

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



# Introductory Chapter: Autoimmune Epithelitis - Discussion about Sjögren's Syndrome and Primary Biliary Cholangitis

*Maria Maślińska*

## 1. Introduction

Epithelial tissue constitutes a barrier between organs and the environment. The epithelium lines external surfaces of internal organs and inner surfaces of the walls of blood vessels. It is also a tissue that exocrine and endocrine glands consist of.

As they separate the organism from the outer environment, the epithelial structures form the first line of defense against external factors but, at the same time, an entry gate for them influencing the development of the body's microbiome and autoimmune diseases, which are associated with the disorders of microbiome composition (dysbiosis) [1, 2]. The epithelium, also as a target for viruses, interacts with the invading pathogens and is actively involved in immune response, whose course depends on particular genetic and epigenetic conditions.

Epithelial cells are often subject to apoptosis, which makes them an important source of autoantigens. Moreover, in many autoimmune diseases, epithelial cells are damaged, which leads to further release and exposition of autoantigens, with the epithelium being subject to the immune response. For example, thyrocytes are responsible for providing the main immunogens (e.g., thyroglobulin, thyroid peroxidase, TSH receptor) in autoimmune thyroiditis [3], synoviocytes are a source of cyclic citrullinated peptides in rheumatoid arthritis, and oligodendrocytes in multiple sclerosis or pancreatic endocrine glandular epithelium (beta-cells) in type 1 diabetes are a source among others of proinsulin or glutamic acid decarboxylase [4]. Hence the suggestion puts forward that autoimmune diseases could be otherwise classified as the autoimmune inflammation of the epithelium [5]. However, there are autoimmune diseases which, due to their effect on the exocrine glands, are particularly associated with epithelial damage and an autoimmune process, the primary Sjögren's syndrome (pSS) among them. The primary Sjögren's syndrome is an autoimmune disease in which the exocrine glandular epithelium is a main source of autoantigens—such as Ro/SS-A and La/SS-B ribonucleoproteins [6]. Quite often pSS may coexist with another autoimmune disorder—a primary biliary cholangitis (PBC). In PBC the epithelium (biliary epithelial cells of small bile duct) is the starting point of the autoimmune process [7]. The pathogenesis of both diseases is similar, with the significant role of epithelial cell apoptosis. **Table 1** presents the immunological and main clinical features of pSS and PBC.

The Sjögren's syndrome is an example of the development of an autoimmune epithelitis and consequences of such a process. The impact of environmental factors on the genetically susceptible subject is vital for the development of pSS. There are multiple genes (e.g., HLA-B8, HLA-Dw3, HLA-DR3, and DRw52) responsible for the individual's susceptibility to the pSS development. Particular attention has been paid to the genes for interferon regulatory factor 5 (IRF5), signal transducer and activator of transcription 4 (STAT4) in the type I interferon (IFN) system, and B lymphocyte kinase (BLK) involved in B-cell activation, which are considered as risk loci in pSS development [10]. Additionally it has been recently revealed that also epigenetic mechanisms, such as DNA methylation, histone modifications, and noncoding RNAs, may influence expression of the involved genes in autoimmune diseases, including pSS [11].

The pSS development is associated with the infection with viruses, which mainly target B cells or display tropism to lacrimal and salivary glands. Such a strong association has been confirmed in case of the Epstein–Barr virus, as well as other viruses: *Cytomegalovirus*, herpes simplex virus, and hepatitis C virus [12].

Primary Sjögren's syndrome	Primary biliary cholangitis
Exocrine glands	Liver
Chronic autoimmune disease	Chronic autoimmune disease
Anti-SS-A and anti-SS-B antibodies	Anti-mitochondrial antibodies (AMA)
ANA antibodies	ANA antibodies may be present
Exocrine glandular epithelium	Biliary epithelial cells
Predominance of CD4+ infiltrate around the salivary duct	Granuloma and predominance of CD4+ infiltrate around the bile duct
Woman > men	Woman > men
Fifth decade of life	Fifth decade of life
Primary/secondary to other autoimmune diseases	Primary/secondary to other autoimmune diseases
Genetic factors—variability in genetic factors	Genetic factors—predominant role
Infectious initiating factors: <i>Herpesviridae</i> particularly Epstein–Barr virus, CMV, herpes	Infectious initiating factors: <i>Escherichia coli</i> , <i>Helicobacter pylori</i> EBV
Symptoms of eye and mouth dryness Extraglandular manifestations (organ impairment, vasculitis, neuropathy)	Fatigue, pruritus, skin hyperpigmentation, hepatosplenomegaly Liver cirrhosis (late stage with ascites, jaundice, hepatic encephalopathy, upper digestive bleeding)
Lymphoma	Hepatocellular carcinoma
<b>EULAR/ACR criteria for diagnosis (2016)</b> 1. Labial salivary gland biopsy (focal lymphocytic sialadenitis) FS ≥ 13 points 2. Anti-SS-A/Ro positivity 3 points 3. OSS ≥ 5 (or van Bijsterveld score ≥ 4 1 point Schirmer's test ≤ 5 mm/5 min 1 point 4. Unstimulated salivary flow ≤ 0.1 mL/min 1 point Diagnosis ≥ 4 point Exclusions:	<b>Diagnostic criteria for PBC</b> 1. Elevated alkaline level of >2× ULN or elevated gamma-glutamyltransferase level of >5× ULN 2. Positivity for AMA antibodies 3. Chronic granulomatous cholangitis at liver biopsy Diagnosis presence of at least two of the three criteria
ULN, upper limit of normal.	

**Table 1.**  
The immunological and main clinical features of pSS and PBC [8, 9].

The epithelitis in pSS starts with an influence of certain external factors, such as viruses, rare bacteria, or ultraviolet radiation on epithelial cells. This leads to cell apoptosis and expression of autoantigens (SS-A and SS-B ribonucleoproteins), which are presented to autoreactive T cells. As it is recently highlighted in the literature, endothelial cells have, therefore, antigen presentation properties, although this is not their main feature, as it is the case with antigen-presenting cells (APCs), such as dendritic cells, macrophages, and B cells. Also salivary gland epithelial cells (SGEC) express MHC class I and MHC class II (HLA-DR) molecules and functional co-stimulator B7.1 (CD80) and B7.2 (CD86) molecules and may transmit signals to T lymphocytes as nonprofessional APCs [13, 14].

Other processes responsible for the development at this stage include the activation of the innate immune system, with the activation of Toll-like receptors (especially TLR3, TLR7, TLR9) and the production of interferon alpha (IFN- $\alpha$ ) by plasma dendritic cells (pDCs) stimulating epithelial cells, dendritic cells, and neutrophils for the production of the B-cell stimulating factor and APRIL [15]. There are infiltrates in the exocrine glands initially composed mainly of T cells, whereas the activation of B lymphocytes by growth factors, such as BAFF and APRIL, results in hypergammaglobulinemia and the production of anti-SS-A and anti-SS-B auto-antibodies as a secondary immune response. B cells and macrophages also produce proinflammatory cytokines, chemokines, and adhesion molecules.

The disease starts with the epithelial inflammation and impaired function of the exocrine glands manifesting themselves, for example, in the enlargement of the glands and reduction of the secretion of saliva or tears. It evolves then into the phase of systemic disease with the organ involvement and general manifestations (fever, weight loss, fatigue). Although the Sjögren's syndrome is most often associated with the functional impairment of lacrimal and salivary glands (symptoms included in the current criteria of diagnosis [16]), it also affects glands of the digestive system, pancreas, liver, gall bladder, respiratory glands, and even sweat glands. Their function is impaired through the reduction of secretion of the aqueous phase and changes in density of the secretion, leading to the emergence of various clinical features: from the feeling of mouth or eye dryness, through recurrent cholelithiasis and nephrolithiasis, to stones in the salivary glands.

The consequence of the involvement of epithelia in pSS and its damage is the emergence of the way of entry for pathogens in the alimentary tract (from the oral cavity to the rectum), as well as in the respiratory tract. In the case of imbalance of the microbiome and the occurrence of dysbiosis, also commensals, which become potential pathogens in such circumstances, may cross the damaged epithelial barrier. Proteins from the epithelial cells of the mouth, intestines, and skin, as well as bacterial (commensal) proteins, may initiate an immune response to Ro60 (theory of Ro60-reactive B cells) and activation of T cells, as consequence of molecular mimicry [17]. The role of fungal (*Candida*) infections in pSS development was also studied, revealing there was no significant relationship between *Candida albicans* and the rate and amount of salivary secretion, although such relationship was found in pathogenic species, such as *C. tropicalis*, *C. glabrata*, and *C. krusei* [18].

In **Table 2** the main clinical manifestations of pSS resulting from the epithelial damage are presented.

What is particularly important, continuous stimulation of B lymphocytes by activating agents, primarily BAFF and APRIL, causes germinal center (GC) formation and the formation of secondary lymphoid tissue, which in turn leads to the increased risk of lymphoma development. The most common lymphoma emerging in the course of pSS is the marginal zone B-cell lymphoma (MZBCL), the mucosa-associated lymphoid tissue (MALT) type being predominant. The diffuse large B-cell lymphoma (DLBCL), rare T-cell lymphoma, or NK-cell lymphoma are

Localization	Effect
Nasal and oral cavity	Oral candidiasis, dental caries, periodontitis otitis media, dry nose, chronic sinusitis, nasal bleeding, weakening of the sense of smell
Bronchi	Difficulty in swallowing, dry cough, hoarseness, recurrent bronchitis and less frequent bronchioles, bronchial hyperresponsiveness and accompanying dry cough, infections
Lungs	Interstitial lung disease
Stomach	Chronic gastritis, malabsorption, susceptibility to <i>H. pylori</i> infection
Gut	Celiac disease, colitis Gluten sensitivity [19, 20]
Liver	Hepatitis, cholangitis
Pancreas	Pancreatitis
Kidneys and urine tract	Interstitial nephritis with distal renal tubular acidosis (dRTA). Glomerulonephritis with coexisting cryoglobulinemia and urolithiasis

**Table 2.**  
*The main clinical manifestations of pSS due to the epithelial damage.*

less common. The occurrence of MZBCL has been observed in about 8% of pSS patients; it is 40 times higher than in the healthy population [21, 22].

2. Focusing on MALT lymphoma

The most important feature of MALT lymphoma is the presence of neoplastic cells (mainly B cells, as well as T cells) within epithelial structures, which may lead to destruction of the glandular architecture, also because of the formation of solid infiltrations.

Lymphomas in pSS are predominantly localized in salivary glands, which has been confirmed in many studies [23], whereas in the general population, MALT lymphoma is most often located in the stomach. The occurrence of MALT lymphoma in the stomach is proven to be associated with *H. pylori* infection [24]. The primary division of MALT lymphomas depending on the location is shown in **Table 3**.

Subtypes of lymphoma due to localization		
MALT	NALT	Nasopharynx-associated lymphoid tissue
	BALT	Bronchus-associated lymphoid tissue
	LALT	Larynx-associated lymphoid tissue
	GALT	Gut-associated lymphoid tissue
SALT	Skin-associated lymphoid tissue	
CALT	Conjunctiva-associated lymphoid tissue	
SDALT	Salivary duct-associated lymphoid tissue	
O-MALT	Organized mucosa-associated lymphatic tissue-specific type of MALT affecting Waldeyer's tonsillar ring	
D-MALT	Diffuse mucosa-associated lymphatic tissue-specific type of the disease, cells not organized into a separate macroscopically and anatomically identifiable mass, but spread throughout the mucosa of different organs	

**Table 3.**  
*Division due to the localization of MALT lymphoma [22, 25].*



### 3. Sjögren's syndrome and primary biliary cholangitis as autoimmune epithelitis: general rules for treatment

#### 3.1 The treatment of primary Sjögren's syndrome involves a dual approach

- A topical treatment, which aims to protect the epithelial barrier of the eye, oral cavity, and vagina
- Inhibition of organ changes, as well as the elimination of general symptoms, such as fatigue, fever, malaise, or lymphadenopathy [26, 27]

##### 3.1.1 Topical treatment

###### 1. Oral cavity

- A. Saliva substitutes: hydroxymethylcellulose-containing oral spray, proper hydration by consuming more liquids, and regularly rinsing the mouth

The stimulation of salivary flow, obtained with the use of pilocarpine or cevimeline, parasympathomimetics, and muscarinic agonists affecting M1 and M3 receptors, after considering possible contraindications for their use.

Antifungal and antimicrobial treatment with medications such as chlorhexidine; the use of nonfluoride remineralizing agents as concomitant therapy.

Diet modification is recommended: eating slightly acidic products such as lemon, supplementing diet with unsaturated fatty acids (omega-3), and avoiding sweets and sweet effervescent beverages.

Quitting smoking is strongly recommended.

###### 2. Dry eye

- A. The modification of environmental factors, which may increase the dry eye symptoms, such as air condition, exposure to dust, and prolonged work at computer screen.

When possible, the discontinuation of treatment with medications resulting in the reduction of tears or disruption of their composition.

Artificial tears, gels, ointments, special contact lenses, topical autologous serum, and special contact lenses.

Punctual plugs (temporary or permanent).

The eyelid therapy: massages and warm compresses.

The eyelid surgery (e.g., blepharoplasty).

Topical immunosuppression: steroids and cyclosporine A.

###### 3. Vaginal dryness

Vaginal dryness treatment is based on the use of intimate moisturizers and sexual lubricants and pH balance stabilizers free from hormones and skin irritants. In some cases the use of estrogen topical medication may be found useful.

##### 3.1.2 General treatment

Immunosuppressive drugs such as azathioprine, methotrexate, leflunomide, mycophenolic acid, cyclosporine A (topical, rare oral), and cyclophosphamide effects are used to inhibit general symptoms and organ involvement [26, 27].

Among biological drugs, rituximab (anti-CD20 monoclonal antibody) has been showing positive results in current clinical trials and is used to inhibit certain aspects of the disease. Rituximab improves saliva flow rate and lacrimal gland function (discussed), diminishes fatigue and malaise, and is recommended in case of cryoglobulinemia or vasculitis-related peripheral nervous system involvement or other severe neurologic manifestations of this disease.

Glucocorticosteroids (GCS) are used in immunosuppressive therapy combined with other immunosuppressive drugs. Pulses of GCS are used in the case of the intensification of organ changes, vasculitis, and nervous system involvement.

Intravenous immunoglobulin administration and plasma exchanges are used in life-threatening cases of nervous system involvement and vasculitis.

**Other:** Vitamin D supplementation and aerobic exercises are recommended.

### **3.2 Treatment of primary biliary cholangitis**

#### *3.2.1 Treatment for itching*

Antihistamines, e.g., loratadine or diphenhydramine, are used. Cholestyramine as the addition to beverages and foods may be used. Rifampicin, an antibiotic which may act as a medicine against itching, may also be administered [28]. Opioid antagonists containing naloxone or naltrexone inhibit pruritus by their effects on the central nervous system [29].

### **3.3 Treatment for dry eyes and mouth as in pSS**

#### *3.3.1 General treatment*

Ursodeoxycholic acid (UDCA) is the main medication used in biliary cholangitis. A complementary therapy with obeticholic acid was introduced in 2016, as second-line treatment. If the UDCA treatment is ineffective, the use of fibrates (e.g., bezafibrate) in combination therapy (UDCA plus fibrate) is also considered; ongoing clinical trials have yielded encouraging results [30]. Of the immunosuppressants, the use of methotrexate (MTX), as a drug which may affect pruritus score, serum level of alkaline phosphatase, or IgM level, is discussed [31], although there were observations that MTX could increase mortality in this group of patients [32]. There were clinical trials with rituximab [33] and with ustekinumab [34], but at the present time, they have not produced positive results to the expected extent. The liver transplant aims at prolonging the patient's life, but it is reported that up to 29% of patients develop a relapse of the disease in the transplanted organ [35]. Therefore, the use of UDCA after transplantation is still recommended.

#### *3.3.2 Changes in the style of life*

PBC is a chronic autoimmune liver disease in which a lifestyle is particularly important. Reducing the intake of foods with high sodium content, avoiding alcohol, as well as being careful with new medications or dietary supplements are extremely important. Physical exercise is recommended to reduce risk of bone loss and muscle weakness.

## **4. Conclusions**

The epithelium is an important element of the human body due to its protective, secretory, and transporting functions. It is also the target for the immunological


processes. The impact of environmental, genetic, and epigenetic factors, leading to the epithelial cell damage/apoptosis, may cause a breakdown of epithelium hemostasis and the development of autoimmune diseases, Sjögren's syndrome being its prominent representative. For years pSS was associated with autoimmune epithelial inflammation and referred to as the "autoimmune epithelitis." However, the spectrum of diseases related to the epithelial autoimmunity is wider including, e.g., primary biliary cholangitis. The damaged epithelium is a source of autoantigens, and a persistent immune cell stimulation may lead to the lymphomas associated with the mucosa. Adoption of a wider perspective, combining the clinical experience and scientific knowledge, in an approach to the problem of epithelitis enables making the connection between emerging symptoms and autoimmune diseases, leading to the earlier diagnosis and introduction of proper treatment. Thus the reduction in an activity of the immune process and inhibition of further damage to the epithelium and of loss of its protective properties can be achieved.

## Author details

Maria Maślińska  
National Institute of Geriatrics, Rheumatology and Rehabilitation, Early Arthritis  
Clinic, Warsaw, Poland

\*Address all correspondence to: [maslinskam@gmail.com](mailto:maslinskam@gmail.com)

## IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 



## References

- [1] Honda K, Littman DR. The microbiota in adaptive immune homeostasis and disease. *Nature*. 2016;**535**(7610):75-84
- [2] Mandl T, Marsal J, Olsson P, Ohlsson B, Andréasson K. Severe intestinal dysbiosis is prevalent in primary Sjögren's syndrome and is associated with systemic disease activity. *Arthritis Research & Therapy*. 2017;**19**(1):237
- [3] Chistiakov DA. Immunogenetics of Hashimoto's thyroiditis. *Journal of Autoimmune Disease*. 2005;**2**(1):1
- [4] Ziegler AG, Nepom GT. Prediction and pathogenesis in type 1 diabetes. *Immunity*. 2010;**32**(4):468-478
- [5] Mitsias D, Kapsogeorgou E, Moutsopoulos H. Sjögren's syndrome: Why autoimmune epithelitis? *Oral Diseases*. 2006;**12**:523-532
- [6] Voulgarelis M, Tzioufas AG. Current aspects of pathogenesis in Sjögren's syndrome. *Therapeutic Advances in Musculoskeletal Disease*. 2010;**2**(6):325-334
- [7] Webb GJ, Siminovitch KA, Hirschfield GM. The immunogenetics of primary biliary cirrhosis: A comprehensive review. *Journal of Autoimmunity*. 2015;**64**:42-52. DOI: 10.1016/j.jaut.2015.07.004
- [8] Selmi C, Meroni PL, Gershwin ME. Primary biliary cirrhosis and Sjögren's syndrome: Autoimmune epithelitis. *Journal of Autoimmunity*. 2011;**39**(1-2):34-42
- [9] Zhu Y, Ma X, Tang X, Hua B. Liver damage in primary biliary cirrhosis and accompanied by primary Sjögren's syndrome: A retrospective pilot study. *Central-European Journal of Immunology*. 2016;**41**, 2:182-187
- [10] Huang XF, Cheng Q, Jiang CM, et al. The immune factors involved in the pathogenesis, diagnosis, and treatment of Sjögren's syndrome. *Clinical and Developmental Immunology*. 2013. Article ID 160491
- [11] Imgenberg-Kreuz J, Sandling JK, Nordmark G. Epigenetic alterations in primary Sjögren's syndrome—An overview. *Clinical Immunology*. 2018;**196**:12-20
- [12] García-Carrasco M, Fuentes-Alexandro S, Escárcega RO, et al. Pathophysiology of Sjögren's syndrome. *Archives of Medical Research*. 2006;**37**(8):921-932
- [13] Kapsogeorgou EK, Moutsopoulos HM, Manoussakis MN. Functional expression of a costimulatory B7.2 (CD86) protein on human salivary gland epithelial cells that interacts with CD28 receptor, but has reduced binding to CTLA4. *Journal of Immunology*. 2001;**166**:3107-3113
- [14] Matsumura R, Umemiya K, Goto T, et al. Glandular and extraglandular expression of costimulatory molecules in patients with Sjögren's syndrome. *Annals of the Rheumatic Diseases*. 2001;**60**:473-482
- [15] Youinou P, Pers JO. Disturbance of cytokine networks in Sjögren's syndrome. *Arthritis Research & Therapy*. 2011;**13**:227
- [16] Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European league against rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. *Arthritis & Rheumatology*. 2016;**69**(1): 35-45. DOI: 10.1002/art.39859
- [17] Szymula A, Rosenthal J, Szczerba BM, Bagavant H, Fu SM, Deshmukh US. T cell epitope mimicry between

- Sjögren's syndrome antigen A (SSA)/Ro60 and oral, gut, skin and vaginal bacteria. *Clinical Immunology*. 2014;**152**(1-2):1-9
- [18] Cackowska-Lass A, Kochańska B, Naumiuk Ł, Samet A. Saliva secretion and prevalence of some microorganisms in the oral cavity in patients with Sjögren's syndrome. *Czasopismo Stomatologiczne*. 2010;**63**(2):79-89
- [19] Szodoray P, Barta Z, Lakos G, Szakáll S, Zeher M. Coeliac disease in Sjögren's syndrome—A study of 111 Hungarian patients. *Rheumatology International*. 2004;**24**(5):278-282
- [20] Lidén M, Kristjánsson G, Valtýsdóttir S, Hällgren R. Gluten sensitivity in patients with primary Sjögren's syndrome. *Scandinavian Journal of Gastroenterology*. 2007;**42**(8):962-967
- [21] Baimpa E, Dahabreh IJ, Voulgarelis M, Moutsopoulos HM. Hematologic manifestations and predictors of lymphoma development in primary Sjögren syndrome: Clinical and pathophysiologic aspects. *Medicine (Baltimore)*. 2009;**88**(5):284-293
- [22] Hayashi D, Devenney-Cakir B, Lee JC, et al. Mucosa-associated lymphoid tissue lymphoma: Multimodality imaging and Histopathologic correlation. *American Journal of Roentgenology*. 2010;**195**(2):W105-W117
- [23] Nocturne G, Mariette X. Sjögren syndrome-associated lymphomas: An update on pathogenesis and management. *British Journal of Haematology*. 2015;**168**:317-327
- [24] El Miedany YM, Baddour M, Ahmed I, Fahmy H. Sjogren's syndrome: Concomitant *H. pylori* infection and possible correlation with clinical parameters. *Joint, Bone, Spine*. 2005;**72**:135-141
- [25] Cesta MF. Normal structure, function, and histology of mucosa-associated lymphoid tissue. *Toxicologic Pathology*. 2006;**34**(5):599-608
- [26] Ramos-Casals M, Brito-Zerón P, Sisó-Almirall A, Bosch X, Tzioufas AG. Topical and systemic medications for the treatment of primary Sjögren's syndrome. *Nature Reviews Rheumatology*. 2012;**8**(7):399-411
- [27] P1 B-Z, Sisó-Almirall A, Bové A, Kostov BA, Ramos-Casals M. Primary Sjögren syndrome: An update on current pharmacotherapy options and future directions. *Expert Opinion on Pharmacotherapy*. 2013;**14**(3):279-289
- [28] Khurana S, Singh P. Rifampin is safe for treatment of pruritus due to chronic cholestasis: A meta-analysis of prospective randomized-controlled trials. *Liver International*. 2006;**26**(8):943-948
- [29] Trivedi HD, Lizaola B, Tapper EB, Bonder A. Management of Pruritus in primary biliary cholangitis: A narrative review. *American Journal of Medicine*. 2017;**130**:744-744.e7
- [30] Corpechot C, Chazouillères O, Rousseau A. A placebo-controlled trial of bezafibrate in primary biliary cholangitis. *New England Journal of Medicine*. 2018;**378**:2171-2181
- [31] Giljaca V, Poropat G, Stimac D, Gluud C. Methotrexate for primary biliary cirrhosis. *Cochrane Database of Systematic Reviews*. 2010;**5**:CD004385
- [32] Gong Y, Gluud C. Methotrexate for primary biliary cirrhosis. *Cochrane Database of Systematic Reviews*. 2005;**3**:CD004385
- [33] Tsuda M, Moritoki Y, Lian ZX, et al. Biochemical and immunologic effects of rituximab in patients with primary biliary cirrhosis and an incomplete response to ursodeoxycholic acid. *Hepatology*. 2012;**55**:512-521

[34] Hirschfield GM, Gershwin ME, Strauss R, et al. Ustekinumab for patients with primary biliary cholangitis who have an inadequate response to ursodeoxycholic acid: A proof-of-concept study. *Hepatology*. 2016;**64**:189-199

[35] Montano-Loza AJ, Bhanji RA, Wasilenko S, Mason AL. Systematic review: Recurrent autoimmune liver diseases after liver transplantation. *Alimentary Pharmacology & Therapeutics*. 2017;**45**:485-500. DOI: 10.1111/apt.13894