

# Liver involvement in rheumatic diseases

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## Abstract

Liver involvement in rheumatic diseases may occur as a primary liver disease, primary rheumatic disease with hepatic manifestations or antirheumatic drug-induced liver disease. The aim of our article is to underline the importance of monitoring and control of the level of aminotransferases and cholestatic enzymes in rheumatic disorders. Some of the rheumatic diseases with constantly elevated liver enzymes need to be investigated in consideration of concomitant primary autoimmune liver disease (such as autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis) or drug hepatotoxicity. Also, we should be aware of hepatitis B reactivation or hepatitis C flare when immunosuppressants are used.

**Key words:** liver, autoimmune, rheumatic diseases.

## Introduction

The autoimmune connective tissue diseases (CTD) have a complex pathogenesis with a multifactorial etiology. In the course of CTD develop an autoimmune response leading to chronic inflammation and that sometimes may cause multiorgan dysfunction.

The liver is a life-sustaining organ which is responsible for detoxification of drugs and other harmful substances, metabolism of hormones, storage and release of proteins, cholesterol and vitamins and also an active organ of immune response.

The liver abnormalities are not included in connective tissue diseases' diagnostic criteria, except adult onset Still's disease (AOSD), in which elevated aminotransferases are subsumed in minor criteria according to the Yamaguchi et al. [1] criteria. For this reason, AOSD will not be discussed in our article.

Liver dysfunction occurs in 43% of patients with connective tissue disorders [2]. In some cases (27–37%) further investigation does not reveal other than rheumatological causes, the biochemical abnormalities are mild or transient and no progressive and clinically relevant changes are found in liver biopsy [2, 3].

The diverse course of the autoimmune rheumatic diseases ranges from asymptomatic elevation of transam-

inases or cholestatic enzymes, jaundice, hepatomegaly, to hepatic cirrhosis or even to acute liver failure. In the histology of liver biopsy, there are no specific features of connective tissue disease and the most frequent findings are: hepatic steatosis, chronic hepatitis, regenerative nodular hyperplasia, hepatic fibrosis, cirrhosis, granulomas, cholangitis, destruction of biliary canaliculus and vasculitis [4, 5].

This article reviews various aspects of liver involvement only in the most common, immunologically mediated rheumatic diseases, which typically have multi-system involvement (Table I).

## Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease of unknown etiology. It affects mostly women in reproductive age. In the pathophysiology, defects in the apoptosis play the main role. This leads to chronic inflammation in various tissues and organs.

The connection between SLE and hepatitis was noticed in the 1950s and it was described as a lupoid hepatitis by Cowling et al. [6] in 1954. Lupoid hepatitis turned out to be one of the variants of autoimmune hepatitis (AIH) which affects young women and manifests with SLE-like symp-

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**Table I.** Rheumatic diseases and reported coexisting liver diseases

Rheumatic diseases	Signs, liver test abnormalities	Reported coexisting liver diseases
Systemic lupus erythematosus	Arthralgia, jaundice, hepatomegaly, splenomegaly, presence of ANA, ALT and AST elevation	Drug side effects NAFLD, NRHL, AIH, PBC Non-specific reactive changes
Anti-phospholipid syndrome	Abdominal pain, ascites, hepatomegaly	Budd-Chiari syndrome NRHL
Rheumatoid arthritis	Cholestasis, GGT elevation	NAFLD, unspecific histological findings, PBC, AIH, NRHL
Felty's syndrome	Splenomegaly, portal hypertension, esophageal variceal bleeding	NRHL
Primary Sjögren's syndrome	Cholestasis, ALT, AST elevation, splenomegaly, portal hypertension, esophageal variceal bleeding	PBC, PSC, AIH, NRHL
Systemic sclerosis	Cholestasis	PBC
Idiopathic inflammatory myopathies	AST > ALT, CK elevation, cholestasis	PBC
Systemic vasculitides: polyarteritis nodosa, Behçet's disease	Hepatomegaly, jaundice, cholestasis, abdominal pain, ascites, hepatomegaly	Hepatitis B, Budd-Chiari syndrome

ANA – anti-nuclear antibodies, ALT – alanine aminotransferase, AST – aspartate aminotransferase, GGT –  $\gamma$ -glutamyl transferase, CK – creatine kinase, NAFLD – nonalcoholic fatty liver disease, NRHL – nodular regenerative hyperplasia of the liver, AIH – autoimmune hepatitis, PBC – primary biliary cholangitis, PSC – primary sclerosing cholangitis

**Table II.** Comparison of systemic lupus erythematosus (SLE)-associated hepatitis and autoimmune hepatitis

Parameters	SLE-associated hepatitis	Autoimmune hepatitis (AIH)
Symptoms	Arthralgia or arthritis, fever, loss of appetite, weakness	Asymptomatic (35%), weakness, mild right upper quadrant pain, nausea, jaundice, arthralgia, rarely rash or fever
ANA	Most patients	80% in type 1 AIH
Lupus anticoagulant	Present	Absent
ds-DNA	Present	May be present (up to 57%)
Anti-SMA	Rarely present	Usually present in type 1 AIH
Anti-LKM	Absent	Present in type 2 AIH
Anti-SLA	Absent	Present in type 3 AIH
Histological findings	Histologically unspecific: lobular infiltrates with paucity of lymphocytes, mild chronic inflammation	Interface hepatitis, lymphocytic infiltrates in portal tracts and extending into the lobule, emperipolesis (active penetration by one cell into and through a larger cell) and hepatic rosette formation
Progression	Benign	Can lead to cirrhosis
Prognosis	Good	10-year survival rate without treatment of AIH is < 27%

ANA – anti-nuclear antibodies, anti-SMA – anti-smooth muscle antibodies, anti-LKM – liver-kidney microsomal antibodies, anti-SLA – soluble liver antigen antibodies

toms such as arthralgia or arthritis, fever, loss of appetite, weakness, presence of anti-nuclear antibodies (ANA) or lupus anticoagulant and hypergammaglobulinemia.

Nevertheless, AIH and SLE are two different diseases, rarely cooccurring with each other, despite common symptoms such as arthralgia, hypergammaglobulinemia and ANA [7, 8].

However, liver dysfunction is observed in 59.7% of the patients affected by SLE. It can have multiple causes and it can be associated with exacerbation of

the disease (28.5%), the drugs side effects (30.9%) or coexistence of the primary hepatic disease (fatty liver disease in 20%, AIH in 4.9%, primary biliary cholangitis (PBC) in 2.4%, cholangitis in 1.6%, alcohol in 1.6% or viral hepatitis in 0.8%) [9].

Moreover, it is worth remembering that jaundice can be the effect of hemolytic anemia in SLE. In the differential diagnosis, AIH and SLE-associated hepatitis must be considered. The serological marker dsDNA antibody is specific for SLE, but it can be also detected in AIH [10].

On the other hand, the antibodies specific for AIH such as soluble liver antigen antibodies (anti-SLA), liver-kidney microsomal antibodies (anti-LKM) or anti-smooth muscle antibodies (anti-SMA) are rarely present in SLE [10, 11].

Liver biopsy is crucial because of characteristic histological findings in AIH (listed in Table II) while hepatitis accompanying SLE is histologically unspecific [11, 12]. It is important to make the proper diagnosis because of differences in the natural history and treatment.

The SLE-associated hepatitis does not need to be treated with corticosteroids and its natural history does not lead to cirrhosis, whereas the prognosis in untreated AIH is highly disadvantageous. The 10-year survival rate without treatment of AIH is less than 27%, and when treated it is approximately from 83.8 to 94% [13–15].

In prospective studies, liver biopsy performed in patients with SLE and elevated liver enzymes showed most frequently nonalcoholic fatty liver disease (NAFLD) (20–73%), vasculitis (21%), nodular regenerative hyperplasia of the liver (NRHL) (5.7%), chronic hepatitis (2.4%), cirrhosis (1.1%) or fibrosis (0.8%) [16].

### Anti-phospholipid syndrome

Anti-phospholipid syndrome was described by Hughes et al. [17, 18] in 1986. It is marked by arterial or venous thrombosis, miscarriages, thrombocytopenia and presence of antiphospholipid antibodies (APL) (such as lupus anticoagulant, anticardiolipin or  $\beta_2$ -glycoprotein) [19].

Antiphospholipid antibodies can be found in many autoimmune or neoplastic diseases and infections. However, it can also be identified accidentally in 2–5% of the healthy population and its prevalence rate increases with age [20].

The most frequent abdominal manifestation of APS is thrombosis of hepatic vessels, from main hepatic arteries or veins to small hepatic vessels. Hepatic vein thrombosis, also named Budd-Chiari syndrome, is caused by occlusion of the hepatic veins and it presents with a classical triad of abdominal pain, ascites and hepatomegaly. It can be the first manifestation of APS [21].

Interestingly, APL probably also play a role in pathophysiology of NRHL [22].

### Rheumatoid arthritis and Felty's syndrome

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease with unknown etiology that primarily affects joints, leading to their destruction, but other organs can also be involved (lungs, heart, kidneys and hemopoietic system). The liver is rarely affected, but abnormalities in liver tests can be detected in 5 to 77% of patients with RA [23].

Cholestasis is most commonly observed and it correlates with the activity of RA. Moreover, Lowe et al. [24] discovered a correlation between level of  $\gamma$ -glutamyl transferase and erythrocyte sedimentation rate.

Histological abnormalities in liver biopsy were found in 74% of patients with RA. 43% of the patients presented with unspecific findings such as mild inflammatory infiltrations in portal tracts or minor focal necrosis of hepatocytes, 22% were diagnosed with NAFLD and 11% with fibrosis, but only 1.1% of them were diagnosed with cirrhosis [25].

Felty's syndrome (FS) was described in 1924 and it is a variant of seropositive RA with splenomegaly and neutropenia. It develops in 1% of patients with long-lasting RA and is characterized by severe destructive changes in joints and higher prevalence of rheumatoid nodules, lymphadenopathy, vasculopathy, leg ulcers and infections in comparison with typical RA [26].

Moreover, higher prevalence of NRHL was noted in patients with FS, contrary to cirrhosis, which is rarely diagnosed. Nodular regenerative hyperplasia of the liver can cause portal hypertension and in consequence esophageal variceal bleeding [27].

On the other hand, as opposed to hepatic cirrhosis, such patients do not suffer from encephalopathy. In patients diagnosed with FS and NRHL, screening gastroscopy should be considered in search of esophageal varices. Variceal band ligation can be used as the primary prevention and transjugular intrahepatic portosystemic shunt (TIPS) as the secondary prevention of variceal bleeding [28].

The splenectomy also may be beneficial in the treatment of portal hypertension [29].

### Primary Sjögren's syndrome

Primary Sjögren's syndrome (pSS) is a chronic autoimmune inflammatory disease that causes lymphocytic infiltrations in exocrine glands, which results in secretion impairment and inflammation in different organs. The characteristic symptoms such as mucous membrane dryness appear in the advanced stage. The diagnosis should be made according to ACR-EULAR classification criteria from 2016 that are based on the weighed sum of 5 items.

The histopathological findings (focal lymphocytic sialadenitis) and the presence of anti-SSA/Ro antibodies are the most typical for pSS. Also, it is essential to exclude a history of head and neck radiotherapy, hepatitis C virus infection, sarcoidosis, amyloidosis, IgG4-related disease and graft vs. host reaction [30].

Other antibodies that can be detected in pSS are anti-SSB/La, rheumatoid factor, and antinuclear anti-

bodies. Nevertheless, they are not specific and are not included in the classification criteria [31].

Not only exocrine glands, but also other organs such as lungs, thyroid, kidneys, pancreas and liver can be affected in pSS. Diverse liver symptoms are observed in 27 to 49% of cases, depending on research [32]. Liver disorders associated with pSS are PBC, AIH, primary sclerosing cholangitis and NRHL [33].

The most common are PBC and AIH, which total more than 50% [34]. Primary biliary cholangitis is a chronic non-infectious cholangitis with undefined etiology that causes destruction of the intrahepatic bile ducts. It is a rare condition that more often affects women, but it is also the most frequently occurring autoimmune liver disorder.

The serologic marker specific to PBC are anti-mitochondrial antibodies that occur in 90–95% of patients. In a multicenter study, AMA were present in 22% of pSS cases, 17% of SLE, 10% of RA and 8% of scleroderma sera [35].

It is worth emphasizing that pSS and PBC have many common features. In both disorders the inflammatory process begins in bile or gland duct epithelium, and is characterized by impaired surface expression of HLA class 2. There are inflammatory infiltrations with CD4 lymphocyte dominance [36].

The coexistence of PBC in pSS is estimated at around 6%. Biopsies from patients with pSS and AMA revealed findings characteristic for PBC in 92% [37]. The asymptomatic patients with AMA should be monitored for development of PBC. It is very important to diagnose PBC at an early stage and start proper treatment with ursodeoxycholic acid [38].

## Systemic sclerosis

Systemic sclerosis (SSc) is a chronic systemic connective tissue disease which presents with progressive fibrosis of skin and internal organs and also injuries of small arteries (vasculopathy).

There are two types of SSc depending on the extent of skin involvement. Limited systemic sclerosis affects skin areas distal to elbows and knees. By contrast, diffuse systemic sclerosis affects skin of the proximal parts of the limbs and torso [39].

The frequency of SSc is higher in middle-aged female patients. Despite rare incidence of the disease, it poses a great social problem associated with progression of disability, high costs of treatment and increased mortality due to organ damage (mainly lung involvement). The most common liver disease accompanying SSc is PBC.

It occurs in 3–17% of patients and may account for more than 50% of liver diseases associated with SSc [40, 41]. Moreover, AMA, specific for PBC, are detected in more than 25% of patients with SSc.

As well as anticentromere antibodies (ACA), which are characteristic for ISSc, were found in more than 30% of patients with PBC and 80% of patients with the overlap syndrome PBC/SSc [41, 42].

Screening for presence of ACA seems to be a reasonable option in patients with PBC, and if positive, capillaroscopy should be performed. If giant capillaries are found, further diagnostic evaluation of SSc should be completed.

In addition, patients with ISSc should be evaluated for AMA presence, and if positive, the observation of cholestasis is recommended.

## Idiopathic inflammatory myopathies

The idiopathic inflammatory myopathies are a heterogeneous group of muscle diseases with diverse symptoms and etiology. The main classes of IIMs are polymyositis (PM), dermatomyositis and inclusion body myositis.

They can occur as a primary muscle disease or be associated with other systemic connective tissue disorders such as mixed connective tissue disease or as an overlap syndrome with Sjögren's disease, SSc, SLE or RA.

The high activity of muscle enzymes such as creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), aldolase and lactate dehydrogenase (LDH) is a marker of muscle cell degeneration or cell membrane damage. Elevated transaminases can be mistakenly interpreted as liver dysfunction. In clinical practice, the AST to ALT ratio should be assessed, and if the result is  $> 1$ , the CK test may be crucial in differential diagnosis.

Also myoglobin level may be helpful in assessment of the level of muscle damage and its concentration correlates with activity of the disease. Liver diseases are very rare in inflammatory myopathies. Only a few cases of PBC were described in patients with inflammatory myopathy [43].

## Systemic vasculitides

Systemic vasculitides are a heterogeneous group of diseases which are characterized by inflammation of blood vessel walls that causes narrowing and occlusion of the vessels. Consequently, this leads to episodes of ischemic changes and necrosis of tissues and organs supplied by these vessels.

Systemic vasculitides can be divided into three major groups based on the size of vessel affected (large, medium or small vessels) according to the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. All types of vasculitides can affect the gastrointestinal system [44].

Polyarteritis nodosa (PAN) is necrotizing inflammation of medium and small vessels that causes organ

**Table III.** Hepatotoxicity of drugs used in rheumatology

Drugs	Hepatotoxic effect	Outcome
NSAIDs	Hepatocellular or cholestatic pattern	Liver damage, reversible after discontinuation of the suspected NSAIDs
Methotrexate	NAFLD	Liver fibrosis and cirrhosis (BMI, alcohol consumption and lack of folic acid supplementation may play a role)
Leflunomide	Elevated liver enzymes	Liver tests normalize during ongoing treatment
Tumor necrosis factor inhibitors	AIH, cholestasis, jaundice, acute liver failure (very rare) hepatitis B reactivation	Some patients require treatment of AIH (glucocorticoids) and discontinuation of anti-TNF-treatment
Tocilizumab	Elevated liver enzymes (transient)	Liver tests normalize during ongoing treatment or after dose reduction
JAK inhibitors	Elevated ALT (transient)	Liver tests normalize during ongoing treatment

NSAIDs – nonsteroidal anti-inflammatory drugs, NAFLD – nonalcoholic fatty liver disease, AIH – autoimmune hepatitis, ALT – alanine aminotransferase, BMI – body mass index

damage in the gastrointestinal system in more than 50% of cases. The liver can also be affected in the course of PAN and it can manifest as hepatomegaly, jaundice, cholestasis without jaundice and even as massive hepatic necrosis. There are two subsets of PAN: primary of unknown etiology and secondary associated with presence of hepatitis B virus (HBV-related PAN).

The approach to treatment of PAN depends on the presence of hepatitis B virus (HBV). Conventional therapy of PAN relies on corticosteroids and additionally on cyclophosphamide in more severe cases. In HBV-related PAN, it is important to start treatment with antiviral agents, plasmapheresis and prednisone 60 mg/per day decreased to zero at the end of the second week.

Prolonged use of steroids or immunosuppressive therapy in HBV-infected patients increase the risk of hepatitis flare-up and may lead to fulminant liver disease [45]. Due to worldwide vaccinations against HBV and common screening, the rate of HBV in PAN has decreased from 30% to 8% [46].

Intrahepatic vessel inflammation can also be present in Takayasu's arteritis, temporal arteritis and granulomatosis with polyangiitis.

Budd-Chiari syndrome is the most common and most serious manifestation of liver disease in Behçet's disease (BD). Patients with BD should be screened for Budd-Chiari syndrome with duplex ultrasonography [47].

## Hepatotoxicity of drugs used in rheumatology

Drug-induced liver injury (DILI) is the main reason for drugs' withdrawal from clinical trials or even from market registered substances. It may occur as a direct result of a drug or its metabolites toxicity affecting hepatocytes (intrinsic DILI) or through immune activation (idiosyncratic DILI).

Intrinsic DILI is predictable (occurs in a large proportion of exposed individuals), dose related and occurs within hours or days (Table III).

A typical example of intrinsic DILI is acetaminophen. Idiosyncrasy is an unexpected side effect of the drug, independent of dose, time and route of administration, and it demonstrates variable latency to onset (from days to weeks). It is associated with congenital or acquired enzymopathy. The pathogenesis of liver damage in idiosyncrasy has not been elucidated.

## Nonsteroidal anti-inflammatory drugs

Typical examples of an idiosyncratic reaction and liver damage are nonsteroidal anti-inflammatory drugs (NSAIDs) and clavulanic acid.

Nonsteroidal anti-inflammatory drugs are the most widely used medications in the world. Since benoxaprofen was recalled in 1982 because of cases of fatal jaundice and renal failure, liver damage due to NSAIDs has been found as a class effect [48].

From 5 to 15% of patients using NSAIDs develop elevated liver enzymes but the liver damage is mild and reversible after drug discontinuation. In view of cross-reactivity among the same class of NSAIDs, re-administration of NSAIDs should be avoided [49].

## Methotrexate

Methotrexate (MTX) belongs to a class of drugs known as antimetabolites and is commonly used in the treatment of many autoimmune diseases such as RA, psoriasis, psoriatic arthritis, juvenile idiopathic arthritis, spondyloarthropathies, SLE, polymyalgia rheumatica, and PM.

The United States Food and Drug Administration (FDA) approved MTX as a therapy for RA in 1988. It has become the standard of care and the first-line therapy

for patients with RA. In patients who have an incomplete response to MTX, it could be administered in combination with either a biological agent or other antirheumatic drugs. Methotrexate has a relatively good safety profile.

The most common side effect is gastrointestinal intolerance such as nausea, stomatitis or diarrhea. Prolonged MTX therapy may increase the risk of hepatotoxicity leading to fatty liver disease, fibrosis and cirrhosis. Factors such as body mass index (BMI), alcohol consumption, concomitant medications such as NSAIDs, and lack of folic acid supplementation may additionally contribute to transaminase elevation. Toxicity of MTX is related to a cumulative dose and the application frequency (daily administration is more harmful than once per week application) [50].

According to an international group of experts' guidelines, the blood count, liver enzymes and creatinine level are recommended to be monitored on a monthly basis for at least 6 months and then every 3 months. If the increase in aminotransferases (AST or ALT)  $> 3 \times$  upper limit of normal (ULN) is confirmed, the administration of MTX should be discontinued. If liver test abnormalities persist, liver biopsy ought to be performed. In case of normalization of aminotransferases, MTX may be reinstated at a lower dose [51].

Also, routine liver biopsy after a cumulative dose of 1, 3 and 8 g can be considered, but guidelines from different societies vary on this issue. When the liver biopsy reveals significant or severe fibrosis or cirrhosis, discontinuation of MTX is highly recommended [52].

### Leflunomide

Leflunomide (LEF) acts by inhibiting pyrimidine's intracellular pathways and preventing lymphocyte proliferation and differentiation. It is registered and regularly prescribed as the first-line treatment for use in patients with psoriatic arthritis and RA.

Common adverse effects for patients receiving leflunomide treatment include gastrointestinal complaints, skin rash and reversible alopecia. ALT/AST elevations  $> 2 \times$  ULN occurred in 1–2% of patients on MTX or LEF monotherapy compared with 5% with the combination of both of them [53].

### Tumor necrosis factor inhibitors

Tumor necrosis factor inhibitors (TNFi) are biological agents that were introduced as rheumatological treatment in the 1990s. Biological disease-modifying antirheumatic drugs (bDMARDs) act against cytokines and inflammatory cells in RA and inhibit the immunological response. A common side effect connected with this

mechanism is activation of the opportunistic infections tuberculosis and HBV [54].

For this reason, the European Association for the Study of the Liver (EASL) recommends preventive use of nucleoside analogues by non-active carriers of Hbs antigen during and 12 months after the biological treatment [55].

On the other hand, in patients with chronic hepatitis C, the anti-TNF therapy seems to be safe and does not provoke an increase of liver enzymes or the viral load [56]. Tumor necrosis factor inhibitors may also rarely cause cholestasis, jaundice, AIH or acute liver failure [57, 58].

### Tocilizumab

Tocilizumab (TCZ) is a humanized, monoclonal antibody against the interleukin-6 receptor and has been successfully developed as a therapeutic agent for treatment of RA, systemic onset juvenile idiopathic arthritis and in many other autoimmune conditions.

Tocilizumab is effective in the improvement of systemic inflammatory symptoms such as anemia and fatigue. Additionally, it improves sleep quality, inhibits serum amyloid A protein production and eliminates amyloid deposition in amyloid A amyloidosis.

The clinically significant adverse events that may occur with TCZ treatment include infections, abnormalities in lipid and liver function tests and gastrointestinal side effects. Tocilizumab treatment can be associated with elevation of liver enzymes, but most of them are transient and occur within 12 months of TCZ initiation and resolve after lowering the dose of tocilizumab/disease-modifying antirheumatic drugs [59].

### Janus kinase inhibitors

Janus kinase (JAK) inhibitors are a new class of drugs – oral targeted synthetic DMARDs, added recently to second line treatment of RA, which inhibit components of the intracellular inflammatory JAK signaling cascade.

The first JAK inhibitors are tofacitinib and baricitinib and were approved in 2017 by the European Medicines Agency (EMA) for treatment of patients with moderate to severe RA and an inadequate response to prior disease-modifying antirheumatic drugs. Tofacitinib is also helpful in treatment of ulcerative colitis and psoriasis. Long-term extension studies have shown that tofacitinib demonstrated a stable safety profile.

The most common adverse events are infections (nasopharyngitis, upper respiratory tract infections, herpes zoster), bone marrow suppression (neutropenia, lymphocytopenia and decrease in platelet count) and hyperlipidemia. Only 1.2% of patients confirmed increased ALT levels  $> 3 \times$  ULN, but most of them subsided spontaneously without discontinuation of the study drug [60].

## Conclusions

Abnormalities in liver function tests are very common in patients with rheumatic diseases. Most frequently, non-specific and transient elevation of the liver function tests is associated with activity of connective tissue disease and does not require any special intervention.

On the other hand, if the abnormal liver function tests (cholestasis or elevated aminotransferases) persist independently of the activity of rheumatic disease, further hepatological investigations should be carried out and primary autoimmune liver diseases, viral hepatitis and drug hepatotoxicity must be excluded.

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