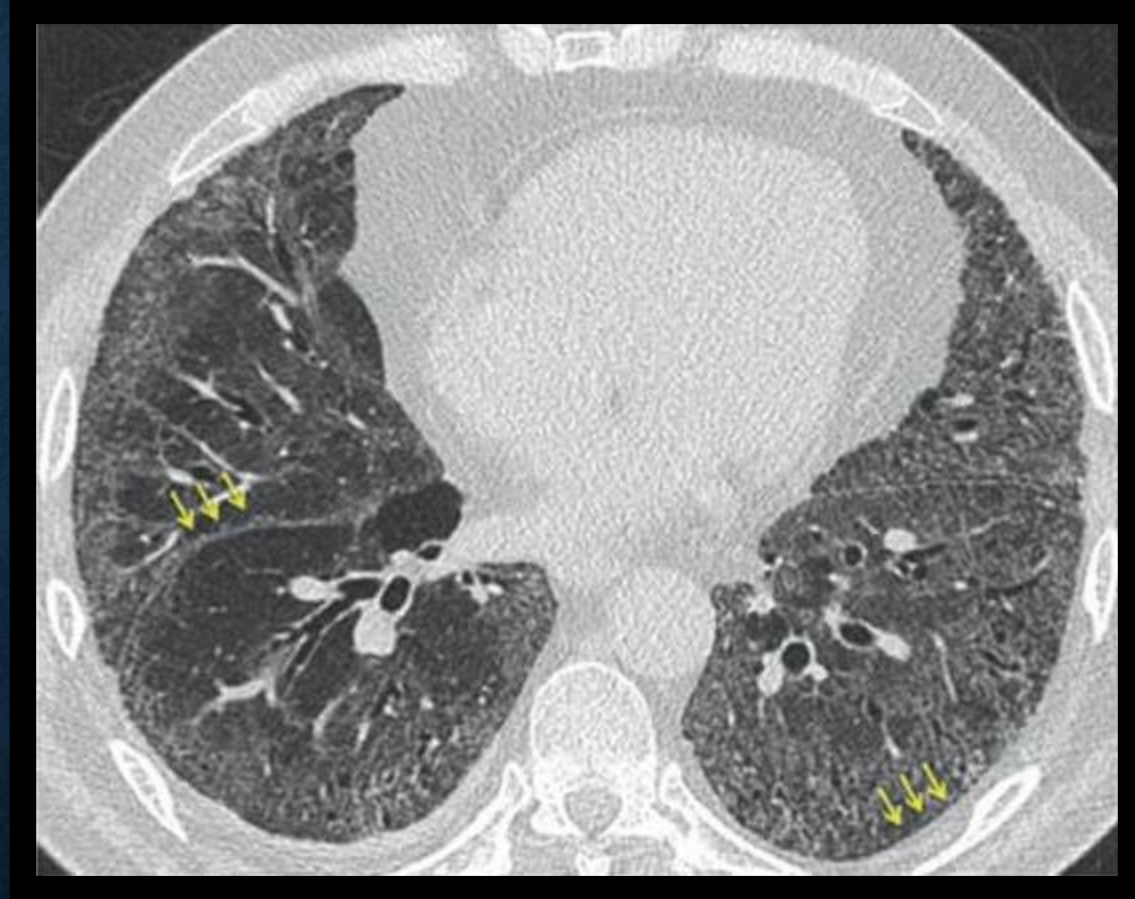
Pleural thickening or effusion^{a,b}

Small centrilobular nodules (follicular bronchiolitis)

Large (rheumatoid) nodules

Findings of bronchiolitis obliterans (i.e., air trapping, mosaic perfusion)

RA HRCT Finding

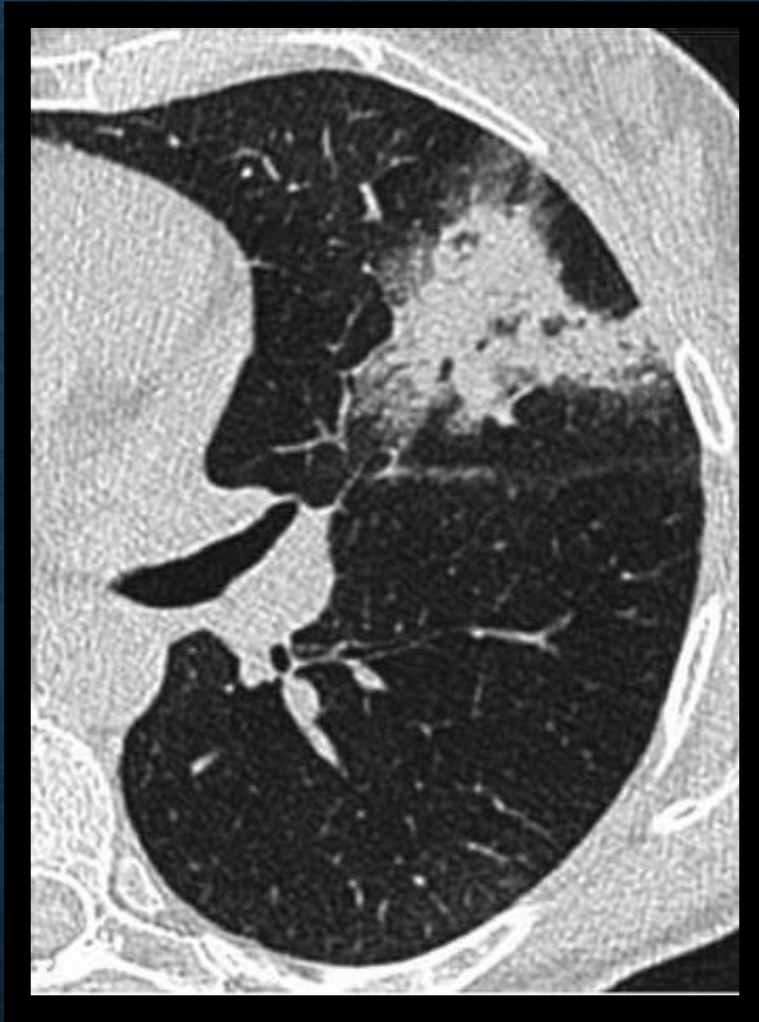


NSIP

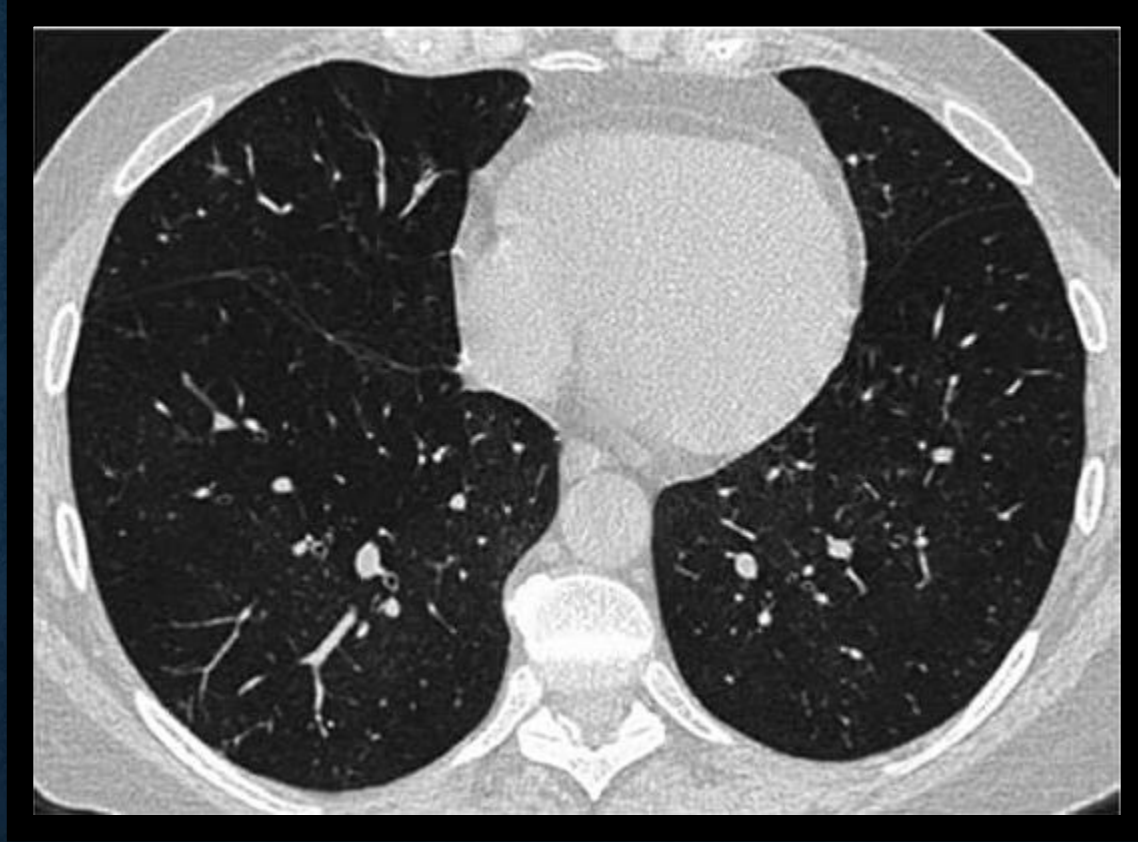




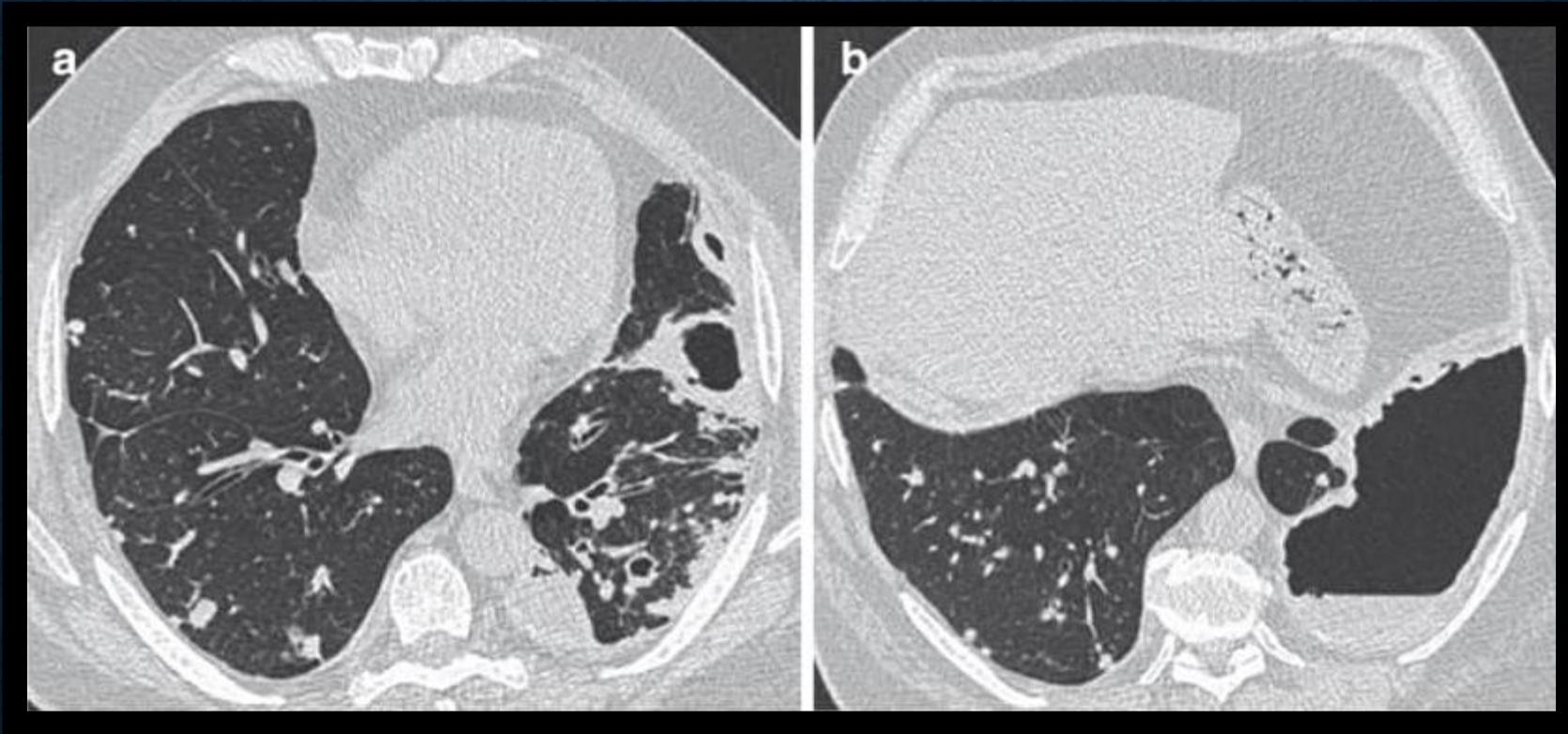
UIP



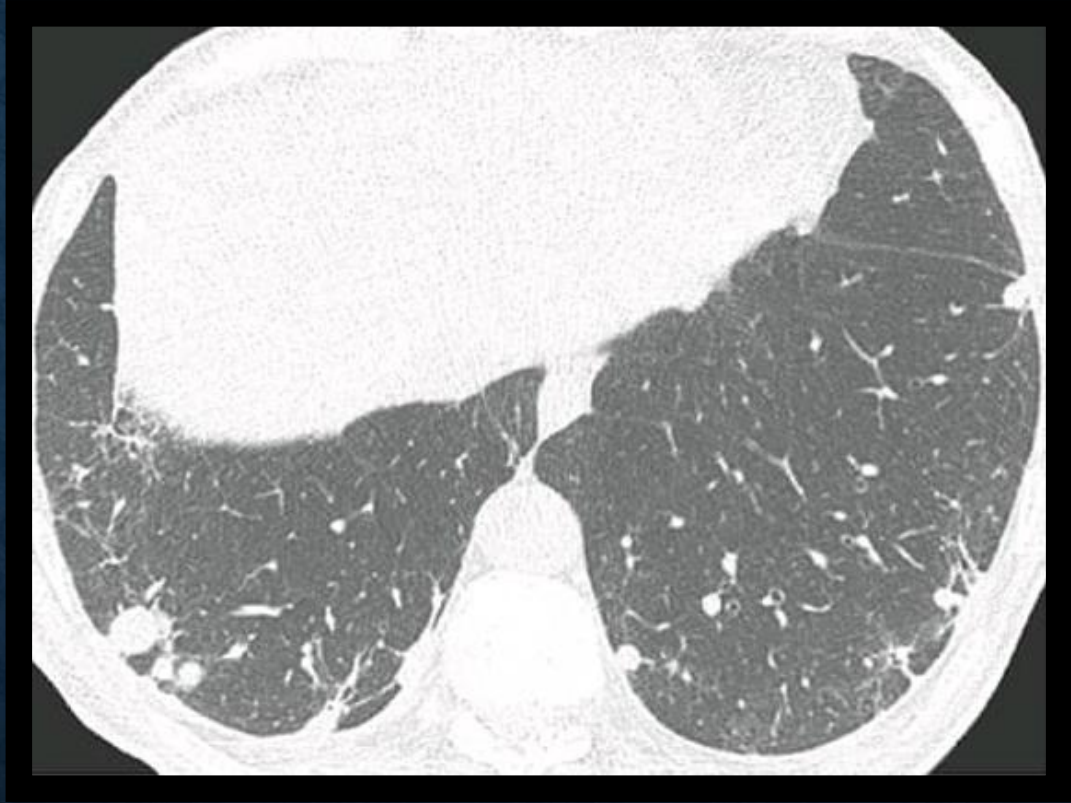
Organizing Pneumonia



Obliterative Bronchiolitis



Pulmonary Nodules

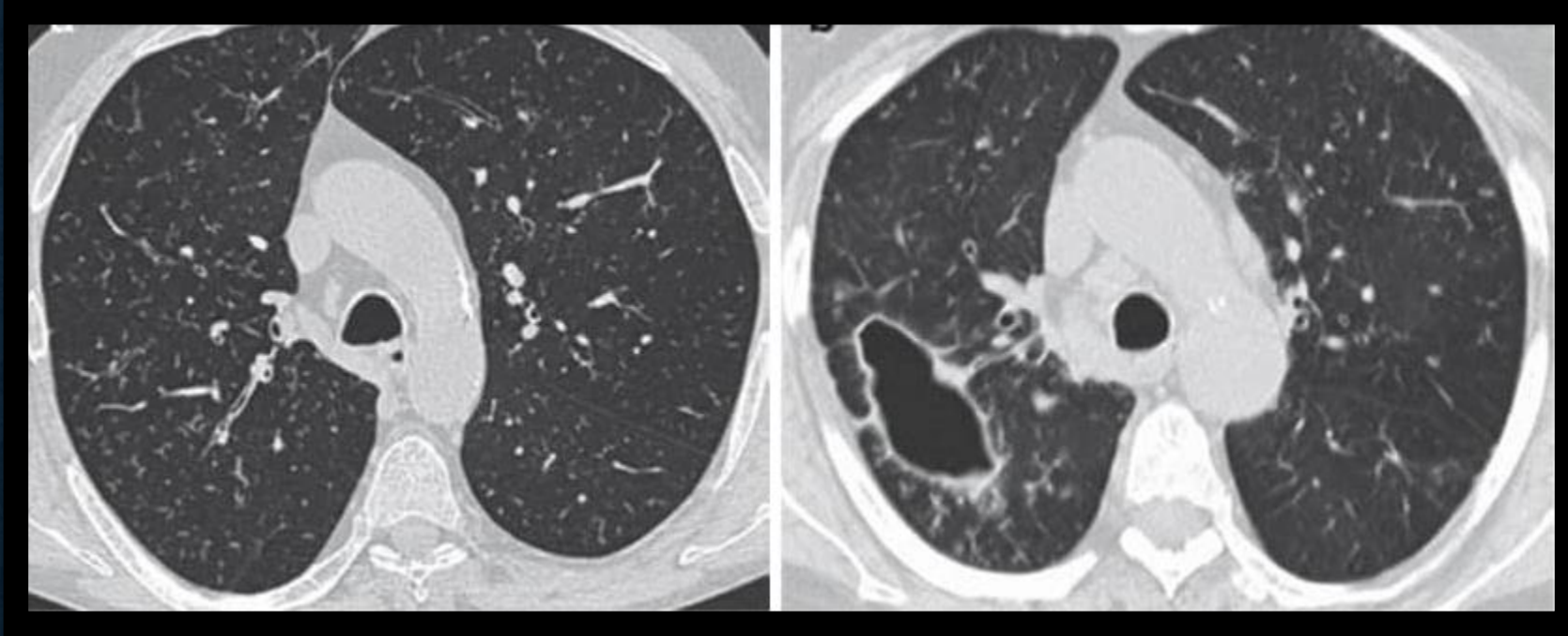




Plural Involvement



DAD



Nontuberculous Mycobacterial Infection

	Risk factors for disease presence	Risk factors for poor outcomes	Biomarkers of disease
Demonstrated in a spectrum of RA-ILD	Older age Male gender Increased respiratory symptoms Function decrements Physiologic decrements Tobacco smoking Increased severity of RA joint disease	Older age Male gender Low baseline FVC% Low DLCO% >10% FVC% decline UIP pattern	High-titer RF Anti-CCP antibodies MMP7 CCL18/PARC SP-D KL-6
Potential targets in RA-ILD	GERD		SP-A IL-6 YKL-40 CCN2 IL-8 ICAM-1 VCAM-1 CXCL9, CXCL10 CRP

Baseline
assessment
of RA-ILD

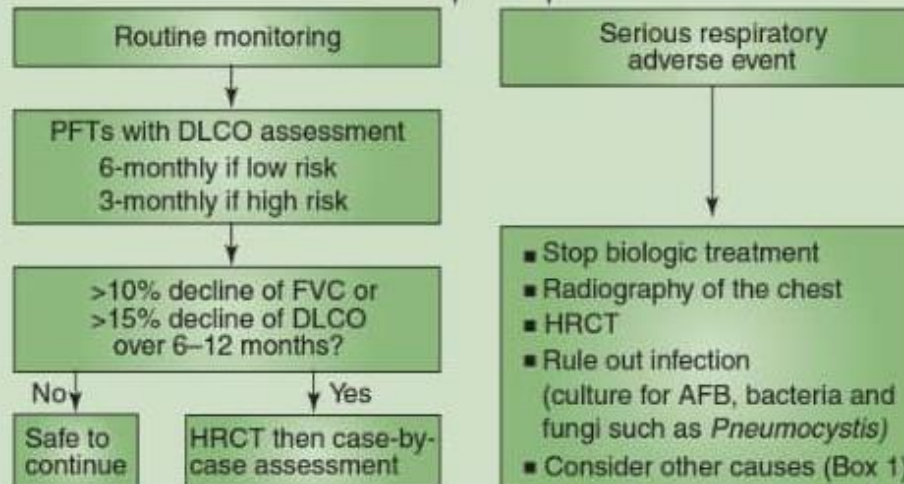
- Clinical assessment
- PFTs with DLCO assessment (serial assessment if feasible)
- HRCT (symptomatic or DLCO <70%)
- Ensure immunizations are up to date
- Serological immunoglobulin testing (if levels of IgG are low, the risk of infection might be increased if considering rituximab: use with caution or use an alternative)

Risk
assessment
for outcome
of RA-ILD

	High	Low
Risk		
HRCT pattern	UIP	Non-UIP
HRCT extent	>20%	<5%
Baseline FVC	<60% of predicted	>90% predicted
Baseline DLCO	<40% of predicted	>80% predicted
6–12 month change in FVC	≥10%	≤5%
6–12 month change in DLCO	≥15%	≤5%

Case-by-case decision about
commencing biologic therapy

Post-biologic
therapy
management



Initial baseline assessment	Measure	Factors associated with poor prognosis
Clinical assessment	MRC breathlessness score	
	Chest auscultation	
	6-min walk test	Oxygen saturations <88% poor prognosis
	Smoking status	
Respiratory physiology	PFTS	FVC <60%
		DLCO <54%
Chest radiograph and HRCT assessment	Extent of fibrosis	>20% lung involvement
	Subtype of ILD	UIP
<i>Pre-non-biologic DMARDs</i>		
Vaccinations	Ensure annual flu vaccination and one off pneumococcal vaccine administered (review 5 yearly)	
<i>Pre-biologic DMARDs</i>		
Vaccinations	Ensure annual flu vaccination and one off pneumococcal vaccine administered (review 5 yearly)	
Tuberculosis screening	Obtain history of TB exposure	
	Perform Mantoux and/or QuantiFERON gold	
Pre-rituximab (in addition to the above)	Immunoglobulin levels (IgG levels)	

Drug group	Reported adverse event	Details
Glucocorticoids	Infection	– Dose and duration of treatment related to infection risk – Co-prescription of bDMARDs may increase risk
NSAIDs	Eosinophilic pneumonia	– Idiosyncratic reactions, sometimes reported in patients on high doses
<i>nbDMARDs</i>		
Methotrexate	– Pneumonitis – Possible increase in infections including reports of opportunistic infections (e.g. <i>Pneumocystis jirovecii</i>, cytomegalovirus, varicella-zoster virus, <i>Nocardia</i>, mycobacteria or other fungi) – Pulmonary lymphoproliferative disease	– Co-prescription of bDMARDs may increase risk of chest/ opportunistic infections
Leflunomide	– Pneumonitis (especially Japanese/Korean patients) – Progression of pulmonary nodules +/- pneumothorax	– Co-prescription of bDMARDs may increase risk of chest/ opportunistic infections
Sulphasalazine	– Pneumonitis – Eosinophilic pneumonias most commonly reported	– Reported sometimes with DRESS
Hydroxychloroquine	– Rare cases of pneumonitis	– Reported sometimes with DRESS
<i>bDMARDs</i>		
TNFis	– Infection such as <i>Streptococcus pneumoniae</i>, <i>Haemophilus influenzae</i> and opportunistic infections (<i>Mycobacterium tuberculosis</i>, mycobacteria other than <i>M. tuberculosis</i>, <i>Mycoplasma</i>, <i>Legionella</i>, <i>Pneumocystis jirovecii</i>) – Pneumonitis – Congestive heart failure – Non-infectious granulomatous disease, e.g. sarcoidosis – Pulmonary vasculitis (rare) – New lung nodules (rare)	– Co-prescription of glucocorticoids (in patients with high disease activity) further increases infection risk

Drug	Licensing date (in RA unless otherwise stated)	Reported to UK MHRA to 2016	
		Type of event	Number (n, fatal)
Rituximab	1997 for lymphoma 2006 for RA by both the EMA and FDA	Interstitial lung disease ^a Obliterative bronchiolitis Alveolitis (including allergic) Pneumonitis Pulmonary vasculitis ARDS	36(8) 6(1) 5(1) 18(4) 1 6(1)
		Total non-infectious respiratory disorders	431
Abatacept	2005: FDA 2007: EMA	Pneumonitis	1
		Total non-infectious respiratory events	23
Tocilizumab	2009: EMA 2010: FDA	Interstitial lung disease ^a Obliterative bronchiolitis Alveolitis (including allergic) Pneumonitis ARDS	8(4) 1 2 3 3(1)
		Total non-infectious respiratory events	94
Anakinra	2002: EMA 2001: FDA	Interstitial lung disease ^a	1
		Total non-infectious respiratory events	19
Tofacitinib	2012: FDA Not approved by EMA by 2016	NA	

Carson et al. [11]	Searles and McKendry criteria [10]	Kremer et al. [12]
<i>Clinical</i>	<i>Clinical</i>	Major criteria
1. Clinical course consistent with hypersensitivity	1. Acute onset dyspnoea	<i>Histology</i>
<i>Radiology</i>	2. Fever $>38.0^{\circ}\text{C}$	1. Hypersensitivity pneumonitis by histopathological examination (without evidence of pathogenic organisms)
2. Resolving infiltrates on chest radiograph after discontinuing methotrexate	3. Tachypnoea $\geq 28/\text{min}$ and dry cough	<i>Radiology</i>
<i>Exclusion of infection</i>	4. Radiological evidence of pulmonary interstitial or alveolar infiltrates	2. Radiological evidence of pulmonary interstitial or alveolar infiltrates
3. Exclude infection or other pulmonary disease	<i>Laboratory</i>	<i>Exclusion of infection</i>
<i>Histology</i>	5. White blood cell count $\leq 15.0 \times 10^9$ with or without eosinophilia	3. Blood (if febrile) or initial sputum cultures negative for pathogenic organisms
4. Pathology consistent with drug-induced injury (i.e. hypersensitivity pneumonitis or toxic drug reaction)	6. $\text{PO}_2 < 7.5$ kPa on air	Minor criteria
Probable: 3 or 4 criteria	<i>Exclusion of infection</i>	<i>Clinical</i>
Possible: 2 criteria	7. Negative blood or sputum cultures (mandatory)	1. Shortness of breath < 8 weeks
Unlikely: 1 criterion	<i>Pulmonary function tests</i>	2. Dry cough
	8. Restrictive defect and decreased diffusion capacity on pulmonary function tests	<i>Laboratory</i>
	<i>Histology</i>	3. Oxygen saturation $< 90\%$
	9. Consistent with bronchiolitis or interstitial pneumonitis with giant cells and without evidence of infection	4. White blood cell count $\leq 15.0 \times 10^9$
	Definite ≥ 6 criteria	<i>Pulmonary function tests</i>
	Probable 5 of 9 criteria present	5. DLCO $< 70\%$ predicted
	Possible 4 of 9 criteria present	<i>Definite</i>
		– Major criteria 1
		– Major criteria 2 and 3 and at least 3 minor criteria
		<i>Probable</i>
		– Major criteria 2 and 3, and 2 minor criteria

TABLE 15-1 HRCT Findings in Drug-Induced Lung Disease

Disease	HRCT findings
DAD	Ground-glass opacity with or without associated crazy-paving pattern and dependent consolidation ^a
NSIP	Ground-glass opacity with or without associated reticulation ^a
Organizing pneumonia (BOOP-like reaction) or eosinophilic pneumonia reaction	Peribronchial and peripheral consolidation ^a
Amiodarone	High attenuation of lung parenchyma and liver ^a

Thanks For Your Attention.