

INTERSTITIAL LUNG DISEASE IN RHEUMATOID ARTHRITIS – CURRENT EVENTS

V. Reshkova

Rheumatology Clinic, "Sv. Ivan Rilski" Multiprofile University Hospital for Active Treatment – Sofia, Bulgaria

Abstract. *Rheumatoid arthritis (RA) is an autoimmune inflammatory joint disease with a chronic-progressive course. It occurs with progressive, symmetrical, erosive arthritis and extra-articular manifestations. The incidence of RA is 1-2% of the population. It affects women and men in a ratio of 9:1. Extra-articular manifestations are found in about 50% of patients with RA: consumptive and astheno-adyynamic syndrome, splenomegaly, pericarditis, vasculitis, subcutaneous nodules, pulmonary involvement. Pulmonary involvement is found in 4 to 68% of patients with RA. The earliest pulmonary complications are respiratory manifestations – interstitial lung disease (ILD), bronchiolitis and cylindrical bronchiectasis. ILD in the course of rheumatoid arthritis occurs twice as often in men between 50 and 60 years of age. Several studies confirm that the most common radiographic presentation of ILD in patients with RA is usual interstitial pneumonia (UIP), with peripheral reticular opacities and honeycombing seen on high-resolution computed tomography (HRCT). It is important for the occurrence, clinical course, and prevention of pulmonary fibrosis manifestations to assess the presence of biomarkers in the serum of the patients with rheumatoid arthritis. 98 articles were found investigating biomarkers in interstitial lung disease associated with rheumatoid arthritis (ILD-RA), with 83 studies being of high quality, 15 being of moderate quality. The biomarkers studied were C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), anti-cyclic citrullinated antibody (anti-CCP), rheumatoid factor (RF), Krebs von den Lungen 6 (KL-6), surfactant protein D (SP-D), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9. (CA19-9), matrix metalloproteinase 7 (MMP-7), chemokine ligand 10 (CXCL-10), neutrophil to lymphocyte ratio (NLR) were studied in patients with rheumatoid arthritis only and also in patients with ILD-RA. Treatment of the disease includes corticosteroids, immunosuppressants, biological therapy, and kinase inhibitors. These medications are used to treat not only rheumatoid arthritis, but also systemic manifestations.*

Key words: *rheumatoid arthritis, ILD, biomarkers, course and relationship*

DEFINITION AND DEMOGRAPHIC CHARACTERISTICS

Rheumatoid arthritis (RA) is an autoimmune inflammatory joint disease with a chronic-progressive course. It presents with progressive, symmetrical, erosive arthritis and extra-articular manifestations [1]. The incidence of RA is 1-2% of the population. It affects women and men in a ratio of 9:1. In about 50% of patients with RA, extra-articular manifestations are detected: consumptive and astheno-adydynamic syndrome, splenomegaly, pericarditis, vasculitis, subcutaneous nodules, pulmonary involvement. The prevalence of interstitial lung disease (ILD) with a serious clinical course is detected in 5% of patients with RA [2]. Depending on the changes on radiography and high-resolution computed tomography (HRCT) of the lung, the incidence of ILD in RA is between 20% and 40%. ILD in the course of RA occurs twice as often in men between 50 and 60 years of age [3].

ETIOLOGY AND PATHOGENESIS OF PULMONARY MANIFESTATIONS IN RA

Biomarkers have a promising role and provide important information about disease activity, progression, and response to treatment in interstitial lung disease associated with rheumatoid arthritis (ILD-RA). They have value in predicting the severity and prognosis of ILD in RA. A link with the HLA system, involving HLA-DRB1 alleles, has been suggested [4]. The rationale for a causal relationship between RA and ILD is driven by the fact that RA is often diagnosed before pulmonary fibrosis. However, several arguments could suggest a causal relationship between ILD and RA. The loss of immune tolerance that occurs with chronic lung injury suggests that ILD may be a risk factor for RA [5].

An independent study, the Multi-Ethnic Study of Atherosclerosis, measured rheumatoid arthritis-associated autoantibodies and obtained cardiac CT scans that assessed subclinical ILD. This study demonstrated an association between elevated

rheumatoid factors (RF), anti-CSR, and subclinical ILD. This finding [6] suggests that autoantibody production and pulmonary inflammation develop before clinical RA in patients with ILD who do not meet the criteria for RA [7]. In a proportion of patients with RA (27% to 48%), the diagnosis of ILD precedes or occurs at the same time as the onset of RA [8, 9, 10]. The majority of people who develop ILD before RA are found to have a CT pattern of ILD [9]. Anti-CCP has been shown to be elevated in 25% of patients with ILD and is associated with the presence of lymphoid aggregates seen in established ILD-RA [11]. The mechanism by which pulmonary fibrosis may accelerate the development of rheumatoid arthritis is related to the breakdown of immune tolerance to citrullinated peptides. Several indirect arguments [12] lead to the hypothesis that the development of seropositive RA involves the lung as the site of initiation of the loss of tolerance to citrullinated peptides:

- 1) patients are exposed to most environmental risk factors for seropositive RA by inhalation (by smoking, silica exposure),

- 2) in patients with early positive anti-CCP, the IgA isotype predominates [13],

- 3) the presence of an enzyme responsible for citrullination and local production of anti-CSR in lung tissue is peptidyl arginine deaminase 2 (PAD2) [14-17],

- 4) the existence of shared citrullinated peptide targets in the lungs and joints of RA patients [17].

These data suggest the possibility that in a subset of patients, the citrullinated protein targets of anti-CCP are lung-specific, leading to pulmonary involvement, fibrosis, synovitis, and clinical RA [18, 19]. Mucosal disease has long been considered a source of anti-CCP associated with seropositive RA, particularly IgA isotypes.

Lymphoid follicles are common in both ILD and RA [11, 16]. It is thought that chronic infection or changes in the microbiome may stimulate protein citrullination through chronic inflammation [20, 21].

It is important for the onset, clinical course, and prevention of manifestations of pulmonary fibrosis to assess the presence of biomarkers in the serum of the patients with rheumatoid arthritis. 98 articles were found investigating biomarkers in ILD-RA, with 83 studies being of high quality, 15 being of moderate quality. The studies were the biomarkers C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), anti-cyclic citrullinated peptide (anti-CCP), rheumatoid factor (RF), Krebs von den Lungen 6 (KL-6), surfactant protein D (SP-D), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), matrix metalloproteinase 7 (MMP-7), chemokine ligand 10 (CXCL-10),

neutrophil to lymphocyte ratio (NLR) in patients with rheumatoid arthritis only and in patients with ILD-RA.

Other biomarkers studied were platelet-to-lymphocyte ratio (PLR), cancer antigen 125 (CA-125) and cancer antigen 153 (CA-153). They did not show significant differences between the two groups. KL-6, MMP-7 and human epididymal protein 4 (HE4) were negatively associated with lung function. KL-6 may determine prognosis in ILD-RA [22].

A fundamental principle of clinical treatment is to attack the underlying cause of any disease. Therefore, understanding the direction of the causal relationship between two related conditions is crucial. RA has been considered a cause of ILD for many years, guiding therapeutic decisions toward the use of immunomodulatory therapy in ILD-RA patients.

The first randomized, double-blind, placebo-controlled trial in patients with ILD-RA found that pirfenidone had a greater effect on slowing the decline in forced vital capacity (FVC) in patients with simple interstitial pneumonia on HRCT [23]. Early identification and treatment of UIP in patients with RA is needed and may offer a new management strategy for RA. Historically, rheumatologists have been reluctant to screen asymptomatic patients with RA for ILD at the time of diagnosis. Screening of RA patients for ILD is warranted. Pulmonologists should also closely monitor the development of ILD, while paying attention to the emergence of RA-specific autoimmunity and joint manifestations [24].

CLINICAL PRESENTATION

AND PATHOHISTOLOGICAL PATTERNS OF ILD-RA

There is considerable heterogeneity in the clinical course and histopathology of ILD-RA. A wide variety of histopathological features of different types of interstitial pneumonitis and airway lesions (constrictive bronchiolitis, follicular bronchiolitis, or diffuse panbronchiolitis) have been described. There is often overlap between different patterns of lung involvement in the same patients, making diagnostic clarification more complicated. Patients with lung involvement present with dyspnea, dry cough, fatigue, and weight loss. There are different clinical phenotypes of ILD-RA, with different course and prognosis. Usual interstitial pneumonia (UIP) is characterized by fibrosis. This is the most common form of ILD-RA. Non-specific interstitial pneumonia (NUIP) is a predominant inflammatory disease and is a less common pattern of parenchymal damage [25, 26].

Idiopathic pulmonary fibrosis (Upper interstitial pneumonia/UIP) is a chronic, fibrosing

interstitial pneumonia. It is characterized by histological features of ordinary interstitial pneumonia, is not affected by therapy and this determines the poor course of the disease [27]. The typical histological pattern of UIP includes: diffuse heart disease, fibroblastic foci represented by myofibroblasts and honeycomb-like changes. Necessary criteria for diagnosing IBF are the exclusion of a secondary cause, computed tomography image, restrictive type of respiratory failure, impaired gas diffusion. In IPF, it has been established that alveolar epithelial cells play a major role. They activate fibroblasts, producing extracellular matrix proteins, through various cytokines – endothelin-1; TGF β (transforming growth factor beta); TNF α (tumor necrosis factor alpha). The typical radiographic appearance is represented by bilateral, symmetrical reticular opacities, localized predominantly subpleurally and posteriorly basally. Honeycomb changes are a characteristic finding in UIP, while ground-glass changes are rare [28].

Idiopathic non-specific interstitial pneumonia (NSIP) occurs more frequently in middle-aged women and is usually associated with SCC. NSIP is divided into cellular and fibrotic forms. Histological changes in NSIP are represented by thickened alveolar septa, a cellular inflammatory infiltrate composed of lymphocytes and plasma cells (cellular NSIP), while the fibrotic form is characterized by progressive fibrosis in the interstitium with preserved alveolar “architecture” [29]. The radiographic appearance includes ground-glass changes localized in the lower lung lobes and peribronchially, with honeycomb changes occurring less frequently [28].

Differentiating UIP from NSIP has important prognostic value, as idiopathic NSIP has a poor prognosis and no appropriate treatment is available, while idiopathic NSIP has a relatively good prognosis and patients respond to anti-inflammatory therapy. Interstitial lung disease associated with rheumatoid arthritis (ILD-RA) presents as interstitial pneumonitis, clinically and radiologically similar to idiopathic pulmonary fibrosis (IPF).

High-resolution computed tomography detects peripheral reticular opacities and honeycombing in 23 to 26% of patients with respiratory symptoms [10]. The prevalence of ground-glass opacity in patients without clinical pulmonary manifestations is only 3%, and none of them had honeycombing. In studies, HRCT findings did not correlate with clinical symptoms and chest X-ray. HRCT is more sensitive and specific than conventional diagnostic methods in identifying interstitial pneumonitis. The risk of seri-

ous infection in patients with ILD-RA is twice that of healthy controls [30].

Drug-induced interstitial pneumonitis should also be considered in patients with RA. Methotrexate (MTX) and leflunomide can cause different patterns of pulmonary involvement [31, 32]. Two forms of interstitial pneumonitis have been reported in association with MTX therapy. Life-threatening methotrexate pneumonitis is the most dangerous complication and occurs in 0.3–11.6% of RA patients treated with MTX. It usually occurs within the first 6 months of drug administration. It is acute and is not related to the cumulative dose of MTX. It begins with a dry cough or dyspnea and lymphadenopathy. Several diagnostic criteria have been proposed, but the diagnosis of methotrexate pneumonitis is mainly made by excluding other causes (opportunistic infection or exacerbations of pre-existing interstitial pneumonitis) [33, 34]. Discontinuation of MTX and high-dose corticosteroid therapy usually results in a favorable outcome. Since approximately half of patients with methotrexate pneumonitis have pre-existing interstitial fibrosis, the presence of such fibrosis is considered a contraindication to the treatment of RA with this drug.

BIOMARKERS IN ILD-RA

From all the studies conducted worldwide, there is no clear consensus on which biomarkers are the most important and which best define the relationship between ILD and RA. 11 biomarkers have been identified to predict the occurrence of ILD-RA, 85 biomarkers to differentiate RA from ILD-RA, 17 markers to assess the severity of Usual-RA, and 14 markers to assess prognosis [35]. The data are presented in Table 1.

The analysis included studies from 13 different countries, conducted in China (30 clinical observations/studies), Japan (18 clinical observations/studies), the USA (17 clinical observations/studies), Spain (6 clinical observations/studies), South Korea and Egypt (5 clinical observations/studies each), Italy (4 clinical observations/studies), England, Turkey, France and Mexico (2 clinical observations/studies each), Sweden, Germany and Saudi Arabia (1 clinical observation/study each).

1. Biomarkers for the diagnosis of ILD-RA

1.1. C-reactive protein

The results of the comparison of 1,574 patients with ILD-RA with 3,688 patients with RA showed much higher concentrations of C-reactive protein in the ILD-RA group compared to the RA group alone ($p < 0.001$).

1.2. ESR

In an analysis of 1,646 patients with ILD-RA and 4,215 patients with RA, it was found that ESR val-

ues were higher in the first group with a statistically significant difference $p < 0.001$. ESR values do not depend on age and gender.

1.3. Rheumatoid factor

In an analysis of 1,755 patients with ILD-RA and 3,519 patients with RA, it was found that the values of rheumatoid factor were higher in the first group with a statistically significant difference $r < 0.001$. (MD = 159.82; 95% CI: 107.06-212.58; $P < 0.001$), with high heterogeneity ($I^2 = 93.33\%$, $P < 0.001$). The values of ESR do not depend on age and gender.

1.4. Anti-CCP antibody

In an analysis of 1,582 patients with ILD-RA and 2,577 patients with RA, it was found that the values of anti-CCP antibody were higher in the first group with a statistically significant difference $p < 0.001$. (MD = 54.68; 95% CI: 28.47-80.88; $P < 0.001$), with significant heterogeneity observed ($I^2 = 87.50\%$, $P < 0.001$). The values of anti-CCP do not depend on age and gender.

1.5. KL-6

In an analysis of 794 patients with ILD-RA and 1,547 patients with RA, it was found that the values of anti-CCP antibody were higher in the first group with a statistically significant difference $p < 0.001$. (MD = 590.25; 95% CI: 448.65-731.84; $P < 0.001$), with significant heterogeneity observed ($I^2 = 94.60\%$, $P < 0.001$). The values of KL-6 do not depend on age, but are higher in male patients [35].

1.6. SP-D

In the analysis of 634 patients with ILD-RA and 1,145 patients with RA, it was found that SP-D values were higher in the first group with a statistically significant difference $p < 0.001$. (MD = 78.59; 95% CI: 51.56-105.62; $P < 0.001$), with noticeable heterogeneity ($I^2 = 97.77\%$, $P < 0.001$) [35].

1.7. MMP-7

In an analysis of 167 patients with ILD-RA and 123 patients with RA, it was found that MMP-7 values were higher in the first group with a statistically significant difference $p < 0.001$ [35].

1.8. Tumor markers

In an analysis of 383 patients with ILD-RA and 1,385 patients with RA, it was found that the values of CEA and CA19-9 were higher in the first group with a statistically significant difference $p < 0.001$. There was no statistically significant difference in the values of CA-125 and CA-153 between the group of patients with RA and those with ILD-RA.

1.9. The values in the studied patients with ILD-RA were higher than those with RA in terms of CXCL-10 and NLR.

Table 1. Biomarkers in ILD-RA for assessment of occurrence, diagnosis, clinical course and prognosis

Biomarker category	Biomarkers associated with RA-ILD
Prediction	Multiple studies: MUC5B mutations, FS-ACPA Single study: Anti-PAD3/4 antibodies, anti-CCP, RF, THBS2, TIMP1, POSTN, CD19, rs6578890 in PPFBP2, fragmented gelsolins,
Diagnosis	Multiple studies: KL-6, MMP-7, SP-D, RF, HE4, anti-CCP, CRP, ESR, CEA, CA19-9, CA-125, CA-153, CXCL10 Single study: MCP-1, CCL2, SDF-1 α , IL-18, CHI3L1, IL-36 α , IL-36 γ , qPCR (T/S ratio), VCAM-1, MCP-1, ADMA, D-dimer, UA, SIRI, sPD-1, cDKK-1, CA, GL, PIP, MMP-1, MMP-2, MMP-9, IL-1RA, sCD40L, CXCL9, EPC, PD-L1, lncRNA(NR_002819,NR_038935,ENST00000603415, ENST00000560199), PLR, Wnt5a, aCEP-1, LOXL2, CCL18, IL-17, CXCL12, CCL5, FGF4, FGF7, hsa-miR-214-5p, hsa-miR-7-5p, PARC, Hsp90, TGF- β 1, sCD25, POSTN, CD16 +MO, ARG1, TYMS, MKI67, OLFM4, BIRC5, MS4A4A, CLEC12A, LINC02967, HLA-DRB1, HLA-DRB1 SE, HLA-DQB1, IL-33, Anti-CarP, Anti-MAA, T cell subsets, NK cell subsets, IL-1 α autoantibodies, anti-ARS antibodies, iPF, DLCO, decanoic acid, morpholine, glycerol, proteomic profiling, CD20+B cells, CD138+plasma cells
Severity assessment	Multiple studies: KL-6, MMP-7, HE4 Single study: anti-CCP, UA, IL-13, IL-13 R α 1, IL-13 R α 2, SP-D, CEA, CA19-9, CA-125, Wnt5a, CXCL10, MMP-9, TIMP-1, coinhibitory molecules on alveolar T cells
Prognosis evaluation	Multiple studies: KL-6 Single study: PADI2(rs2057094,rs2076615), PADI4 (rs1748033), IL-6, IL-18, IL-11, MMP-13, CXCL11, Wnt5a, monocytes, neutrophils, KL-6 change rate over years, RF,HRCT

Anti-PAD3/4 antibodies, Anti-PAD3/4 antibodies; anti-CCP, anti-cyclic citrullinated peptide antibody; RF, rheumatoid factor; KL-6, krebs von den lungen-6; MMP-7, matrix metalloproteinase-7; SP-D, surfactant protein D; HE4, human epididymis protein 4; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CA-125, cancer antigen 125; CA-153, cancer antigen 153; CXCL10, C-X-C motif chemokine ligand 10; MCP-1, monocyte chemoattractant protein-1; CCL2, chemokine (C-C motif) ligand 2; SDF-1 α , stromal cell-derived factor 1 alpha; IL-18, interleukin-18; CHI3L1, chitinase-3-like protein; IL-36 α , interleukin-36 alpha; IL-36 γ , interleukin-36 gamma; qPCR (T/S ratio), quantitative polymerase chain reaction (T/S ratio); VCAM-1, vascular cell adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; ADMA, asymmetric dimethylarginine; UA, uric acid; SIRI, Simplified Index for the Robustness of Inflammation; sPD-1, soluble programmed cell death protein 1; cDKK-1, Circulating Dickkopf-1; CA, caprylic acid; GL, glycerol; PIP, piperidine; MMP-1, matrix metalloproteinase-1; MMP-2, matrix metalloproteinase-2; MMP-9, matrix metalloproteinase-9; IL-1RA, interleukin-1 receptor antagonists; sCD40L, soluble CD40 ligand; CXCL9, C-X-C motif chemokine ligand 9, EPC, endothelial progenitor cells; PD-L1, programmed cell death ligand 1; PLR, platelet-to-lymphocyte ratio; Wnt5a, non-canonical Wnt signaling representative ligand Wnt5a; aCEP-1, anti-C-terminal epitope antibody 1; LOXL2, lysyl oxidase-like 2; CCL18, C-C motif chemokine ligand 18; IL-17, interleukin-17; CXCL12, C-X-C motif chemokine ligand 12; CCL5, C-C motif chemokine ligand 5; FGF4, fibroblast growth factor 4; FGF7, fibroblast growth factor 7; PARC, pulmonary and activation-regulated chemokine; Hsp90, heat shock protein 90; TGF- β 1, transforming growth factor beta 1; sCD25, soluble CD25; POSTN, periostin; CD16+MO, CD16-positive monocytes; ARG1, arginase 1; TYMS, thymidylate synthase; SORT1, sortilin 1; MKI67, marker of proliferation Ki-67; OLFM4, Olfactomedin 4; BIRC5, baculoviral IAP repeat containing 5; MS4A4A, membrane-spanning 4-domains subfamily A member 4A; CLEC12A, C-type lectin domain family 12 member A; LINC02967, long intergenic non-protein coding RNA 2967; HLA-DRB1 SE, human leukocyte antigen class II DRB1 shared epitope; IL-33, interleukin-33; Anti-CarP, anti-carbamylated protein antibodies; Anti-MAA, malondialdehyde-acetaldehyde; IL-1 α autoantibodies, interleukin-1 alpha autoantibodies; anti-ARS antibodies, anti-aminocycl-tRNA synthetase antibody; iPF, immature platelet fraction; IL-13 R α 1, interleukin-13 receptor alpha 1; TIMP-1, tissue inhibitor of metalloproteinases; FS-ACPA, fine-specificity anti-citrullinated protein antibodies; THBS2, thrombospondin-2; TIMP1, tissue inhibitor of metalloproteinases 1; CD19, cluster of differentiation 19; DLCO, diffusing capacity of the lungs for carbon monoxide; HRCT, high-resolution computed tomography.

2. Biomarkers for assessing the severity of ILD-RA

Three biomarkers were included for assessing the severity: KL-6, MMP-7, HE4. Two studies including 237 patients with ILD-RA analyzed the correlation

of KL-6 with FVC and DLCO. A negative correlation of the above indicators was found (FVC r -0.26, DLCO r -0.33, $p < 0.001$) [35]. They are presented in Table 1.

Three studies with 243 patients with ILD-RA analyzed the correlation between MMP-7 and DLCO. A negative correlation was found ($P < 0.001$), with low heterogeneity among studies ($I^2 = 0.00\%$, $P = 0.72$).

Two studies with 94 patients with ILD-RA analyzed the correlation between HE4 and FVC%. A negative correlation was found, i.e., reduced FVC% was associated with increased HE4 values with low heterogeneity among studies ($I^2 = 0.00\%$, $P = 0.42$).

3. Biomarkers for assessing the prognosis of ILD-RA

Two studies with 146 patients with ILD-RA analyzed the prognosis of KL-6 in ILD-RA. The results showed an association between KL-6 concentration and poor prognosis of ILD-RA (HR = 3.01; 95% CI: 1.57-5.76; $P < 0.001$) (Table 1).

4. Other biomarkers (CXCL-10, PLR, NLR)

A group of 167 patients with ILD-RA and 123 patients with RA alone were studied for plasma MMP-7 levels. The results showed significantly higher MMP-7 concentrations in the ILD-RA group compared to the RA group ($P < 0.001$), with low heterogeneity ($I^2 = 33.82\%$, $P = 0.22$).

When examining serum CXCL-10 levels in 115 patients with ILD-RA and 112 patients with RA, an increased concentration was observed in the ILD-RA group (MD = 141.09; 95% CI: 81.24-200.94; $P < 0.001$) [35].

Two studies, including 387 patients with ILD-RA and 1,413 patients with RA, analyzed PLR and NLR. A difference was found in NLR concentration between the two groups of patients, but not for PLR ($P = 0.64$).

ILD-RA and idiopathic pulmonary fibrosis (IPF) are distinct diseases, but they share similar clinical, radiographic, and genetic features. Uncommon interstitial pneumonia (UIP) occurs in both IPF and ILD-RA. The presence of UIP in ILD-RA is a poor prognostic marker. Biomarkers in ILD-RA have a role in identifying potential shared pathophysiology with IPF.

Biomarkers hold promising clinical value for prediction, diagnosis, assessment of severity, and prognosis in ILD-RA. The effectiveness of these biomarkers may be influenced by environmental factors, genetics, ethnicity, lifestyle, and differences in detection methods across regions.

Significant differences in ESR and anti-CCP antibody concentrations were observed between patients with ILD-RA and RA in Asia and Africa, but not

in the Americas and Europe. CRP concentrations were significantly higher in patients in Asia, Europe and Africa, but not in the Americas.

RF concentrations are significantly higher in patients with ILD-RA across all regions, suggesting its potential utility.

Certain genetic variations may exist in Asian and African populations that affect the production of anti-CCP antibodies by the immune system and regulate inflammatory responses. This genetic polymorphism can lead to significant differences in ESR and anti-CCP antibody levels.

Environmental factors also play a key role – air pollution and high incidence of infectious diseases in certain regions affect immune function and inflammatory responses, leading to increased ESR and changes in anti-CCP antibody concentrations. CRP concentration was significantly higher in the elderly ILD-RA group (age ≥ 60) compared with RA patients. This difference was not observed in younger people, possibly due to physiological changes or reduced immunity in older ILD-RA patients. Biomarkers associated with interstitial lung disease encompass a variety of types related to alveolar epithelial cell damage, fibroproliferation, extracellular matrix remodeling, and immune dysfunction [36] and these markers are SP-D [37], KL-6 [38], and MMP-7 [39].

The proportion of males is the source of heterogeneity for KL-6 and this suggests that there may be differences in KL-6 levels between the sexes. Blood cell-based indices, such as neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have been reported as biomarkers of systemic inflammatory response, playing a significant role in various cancers, autoimmune rheumatic diseases and cardiovascular diseases. It is suggested that combining KL-6 with SP-D may improve diagnostic capabilities for ILD-RA, offering a new approach for selecting appropriate biomarkers for ILD-RA. KL-6 is weakly associated with forced vital capacity (FVC) and DLCO, and HE4 is weakly associated with percent predicted forced vital capacity (FVC%).

MMP-7 is moderately associated with the lung's diffusing capacity for carbon monoxide (DLCO). This suggests that MMP-7, KL-6, and HE4 may reflect changes in lung function to some extent. For patients with idiopathic pulmonary fibrosis, FVC and DLCO are the most sensitive parameters for assessing clinical outcome. There is a strong correlation between progressively declining FVC and DLCO values and the clinical severity of ILD [40]. ILD-induced deterioration of lung function affects prognosis and increases mortality. Early detection, timely treatment, and

appropriate intervention are crucial to improve clinical symptoms and survival in patients with ILD-RA.

Treatment of ILD-RA. There is no typical algorithm for the treatment of ILD-RA.

Treatment can be initiated at the onset of symptoms, with definite pulmonary involvement as determined by HRCT, or a decrease in predicted forced vital capacity (FVC) of > 10%. Treatment is specific to the symptoms of each individual patient, although immunosuppressants are commonly used in all presentations [41].

Non-selective immunosuppressants (e.g. mycophenolate mofetil or cyclophosphamide) may be combined with corticosteroids.

The therapeutic approach in ILD-RA is determined by the degree of pulmonary involvement. Corticosteroids (0.5-1 mg/kg) are administered in combination with an immunosuppressant. The approved immunosuppressants with proven efficacy in CTDs-ILD are:

1. Cyclophosphamide 10-15 mg/kg, administered intravenously at four weekly intervals for 6 months. The treatment has shown improved lung function (FVC) compared to placebo over a 12-month period in symptomatic patients. There are minor efficacy benefits that wane after 24 months.

2. Mycophenolate mofetyl 2 gr. Improvement in FVC over 24 months similar to cyclophosphamide, but with better tolerability/less toxicity. 2. No placebo-controlled studies; different patient populations and doses of mycophenolate mofetil in studies compared with cyclophosphamide.

3. Azathioprine. A trend towards improvement in FVC at 1-year follow-up was found when used as maintenance therapy after cyclophosphamide/corticosteroids. There is limited evidence of efficacy in studies comparing azathioprine with cyclophosphamide: the deterioration of lung function does not stop.

4. Corticosteroids. There is evidence of improved lung function when combined with cyclophosphamide.

5. Rituximab anti-CD20 monoclonal antibody improves lung function (FVC and DLCO) [41].

6. Antifibrotic agents. The ultimate pathway of action is common to several pathogenetic mechanisms involved in the dysregulation of the immune and vascular systems. Tyrosine kinase inhibitors inhibit intracellular signaling pathways involved in vascular changes and excessive fibrosis.

Nintedanib is the only tyrosine kinase inhibitor currently approved for use in ILD-RA. Pirfenidone reduces fibrosis by decreasing the production of growth factors and collagen. It is FDA-approved for the treatment of idiopathic pulmonary fibrosis. Lim-

ited data suggest some effect on limiting lung function decline in patients with ILD-RA, further studies are needed to provide additional data [41]. In daily practice, biological disease-modifying antirheumatic drugs are used for the treatment of RA (anti-TNFi and anti-interleukin (IL6) antibodies). When administered early after diagnosis, these medications significantly reduce joint and systemic inflammation and slow down structural damage [41].

MULTIDISCIPLINARY APPROACH

The multidisciplinary approach is the "gold standard" for the diagnosis of ILD. Achieving a multidisciplinary diagnosis is a dynamic process that requires constant contact between a rheumatologist, a pulmonologist, a radiologist, and, if necessary, a pathologist.

The multidisciplinary approach does not diminish the importance of lung biopsy – rather, it identifies cases in which biopsy is more informative than lung CT and cases in which biopsy is not necessary. When the pathologist recognizes the histological pattern, for example, NSIP or UIP, the clinician should discuss possible causes.

Academic physicians have better diagnostic outcomes than general practitioners, which highlights the need for these patients to be assessed in specialized university settings with the potential for a multidisciplinary approach. For diseases with a heterogeneous clinical course and for those that are difficult to classify, a classification of the course of the disease is proposed in addition to the classification of ILD. The composition of the multidisciplinary team is: pulmonologist, radiologist, pathologist, rheumatologist, cardiologist, transplantologist, thoracic surgeon, rehabilitator.

CONCLUSION

The diagnosis and treatment of ILD remains a major challenge for clinicians. However, modern clinical evaluation, together with imaging and diagnostic procedures, can achieve a reliable diagnosis and obviate the need for invasive procedures. Treatment of inflammatory ILD without extensive fibrosis may be successful with anti-inflammatory and immunosuppressive agents. In the presence of extensive fibrosis, these treatments are ineffective, especially in IPF. Patients with progressive disease for which no effective treatment is available should be encouraged to enter clinical trials, and those who are eligible should be referred for lung transplantation. Treatment of comorbid conditions can also signifi-

cantly help patients. Efforts should be directed towards ensuring optimal quality of life and palliative care for those with advanced progressive disease.

The diagnosis of ILD necessarily requires the search for clinical and immunological characteristics of inflammatory joint disease. This determines early diagnosis and correct therapeutic behavior. It is necessary to conduct screening imaging and functional studies to prove or rule out ILD. ILD-RA requires a multidisciplinary approach, including clinical, radiographic, and histological examinations, ensuring a more accurate diagnosis and correct therapeutic approach.

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Постъпил за печат: 20.10.2025 г.

Submitted: 20.10.2025

✉ **Адрес за кореспонденция:**

Доц. д-р Валентина Решкова, дмн
Клиника по ревматология
УМБАЛ „Св. Иван Рилски“
ул „Урвич“ 13
1612 София
e-mail: v_reshkova@abv.bg

✉ **Correspondence address:**

Assoc. Prof. Dr. Valentina Reshkova, MD, PhD, DSc
Clinic of Rheumatology
University Hospital “Sv. Ivan Rilski”
13 Urvich Street
1612 Sofia
e-mail: v_reshkova@abv.bg