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Chapter 5

Autoimmunity of Gastrointestinal Tract

Anna Pituch-Noworolska and Monika Mach-Tomalska

Additional information is available at the end of the chapter

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Abstract

Gastrointestinal tract diseases are recognised as autoimmune based on typical histopathology, presence of autoantibodies in serum and clinical response to immunosuppressive therapy. Like in other autoimmune diseases, the inducing factor is unknown; however, accumulating data suggests an increasing role of microbiota homeostasis and relation between the immune system (mucous-associated lymphoid tissue) and microbiota in intestinal lumen. The inflammation process is now described as autoinflammation with inflammasome formation or autoimmune chronic inflammation with overproduction of pro-inflammatory cytokines. Diagnostic procedures include autoantibodies assay, histology of biopsy from intestinal mucous, genetic background (especially in celiac disease) and clinical symptoms. Therapy is adjusted to pathomechanism including regulation of microbiota homeostasis with pre-biotics and probiotics, inhibition of inflammatory process with steroids, classical immunosuppression and anti-cytokine monoclonal antibodies and haematopoietic stem cells transplantation in severe cases with therapy resistance, progression and life-threatening course. The aim of this chapter is to review mechanisms of autoinflammation and autoimmunity, diagnosis and therapy of gastrointestinal tract.

Keywords: autoimmunity, autoinflammation, microbiota homeostasis, pro-inflammatory cytokines, autoantibodies, immunosuppression, monoclonal antibodies

1. Introduction

Autoimmunity is the aberrant reaction of specific immune system to autoantigens. The stimuli leading to recognition of own determinants, receptors, cell products as antigens, followed by activation of T and B lymphocytes are unknown. The genetic background is described in few diseases from a long list of autoimmune syndromes. This aberrant reaction of immune system is irreversible, so the diagnosis of autoimmune process makes it lifelong one. The criteria of auto-
immune process include tissue infiltration with immunocompetent cells, overproduction of pro-inflammatory cytokines, and production of autoantibodies by plasmocytes. This process is going for years before clinical manifestation as an effect of non-reparable tissue damage. Autoimmune diseases are classified as systemic or organ-specific, based on origin of autoantigen and involved organs being the target for autoantibodies and deposits of immune complexes binding and activating complement cascade. The presence of autoantibodies in serum is one of the laboratory criteria for the ongoing autoimmune process; moreover, the precise description of the type and amount of autoantibodies suggests the type of disease. The aim of this chapter is to review mechanisms of autoinflammation and autoimmunity, diagnosis and therapy of gastrointestinal tract.

2. Physiology of gastrointestinal tract mucous membrane

2.1. The role of microbiota

In our intestinal lumen exists about $10^{14}$ commensal organisms in symbiotic relation with the host. The interaction of microbiota and intestinal immune system including innate and adoptive immune mechanisms is bidirectional—microorganisms are influencing activity of cells present in epithelial cell monolayer and activity of immune cells is regulating commensal microbiota compound, localization and attachment to epithelial cells [1, 2]. The newborn babies acquire the microbiota during vaginal birth. It is obvious that caesarean section obviates contact with vaginal microenvironment and that resulted in differences of microbiota. The colonization of intestine at birth affects innate and adaptive immune system associated with mucous membrane of gut [3]. The response of immune system differentiating between commensal and invasive pathogens is not fully elucidated yet. The role of toll-like receptors (TLR), especially TLR5 for bacterial flagellin, is described based on inflammation in deficiency of this receptor. TLRs are pathogen recognition sensors detecting bacteria, viruses and fungi. Stimulation of TLRs and NOD-like receptors (NLRs) leads to the production of pro-inflammatory cytokines and formation of protein complex called inflammasome. NLRs are the group of intra-cellular pattern recognition receptors (PRRs) involved in the recognition of many DAMPs and PAPMs (danger and pathogen-associated molecular patterns) in commensal and pathogenic microbiota. Inflammasome is a crucial structure for defence to pathogens but, from the other perspective, is involved in pathogenesis of autoinflammatory and autoimmune diseases following the prolonged inflammatory process [4–6]. The forming of inflammasome is not the only way of interaction between microbiota and immune systems. Another is based on influence of bacterial metabolites and its components such as fatty acids on epithelial cells inducing production of antimicrobial peptides (AMP). Stimulated epithelial cells produce IL-25 directly reacting with myeloid cells present in mucous. The cascade of activation resulted in stimulation of ILC3 subpopulation of immune system and production of cytokines [5].

2.2. The immune system of mucous membrane

The mucous membrane is one of our defence mechanisms against pathogenic microorganism intake with food into intestinal lumen. Its basic role is to regulate the response of immune
system to pathogens and the homeostasis of commensal microbiota. The epithelial layer consists of different cells like epithelial cells, M cells, Paneth cells and goblet cells with specific function of mucous production. There are differences of stages of in situ maturating along transposition from crypts to the surface of epithelial layer. Moreover, some observations suggest the cross-talk between epithelial cells and commensal microbiota facilitating to maintain homeostasis and to improve response to infectious pathogens. Paneth cells are localized close to crypts in the villi of small intestine. The expression of MyD88 molecule is important for TLR-MyD88-dependent pathway of microbiota recognition. Stimulation of this way results in the production of antimicrobial factors such as defensin, CRP-ductin, RegIII-γ and others to protect the optimal environment for crypts’ stem cells. The goblet cells are also regulated partially through TLRs. The main role of goblet cells is production of mucins inhibiting the attachment of bacterial (commensal or pathogenic) to epithelial cells layer, particularly mucin-2, a main colonic gel-forming one. The role of M cells is based on uptake of antigens from luminal spaces and induction of antigen-specific immune response. Their localization in the follicles-associated epithelia of Payer’s patches and/or isolated lymphoid follicles facilitates the induction of antigen-specific immune response within the mucous membrane. The last study showed that M cells are the entry point for intra-tissues commensal flora inducing IgA production in Peyer’s patches. The last equally important cells from epithelial layer are columnar epithelial cells forming very tight monolayer surface barrier, being regulated by the commensal microbiota. The role of bridge between the innate and adaptive immune systems in mucous membrane plays interleukin 23 (IL-23). The axis IL-23/IL-17 is important for IL-17 producing cells-Th17 subpopulation of T lymphocytes. In mucosal sites, the cell populations consist of T lymphocytes derived mainly from TCRγ/δ subpopulation, Th17 lymphocytes, mature T lymphocytes TCRα/β (CD3/CD4, CD3/CD8) and dendritic cells, NK cells. IL-23 induces cytokines production by innate lymphoid cells (ILCs) discovered in the mucous system. ILCs belong to three different types—group 1: ILC1 and NK cells producing IFN-γ, group 2: ILC2 natural helper cells expressing retinoid acid receptor (RAR) and group 3: ILC3 including foetal lymphoid tissue inducer cells, population of NK cells (NK22, NKp46 positive/negative). ILCs produce IL-17A, IL-17F or IL-22. These groups differ in expression of receptors and, in consequence, play different regulatory roles in maintaining the homeostasis, induction of immune system response and inflammatory process. Th17 lymphocytes, localized in lamina propria, produce large amounts of cytokines: IL-17A, IL-17F, IL-21 and IL-22 after stimulation with IL-6 and TGF-β. Increased expression of IL-23 receptor on Th17 lymphocytes induces positive autoregulatory feedback loop. Cytokines produced by Th17 clear microbes reaching lamina propria, maintain tightness of mucous barrier. This subpopulation of T lymphocytes is very important in induction of inflammation, so the regulation of functions inhibits or induces this process. Moreover, within T lymphocytes was described small subpopulation with phenotype CD3/CD4/CD25 and FoxP3 called T regulatory cell with main function of regulation and control of the autoimmune process. Those Tregs are main producers of anti-inflammatory cytokines—IL-10 and TGF-β balancing pro-inflammatory derived activation of cells. The low number or dysfunction of these cells facilitates autoimmunity development. Those, depletion of Treg may explain the high frequency of autoimmune diseases among patients with humoral immunity deficiencies.
2.3. The role of IgA

Dimeric, secretory IgA (sIgA) is produced locally by B cells and plasma cells present in lamina propria, isolated lymphoid follicles (ILF) and subepithelial dome (SED) of Peyer’s patches in intestine wall. The J chain (joining chain) responsible for the dimeric structure of IgA contributes in binding of IgA to polymeric immunoglobulin receptor (pIgR) facilitating the transport through epithelial cells and release into intestinal lumen. The data about the role of sIgA systematically increase based on clinical symptoms and disturbances of gut microbiota homeostasis in patients with isolated IgA deficiency when IgG and IgM are replacing sIgA. Now, the sIgA role is well known. Molecules of sIgA bind to pathogens and block the attachment to epithelial cells and invasion into intestinal tissue. This activity of sIgA, called immunological exclusion, is very effective in defence of epithelial cells during the mucosal infections [8]. Moreover, IgA facilitates contact of the different particles from intestinal lumen with dendritic cells localized in SED of Peyer’s patches. IgA also plays a regulating role for commensal microbiota with large fraction coated with IgA in normal, homeostatic conditions [8]. Plasmablast-producing IgA is generated locally in GALT from naïve B cell, mainly in Peyer’s patches. IgA plasmablast migrates into intestinal lamina propria and maturates into IgA-antibody secreting cells (IgA-ASC) along this way. The regulation of this migration is based on the combination of cytokines and adhesion molecules expression e.g. CCR9 and CCR10—mucosa-specific chemokine receptors on IgA-ASC. The expression of ligands for these receptors showed different patterns depending on localization in intestine—jejunum or large bowel. Moreover, the types of antigens and their stimulation of IgA production are important for regulating IgA-dependent response in different parts of intestine. IgA production and maturation of plasmablasts are regulated by T cell–derived cytokines. T lymphocytes are involved in the formation of germinal centres and generation of IgA producing cells through, e.g., induction of activation-induced cytidine deaminase (AID) expression in B lymphocytes. This enzyme is critical for the process of a class switch recombination and hypermutation leading to production of IgA. Subpopulations of T cells—Th17 and Treg cells—play the special regulatory role for IgA transport through induction of expression of polymeric immunoglobulin (pIgR) receptor on epithelial cells. In promotion of IgA-producing cells, the following cytokines T lymphocytes-derived are involved—TGF-β, IL-4, IL-10 and IL-21. TGF-β acts on B lymphocytes as a promoter of naïve B cell proliferation and maturation, where IL-21 promotes the generation of IgA plasmablasts. The best effect on IgA production is noted when both cytokines are present and acts synergistically [9, 10].

3. Mechanisms of autoinflammatory process

3.1. The inflammation as a process occurs at the following situations

- First—acute response of immune system to pathogens invading the tissue after breaking the natural defence e.g. epithelial cells layer of mucous membrane etc. This process is terminated after elimination of pathogens with subsequent healing of damaged tissue process.
• Second—prolonged response due to recurrent fever episodes, recurrent inflammasome formation and overproduction of pro-inflammatory cytokines mediated by innate immune system. Here it belongs to a wide range of periodic fever syndromes. Nowadays, it is suggested, that Crohn’s disease, as the result of aberrant bacterial sensing, is fulfilling the criteria of autoinflammatory process.

• Third—chronic inflammatory reactions with production of autoantibodies against tissue and/or cellular elements resulting with irreversible damage of cells, tissues and organs. This self-directed and sustained chronic inflammation is typical for autoimmunity, mediated by adaptive immune system, immune complexes formation and complement activation [6, 11–13].

3.2. Inflammasome and innate immune system

The receptors of innate immunity components (cells) reacting with pathogen molecular patterns are called—pathogen patterns recognition receptors (PRRs). PRRs are reacting with pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). Within different types of PRRs, most important for inflammasome formation are ones from the nucleotide-binding domain leucine-rich repeat (NLRs) family. In human this family contains 22 genes, but the formation of inflammasomes (large protein complex) is associated with NLRP3, NLRP1, NLRC4 and AIM2. Inflammasome is a mediator of autoactivation of Caspase-1 and that in turn leads to activation of IL-1β and IL-18 [6, 13]. The inflammatory process with the inflammasome formation is associated with activation of neutrophils, monocytes and macrophages. Among the chronic inflammatory diseases of the gastrointestinal tract, Crohn’s disease seems to be mediated by autoinflammatory than autoimmune pathomechanisms.

3.3. From autoinflammation to autoimmunity

The products of inflammasome such as IL-1β and IL-18 influence not only innate immune system but also adaptive system, through activation of T and B lymphocytes. The up-regulation of IL-2 R (receptor for IL-2) expression on T cells, boosts of B cells–derived production of antibodies, supports prolonged survival of T and B lymphocytes. The other effects of these cytokines is acceleration of Th17 (by IL-1β) and Th1 (by IL-18), functional subpopulations of T cells, maturation [6]. The activity of overproduced cytokines in inflammasome bridges the innate and adaptive immunity system in reactions to pathogens. Apparently, there are some diseases with pathomechanisms of both types of chronic inflammatory reactions as a continuum from typical autoinflammatory to autoimmune disease. This hypothesis formed by Kastner [12] was based on shift of components of tissue infiltrations along the time of disease—during autoinflammatory stages, the majority of cells were—neutrophils, monocytes, macrophages and dendritic cells—smoothly transforming to infiltration typical for autoimmune process such as activated T and B lymphocytes producing typical profiles of cytokines, e.g. Th1, Th17 and autoantibodies [12].
4. Mechanisms of autoimmunity

4.1. Activity of immunocompetent cells and overproduction of cytokines

Mechanisms of supporting the self-tolerance are based on suppression of effector T lymphocytes proliferation and down-regulation of immune response [14]. The peripheral tolerance is regulated with different mechanisms, but a crucial role in maintaining this tolerance is played by regulatory T cells (Tregs). The dysfunction and/or decreased number of Tregs is associated with increased risk of autoimmunity, seen as a case in patients with humoral immunodeficiency (e.g. CVID), where more than 60% of patients demonstrate a low number of Tregs and co-existent autoimmune diseases such as diabetes mellitus type 1, systemic lupus erythematosus, celiac disease, thyroid diseases, etc. Naive Tregs are generated in thymus and transformed to inducible Treg (iTreg) in periphery, mainly in the gut. Tregs produce anti-inflammatory cytokines—TGF-β1, IL-10, IL-35 [14–16]. Immune response to pathogens includes differentiation of T lymphocytes into two functional subpopulations—T helper 1 (Th1) producing pro-inflammatory cytokines and T helper 2 (Th2) producing anti-inflammatory cytokines. Additional subpopulations of T lymphocytes are Th17 cells releasing IL-17 (IL-17A, IL-17F). The list of cytokines derived from cells involved in pathogens’ response is long, and among them, cytokines such as TNF and IL-22 also play an important role.

Activation of Th1 lymphocytes results in high level of IFN-γ and IL-2 and/or TNF. The Th1-derived profile of cytokines supports inflammation and induces fever and infiltrations in target tissues. Intra-cellular bacterias and micobacteria are killed by macrophages activated with Th17-derived cytokines [16, 17]. Th2 subpopulation balances pro-inflammatory cytokines activity due to anti-inflammatory suppressing role of IL-4, IL-5 and IL-13 [14–16]. The profile of cytokines typical for given subpopulation of Th cells is not limited and Th2 are producing small amount of TNF and IL-2 with pro-inflammatory activity. Stimulation of B cells towards immunoglobulins class switching is also associated with Th2 cells [16]. Stimulated B lymphocytes produce specific antibodies either, differentiate into memory cells subpopulation or mature into plasmablast and long-life plasmocytes. In terms of autoimmunity B cell differentiation and maturation is directed to autoantigens and result in autoantibodies production.

In last few years dysfunction of autophagy was declared a new crucial mechanism for development of inflammatory bowel diseases. In physiology autophagy is one of cellular stress response indispensable for adaptation to starvation, degradation of aberrant proteins or organelles. Moreover, genes loci associated with increased risk for IBD are shared with genes required for autophagy, suggesting possibility of autophagy disorders in IBD. In mucous membrane function, the disorders of autophagy affect some aspects of innate and acquired inflammatory response, e.g. function of Paneth cells, cytokines production, pathogens clearance and, what was showed in last time, decrease function of goblet cells and absorptive function of microvilli [18, 19].

4.2. Production and role of autoantibodies

The natural antibodies of IgM class with moderate self-antigen affinity play first-line role in defence against pathogens. The autoantibodies showing high affinity to our own antigens are
IgG class and are concerned as pathologic, although they are detected in low titres in serum of healthy individuals [20]. The reaction of IgG autoantibodies with antigens, circulating in serum or present in tissue, forms complexes activating complement pathway. Complement activation mediating tissue damage is concerned in systemic autoimmune disease e.g. SLE, less expressed in organ-specific diseases, when antibodies react with target antigen presented in given organ e.g. thyroid, Langerhans islet or suprarenal gland cells, ovary cells and others. Beside the role in tissue damage process, the presence of autoantibodies is the marker of autoimmune process and/or mechanism leading to clinical symptoms. Type and titre of antibodies circulating in serum support clinical diagnosis and help in differential diagnosis of overlapping syndromes. Association of autoantibody levels with clinical course of disease is rare, but important for therapy adjustment e.g. dsDNA level in SLE. In systemic autoimmune diseases the role of B-1 subset of B lymphocytes in autoantibodies production was suggested due to high effectiveness of B-1 cells in presenting antigen process [20]. The long list of different types of autoantibodies reflects the long list of structures inducing antigen-dependent B cells response. Autoantibodies against nuclear proteins and organelles are believed to be a consequence of exposing previously hidden antigens due to apoptosis, the presence of cell debris and disturbances of dying cell cleavage. The good example for cell debris serving as antigen is production of antibodies to cyclic citrullinated peptides (CCP) in rheumatoid arthritis as a result of acquired neoepitope after prolonged inflammation. The autoantibodies used as a marker of autoimmune disease are helpful in diagnosis in overt disease; however, they are present also in detectable traces in sera symptom-free patients’ family members, indicating a higher risk of autoimmune disease than that in general population. The careful monitoring is important to avoid not only overdiagnosis but also delay in diagnosis. Another problem is tied to sensitivity, specificity and frequency of autoantibodies—some of them are clinically significant, but observed in minority of patients, in opposite to antibodies noted in high amount of patients, but with low specificity e.g. rheumatoid factor for rheumatoid arthritis.

In gastrointestinal tract autoantibodies are indicative for autoimmune gastritis, liver diseases, biliary tract pathologies, ulcerative colitis and celiac disease. According to definition and criteria of autoimmune and autoinflammatory disease, Crohn’s disease is nowadays considered to be autoinflammatory syndrome due to activation of innate immune system and lack of autoantibodies production. The autoantibodies typical for gastrointestinal diseases are shown in Tables 1 and 2.

<table>
<thead>
<tr>
<th>Diseases and autoantibodies to</th>
<th>Assay</th>
<th>Clinical significance and comments</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac disease (CD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissues transglutaminase</td>
<td>ELISA</td>
<td>Highly specific, quantitative assay, diagnosis and monitoring GFD</td>
<td>Significant in IgA class, IgG in isolated IgA deficiency</td>
</tr>
<tr>
<td>Reticulin (endomysial)</td>
<td>IIF</td>
<td>Qualitative assay</td>
<td></td>
</tr>
<tr>
<td>Atrophic gastritis (AIG)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parietal cells (PCA) (antigen: H+/K+ATPase)</td>
<td>IIF</td>
<td>Specific for gastritis, quantitative assay is significant for diagnosis and monitoring</td>
<td>Often associated with thyroid autoimmunity</td>
</tr>
<tr>
<td>Diseases and autoantibodies to</td>
<td>Assay</td>
<td>Clinical significance and comments</td>
<td>Comments</td>
</tr>
<tr>
<td>-------------------------------</td>
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</tr>
<tr>
<td>Intestine diseases (IBD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ULCERATIVE COLITIS: goblet cells (anti-mucin)</td>
<td>IIF</td>
<td>About 60% patients of UC, about 30% of Crohn’s disease</td>
<td>Differences between regions of large bowel</td>
</tr>
<tr>
<td>pANCA (anti-MPO)</td>
<td>IIF</td>
<td>About 80% of UC patients</td>
<td>Present in PBC and AIH patients</td>
</tr>
<tr>
<td>Crohn’s disease:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCA</td>
<td>ELISA</td>
<td>About 80% of Crohn’s patients</td>
<td>Up to 25% in 1st degree relatives</td>
</tr>
<tr>
<td>Anti-pancreatic (PAB) (anti-acinar cells)</td>
<td>IIF</td>
<td>About 30% of Crohn’s patients with disease localized in proximal jejunum</td>
<td>High specificity but low frequency</td>
</tr>
</tbody>
</table>

Table 1. Autoantibodies detected in serum patients with gastrointestinal disease, their clinical significance in diagnosis and differential diagnosis. *Acc.* [29, 33, 34, 38, 39, 43, 56].

<table>
<thead>
<tr>
<th>Type of antibodies</th>
<th>Patients</th>
<th>Antigen</th>
<th>Other comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIH type 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antinuclear (ANA)</td>
<td>35–40%</td>
<td>Chromatin, histones, centromere, dsDNA, ssDNA, ribonucleoprotein complexes</td>
<td>Non-specific for AIH, seen in other autoimmune diseases</td>
</tr>
<tr>
<td>Anti-smooth muscles (SMA)</td>
<td>85%</td>
<td>Microfilaments, intermediate filaments-vimentin, desmin, polymerised F-actin</td>
<td>Subset of SMA, poor prognosis</td>
</tr>
<tr>
<td>Anti-actin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinuclear antineutrophil antibodies (pANCA)</td>
<td>100%</td>
<td>Peripheral nuclear membrane components (pANNA), myeloperoxidase (pANCA)</td>
<td>pANNA specific for AIH-1 in absence of other antibodies</td>
</tr>
<tr>
<td>AIH type 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver kidney microsomal (LKMA)</td>
<td>100%</td>
<td>Cytochrome P450D6</td>
<td>Present in HCV, CMV and HSV infections</td>
</tr>
<tr>
<td>Soluble liver antigen (SLA)</td>
<td>58–60%</td>
<td>O-phosphoserine tRNA, SEC tRNA synthetase</td>
<td>Aggressive course, relapses, poor prognosis</td>
</tr>
<tr>
<td>Liver cytosol-1 (LC-1)</td>
<td>60%</td>
<td>Formiminotransferase cyclodeaminase</td>
<td>Rapid progress to cirrhosis</td>
</tr>
<tr>
<td>PBC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMA2, 4, 8, 9</td>
<td>90–100%</td>
<td>AMA 2-inner membrane, AMA 4- 8- 9 outer membrane of mitochondrion</td>
<td>Titre and type are not related to course of PBC</td>
</tr>
<tr>
<td>PSC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinuclear antineutrophil antibodies (pANCA)</td>
<td>90%</td>
<td>Non-specific, often in patients with PSC and IBD</td>
<td>Non-specific, often in patients with PSC and IBD</td>
</tr>
</tbody>
</table>

Table 2. Autoantibodies used for diagnosis of liver and biliary tract diseases. *Acc.* [34, 42, 44, 46, 59].
4.3. Tissue damage

In systemic autoimmune diseases, autoantibodies are playing role in tissue damage through formation of immune complexes activating classical complement cascade leading to membrane attack complex (MAC) formation. Excluding celiac disease, the role of autoantibodies in gut autoimmunity, is not fully understood, generally used as marker of process, then mechanism of tissue damage. Based on these observations, changes in tissue with irreversible damage might be described as three different components:

• First—infiltration of lymphocytes from deep crypt level to the top of villi. Flow cytometry and histochemistry analysis characterise these cells as T lymphocytes, activated T cells, B cells, plasmoblasts and plasmocytes locally producing autoantibodies. Number of intraepithelial lymphocytes (IEL) is high and infiltrating cells often formed secondary lymph nodules. Chronic inflammation is sustained by production of pro-inflammatory cytokines, and results in visible thickening of intestine wall.

• Second—presence of fibroblasts and progressing fibrotic process e.g. in liver leading to cirrhosis, in small and large ducts of biliary system leading to their walls thickening and narrowing the lumen and at the end their obstruction.

• Third—presence of other cells e.g. neutrophils, macrophages in infiltrations. These short living cells are dying within infiltrations in neighbourhood of hyper-activated adaptive immune system, what facilitates recognition of antigens and production of autoantibodies e.g. antinuclear, to myeloperoxidase (pANCA) and to others organelles. These cells produce various factors attracting new cells to come and support progression of infiltrations. They also produce variety of different trophic factors e.g. VEGF supporting neovascularisation for better nutrition of cells forming increasing infiltrations and process of fibrosis. Neutrophils form microabscesses within intestinal wall and macroabscesses between intestine loops [21–27].

Lymphocytes present in inflammation site under the epithelial layer are activated in sequential steps to develop and support chronic inflammation resulting in tissue damage. Initially, Th0 cells are activated and differentiate into different T lymphocytes functional subpopulation—Th1 with stimulation of IL-12, IL-18; Th17 with stimulation of IL-6 and TGF-β and Th2 with help of IL-4. IFN-γ and TNF, produced by Th1, activate macrophages and, in autocrine and paracrine mechanisms, stimulate further production of TNF. This activation is associated with induction of epithelial cells apoptosis and damage to first defending cellular barrier. High level of TNF facilitates maturation of stromal cells into myofibroblasts releasing metalloproteinases—tissue degrading enzymes (MMPs). IL-17 produced by Th17 is responsible for recruiting neutrophils into infiltrations during active inflammation. Even more complex and indirect is the role of IL-21, another cytokine produced by Th17, engaged in supporting of MMPs production followed by enterocyte apoptosis and basement membrane degradation [4]. In process of inflammatory infiltration formation, there is additional small subpopulation of cells with lymphocytic morphology, but without lineage determinants expression. These cells are called innate lymphoid cells (ILCs) and have ability to produce cytokines [17, 21].
5. Genetic associations of celiac disease and inflammatory bowel diseases

Observations of familiar occurrence of celiac disease indicated genetic background associated with MHC determinants. Now, this background is defined as expression of HLA-DQ2 and/or HLA-DQ8 in patients’ cells. Expression of one or both of these determinants in relatives of celiac disease patient suggests introduction of diagnostic procedures for atypical (latent, late-onset) form of celiac disease \[27–29\]. In Crohn’s disease (CD) and ulcerative colitis (UC) the genetic background was unknown until discovery of variation of NOD2 gene and IL-23 receptor gene. NOD2 is associated with severe, stricturing/penetrating course of Crohn’s disease thus helps in selecting patients for more aggressive therapy. Similar association is described for DRB1*0103 and severe clinical course of UC \[30, 31\]. The high number of susceptibility loci discovered in Crohn’s disease, now is described also for ulcerative colitis. The list of susceptibility loci for CD and UC is shown in Table 3 with column list loci common for both diseases \[30, 32\]. The precise role of these loci in facilitation of development of autoimmune disease (UC) or autoinflammatory disease (CD) of gastrointestinal tract is unknown. Although, the specific role of particular genes is known—genes NOD2, IIRGM, ATG16L1 in autophagy and innate immunity mediated processing of bacteria in autoinflammatory process, genes HNF4A, LAMB1, CDH1 in epithelial barrier function, see Table 3.

6. Serological diagnosis and monitoring of disease’s course

The autoantibodies and antibodies in serum are detected by using indirect immunofluorescence, ELISA technique, blotting technique and radioimmune assay (RIA). In indirect immunofluorescence (IIF), the antibodies react with tissue sections and the results are visible as

<table>
<thead>
<tr>
<th>Susceptibility loci in Crohn’s disease</th>
<th>Susceptibility loci common in Crohn’s and ulcerative colitis</th>
<th>Susceptibility loci in ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOD2, ATG16, IIRGM, LRRK2</td>
<td>IL23R, IL12B, STAT3, AK2, TYK2</td>
<td>ECM1, NHF4A, CDH1, LAMB1, GNA12</td>
</tr>
<tr>
<td>PTPN22, CCR6, IL2RA, IL18RAP, IL27,</td>
<td>MST1, IL10, CARD9, REL, PRDM1, TNFSF15, ICOSLG, IL1R2,</td>
<td>INFγ/IL26, IL8RA/IL8RB, IL2/IL21, IL7R,</td>
</tr>
<tr>
<td>ERAP2, ITLN1, CCL2/CCL7, TNFSF11,</td>
<td>YDJC, SMAD3, PTPN2</td>
<td>TNFSF14, IRF5, LSP1</td>
</tr>
<tr>
<td>BACH2, TAGAP, VAMP3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DENND1B, DNMT3A, GCKR, THADA,</td>
<td>NXX2-3, CREM, C11Orf30, ORMDL3, RTEL1, PTGER4, KIF21B,</td>
<td>OTUD3/PLA2G2E, DAP, PIM3, CAPN10</td>
</tr>
<tr>
<td>SPI10, PRDX5, ZFEP6L1, ZMIZ1, MUC1,</td>
<td>CDKAL1, ZNF365</td>
<td></td>
</tr>
<tr>
<td>CPEB4, FADS1, Sq31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA DRB1*0103</td>
<td></td>
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</tr>
</tbody>
</table>

Table 3. List of susceptibility loci for inflammatory chronic disease of small (Crohn’s disease) and large intestine (ulcerative colitis). Acc. \[19, 30\].
fluorescence of indicator tissue or cell structure (e.g. nucleus, nucleolus, centromeres, nucleus membrane proteins) after reaction with antibody. IIF helps to answer if the antibodies are present in patient’s serum and what is an antigen. Semiquantitative IIF indicating titre of antibodies is based on patient’s serum dilution to end-titre of positive reaction and comparison to end-titre of control serum. In case of antinuclear antibodies presence in serum, IIF is an initial step for making diagnosis. Positive result of IIF assay (end-titre higher than control) is followed by ELISA (enzyme-linked immunosorbent assay) or blotting test with eluated, precisely described antigen, e.g. dsDNA, SS-A, SS-B, Jo-1 and others associated with particular autoimmune disease, e.g. SLE, systemic sclerosis, polymyositis, neonate lupus. IIF is still used for detection of parietal cells, goblet cells antibodies, pANCA, anti-mitochondrial, LKMA and anti-smooth muscles antibodies. In ELISA, results are quantitative based on colorimetric reaction with enzyme substrate. ELISA is used for detection of antibodies to tissue transglutaminase (TTG) in diagnosis and monitoring of celiac disease, ASCA in Crohn’s disease, SLA antibodies in AIH. Now, ASCA are selected from Saccharomyces cerevisiae membrane antigens—laminaribiose, chitobiose, mannobioside, laminarin, chitin and are detected in ELISA tests. The blotting technique tests are used for anti-mitochondrial antibodies type 2,4,9, antinuclear antibodies for eluated antigens detection. The RIA is last method used for antibodies detection based on counting of isotope radiation after reaction of autoantibodies with eluated antigen. This method is used for detection of antibodies circulating in low level, often below detection by above-mentioned methods, but still important for diagnosis or monitoring of disease. The typical use of RIA is detection of anti-TSH receptor antibodies in patients with thyroid diseases, autoantibodies in diabetes mellitus type 1 (GABA, insulin antibodies and others). RIA is not a common technique, because of the requirement of special isotopic laboratory. Detection of autoantibodies is generally used for diagnosis of autoimmune diseases in symptomatic individuals or in population with high risk of given disease and/or with unspecific symptoms, e.g. growth below expected, underweight, chronic diarrhoea and others typical for celiac disease. Some of antibodies are used for monitoring of therapy results—TTG antibodies in celiac patients on gluten free diet (GFD), dsDNA for SLE therapy, anti-TPO antibodies for Hashimoto disease on supplement therapy [33–46].

7. Microscopic diagnosis of inflammatory bowel diseases and celiac disease

Microscopic evaluation of mucous membrane in celiac disease, Crohn’s disease and ulcerative colitis showed infiltration containing immunocompetent cells with majority of lymphoid phenotype. Biopsy is indicated for staging of villi damage in classic and atypical celiac disease, description of cellular infiltrations in Crohn’s disease and ulcerative colitis. In liver diseases biopsy is essential for diagnosis and monitoring the progress of fibrosis changes leading to cirrhosis. Biopsy is usually taken during endoscopy of the upper and lower gastrointestinal tract from different parts of intestine, in majority cases from places with visible macroscopic changes. In many cases, biopsy specimens taken from normally looking mucous membrane showed the microscopic changes (infiltrations with lymphocytes and neutrophils, increased number of EIL and other), what suggested occurrence of chronic subclinical inflammatory process [24–27, 31].
8. Clinical symptoms of autoimmune diseases of gastrointestinal tract

8.1. Celiac disease

Classical celiac disease is observed in small children after introduction of gliadin, secalin or hordein (components of gluten) in diet. Typical symptoms include chronic diarrhoea, inhibition of weight gain or weight loss, abdominal pain, recurrent aphthous, changes in behaviour—‘negativity’, (“mister/miss no”). In delay of diagnosis the inhibition of growth, changes in enamel, low protein level lead to muscles atrophy confirmed inadequate absorption. Nowadays, this typical clinical picture is noted in no more than 15% of patients with genetically proved diagnosed celiac disease. Celiac disease may be diagnosed in any age, even in people after 50 years old. This celiac disease diagnosed later than in small children is called—latent, atypical or silent. Symptoms seen in adults are different than observed in small children. More often there are effects of defective absorption such as—anaemia due to iron deficiency, osteopenia/osteoporosis, enamel defects, aphths, (aphthous stomatitis), feeling of malaise chronic or intermittent diarrhoea, but also constipation, abdominal pain, discomfort, vomitus. Celiac disease is often associated with other autoimmune disease e.g. diabetes mellitus type 1, autoimmune thyroid diseases, autoimmune liver disease, autoimmune thrombocytopenia (mainly chronic), autoimmune Addison’s disease. Moreover, celiac disease occurred about 20 times more frequently, in children with isolated IgA deficiency, CVID with low level of IgA and in about 80% of patients with dermatitis herpetiformis. Untreated celiac disease in young adults leads to unexplained subfertility, recurrent miscarriages, increasing the risk of lymphoma and gastric/large bowel carcinoma. The therapy is based on restricted gluten-free diet (GFD) [26–29, 47–50]. In humoral immunodeficiency, in about 5% of patients, the celiac disease is refractory to GFD. In refractory celiac disease (RCD), all clinical symptoms such as progressing malabsorption causing inhibition of growth, loss of weight, undernourishing, low level of vitamins, iron and proteins are observed. Moreover, introduction of immunosuppressive therapy resolves symptoms transiently or even. Patients required enteral or total parietal nutrition (TPN) for long time as supportive therapy. The use of monoclonal antibodies against TNF and/or IL-6, different combinations of immunosuppressive drugs result in partial and terminal remission in majority of patients. These patients are candidates for HSCT, even in poor clinical condition, because only this therapy offers possibility to cure the disease and save their life [51]. As alternative to HSCT from unrelated donor, autoHSCT was used for such patients with success in five out of eight patients with five-year survival in 66% [52].

8.2. Crohn’s disease

Crohn’s disease is lifelong disease with symptoms of chronic inflammation mediated by immune system. Like in other chronic inflammatory diseases, the inducing factor is unknown, but it is believed, that interaction between genetic background and environmental factors, mainly intestinal microbiota, leads to the disease. In last 20 years two tendencies are noted: increased number of patients and decrease in age, so children before age of 2 years fulfilling the criteria of CD are observed [19, 25, 31, 53]. The clinical symptoms are very heterogeneous, due to localization of inflammation in any part of gastrointestinal tract from mouth to anus, age of patient,
time of process before onset [19]. Moreover, in many patients symptoms from gastrointestinal tract are mild or unspecific, but extra-intestinal symptoms signal chronic disease. The perianal abscesses, recurrent aphthous stomatitis, fistulas, anal fissures, joints pain are noted before typical gastrointestinal symptoms like chronic or intermittens diarrhoea, pain, blood in stool and others. In young children very often the acute stage of disease is severe followed by aggressive course. Disease activity is grading as mild (Crohn’s disease activity index—CDAI—150–220), moderate (CDAI—220–450) and severe (CDAI >450) [25]. Therapy is adjusted to symptoms and grading of disease at diagnosis. The antibodies to saccharomyces cerevisiae (ASCA) in IgA (and/or IgG class) are detected in high level what suggests increased intestinal barrier permeability and contact of microbiota with immunocompetent cells [19, 21, 22, 53]. Autoantibodies to acinar pancreatic cells are noted in patients with CD localized in proximal jejunum. However, the percentage of patients demonstrating these antibodies is low (about 30%), so there are not useful for diagnosis of CD. ASCA antibodies are not correlated with grading and course of disease, although, during the remission, level of ASCA is lower than in acute stage. The criterion of remission is resolving clinical symptoms up to CDAI <150 and maintenance at least for 12 months. The course of CD is unpredictable, so the remission maybe long lasting, short with relapses or chronic disease without remission. Localized disease limited to ileocaecal region only, may change into extensive disease affecting other regions in more than 100 cm in extent. In majority of patient response to steroids is very good with long remission, but in some patients, steroid-dependent form of disease or steroid-resistant form are observed. In both situations risk of accumulative side effects of steroids is high limiting prolong use of steroids, indicating introduction of second line therapy. Relapse is recognised, when symptoms are recurrent independently from therapy-maintaining remission. Diagnosis and monitoring of therapy is based on macroscopic and microscopic detection of features typical for CD. Biopsies during endoscopy are taken from involved and uninvolved areas for examination of focal or chronic inflammation, lymphocytic infiltrations, crypt irregularity, granulomas, irregular architecture of villi and other features typical for CD. In remission, biopsies from similar areas show healing of inflammation in different stages [25]. Introduction of monoclonal antibodies against TNF into therapy of CD revolutionised the therapy and medical care of CD patients, with improvement of long remission rate, comfort of live and survival of CD patients [31, 53].

8.3. Ulcerative colitis

Ulcerative colitis (UC) is a chronic inflammatory process localised exclusively in large bowel affected mucous in continuum. The course of disease is remitting and relapsing like Crohn’s disease. The problem of precise diagnosis is in cases with Crohn’s disease localised in large bowel overlapping clinical symptoms. Clinical symptoms in typical case of UC are associated with chronic diarrhoea, blood and mucin in stools, rectal bleeding, abdominal pain, cramps, feeling of rectal urgency and many others. The extra-intestinal symptoms are rare, present in about 10% patients with UC, as arthropathy, erythema nodosum preceding onset of typical symptoms from large bowel. In serum antibodies to pANCA are seen in about 80% of patients with typical clinical symptoms. Multiple biopsy of mucous membrane usually supports the clinical diagnosis of UC and helps in discrimination between Crohn’s disease localized in large bowel and UC. Microscopic features are divided into—architectural changes, epithelial
abnormalities and inflammatory features. Architectural features included crypt branching, crypt distortion, atrophy and surface irregularity. Epithelial cell abnormalities are—mucin depletion, metaplasia of Paneth cells. Inflammation is associated with infiltration lamina propria with lymphocytes, plasma cells and neutrophils, aggregates of lymphoid cells, in number of patients in lamina propria are numerous eosinophilic neutrophils. Cellular infiltrations are diffusive and transmucosal. Neutrophils migrating through crypts’ epithelium are producing crypts’ disruption and abscesses resulting in cell damage. Moreover, the stromal changes are associated with diffuse thickening of muscularis mucosa noted in patients with longstanding active disease or quiescent form of UC. Grading of UC is similar to Crohn’s disease as mild, moderate and severe based on number of bloody stools, temperature, pulse, CRP and anaemia as result of mucous bleeding. In remission the lesions of large bowel mucous are healed and clinical symptoms resolved. Relapses are rare or frequent, in some patients are continuous without clinical and histological remission [24]. Like Crohn’s disease patients are steroid-dependent or steroid-refractory, what means that therapy with steroids is not effective or effective only with high dose of steroids with risk of accumulation of side effects. Reduction of steroids dose resulted in recurrent active disease. Despite of steroid in first line 5-aminosalicylates are used but in patients with UC classified as moderate grade of disease activity. The second line of therapy included 6-mercaptopurine or azathioprine with good results in majority of patients. Good response to azathioprine or 6-mercaptopurine is associated with reduction of steroid dose what helps to avoid accumulation of side effects. Resistance to immunosuppressive therapy is indication for surgery or for biological therapy. Use of anti-TNF monoclonal antibodies gave remission in about 30% of patients. Monoclonal antibodies are used very often after surgery to prevent or reducing postoperative relapses. However, use of monoclonal antibodies, immunosuppressive therapy the rates of surgery in UC have not changed significantly [24, 54, 55]. Monoclonal antibodies used in therapy of UC are shown in Table 4.

8.4. Atrophic gastritis

Antibodies to parietal cells (PCA) are typical for autoimmune chronic gastritis (AIG) associated with megaloblastic anaemia in consequence of vit B12 and intrinsic factor low level due to disturbances of gastric mucous function. AIG suggested from clinical symptoms after demonstration of antibodies should be proven with gastroscopy and histological assay of mucous. Biopsy of gastric mucous is important for diagnosis of gastric cancer and premalignant stages. This wide diagnosis is important, due to prevalence of AIG in men. AIG is a progressing disease with atrophy of mucous membrane of corpus and fundus of stomach. AIG is very often noted as associated disease of thyroid autoimmune disease, diabetes type 1 in polyendocrine syndromes. In therapy, besides diet and parasols, vitamin B12 and intrinsic factor are administered parenterally with good effect in majority of patients [56, 57].

8.5. Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) was the first autoimmune disease associated with jaundice and liver cirrhosis with autoantibodies in serum significant for differential diagnosis
of autoimmune overlapping liver diseases. The anti-mitochondrial antibodies (AMA) are noted only in this type of biliary tract autoimmune diseases. There are typical for this type of cholangitis significant for serological diagnosis of PBC and differential diagnosis of overlapping autoimmune liver diseases [36, 58, 59]. Now, depending of antigens coming from different elements of mitochondria 9 types of AMA are described, but only AMA2, AMA4, AMA8 and AMA9 are specific for PBC and used for serological diagnosis [35, 44, 46]. ELISA technique is used for quantitative assay of AMA, but the amount of AMA is not associated with severity of symptoms and clinical course. Practically, it is enough to detect AMA2 in the serum to suggest the diagnosis of PBC [35, 59]. The study of association between MHC determinant and autoimmune disease showed the association of PBC with determinants: HLA-DR8, HLA-DR11 and HLA-DR13 in part of patients [59]. The inflammation and fibrotic process is progressing leading to cholestasis, portal fibrosis, liver cirrhosis and failure as end-stage of disease. Histological studies of biopsy showed 4 stages of PBC from portal inflammation (stage 1), through peri-portal fibrotic changes (stage 2) and bridging fibrosis (stage 3) up to symptomatic cirrhosis (stage 4) [59]. The clinical symptoms are unspecific for long time with the cholestasis as symptom of biliary ducts failure due to fibrosis followed by liver cirrhosis.

<table>
<thead>
<tr>
<th>Target</th>
<th>Monoclonal antibody</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF</td>
<td>Infliximab, Golimumab</td>
<td>CD, UC, RCD</td>
</tr>
<tr>
<td></td>
<td>Adalimumab, Humira</td>
<td>CD, UC, RCD</td>
</tr>
<tr>
<td></td>
<td>Certolizumab pegol</td>
<td>CD</td>
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<tr>
<td></td>
<td>Etanercept</td>
<td>CD</td>
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<tr>
<td>α4-integrin</td>
<td>Natalizumab</td>
<td>CD, UC</td>
</tr>
<tr>
<td>α4β7-integrin</td>
<td>Vedolizumab, Abrilumab</td>
<td>CD, UC</td>
</tr>
<tr>
<td>IL-12/IL-23</td>
<td>Ustekinumab, Briakinumab</td>
<td>CD</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Fontolizumab</td>
<td>CD</td>
</tr>
<tr>
<td>IL-6 receptor</td>
<td>Tocilizumab</td>
<td>CD</td>
</tr>
<tr>
<td>IL-2 receptor</td>
<td>Daclizumab</td>
<td>UC</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>Abatacept</td>
<td>CD, UC</td>
</tr>
<tr>
<td>CD20</td>
<td>Rixumab</td>
<td>CD, UC, RCD</td>
</tr>
<tr>
<td>JAK1,2,3</td>
<td>Tofacitinib</td>
<td>CD</td>
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<tr>
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<td>Masitinib</td>
<td>CD</td>
</tr>
<tr>
<td>Anti-sense ICAM-1 inhibitor</td>
<td>Alicaforsen</td>
<td>CD</td>
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</tbody>
</table>

Note: CD, Crohn's disease; UC, ulcerative colitis; RCD, refractory celiac disease.

Table 4. Monoclonal antibodies used in therapy of autoimmune and autoinflammatory diseases of gastrointestinal tract and liver. Acc. [53].
8.6. Primary sclerosing cholangitis and autoimmune sclerosing cholangitis

The primary sclerosing cholangitis (PSC) and autoimmune sclerosing cholangitis (ASC) belong to group of biliary ducts inflammation overlapping with chronic hepatitis leading to cirrhosis. HLA-DR1 and HLA-DQ1 are often noted within patients with PSC [59]. In these diseases the anti-mitochondrial antibodies (AMA) are absent; however, the other antibodies (pANCA) are present in 60–90% of patients [46]. These antibodies are not specific for PSC, but are supporting autoimmune mechanism in PSC. The histological changes are noted in intra-hepatic and extra-hepatic biliary ducts involving small and large ducts [58]. Diffused inflammation followed with fibrosis of biliary ducts is steroid resistant in majority of patients [36]. The development of PSC and ASC is insidious and symptomless upon the moment of onset of jaundice. Patients are claiming unspecific symptoms like abdominal pain (upper right quadrant), feeling fatigue and malaise, sometimes—pruritus. PSC is a disease associated with autoimmune hepatitis but very often is a co-existent disease in ulcerative colitis and other chronic inflammatory bowel diseases. Another association of PSC is IgG4-related disease; rare clinical symptoms present in different organs, including e.g. pancreas inflammation. The immunological assays show high level of IgG4 subclass of IgG what is critical for diagnosis of basic disease. The stenosis and fibrotic changes in biliary ducts extra- and intra-hepatic, changes in liver hilar are similar to PSC and ASC. However, in IgG4-related disease the therapy based on steroids is effective, what helps to differentiate from other forms of sclerosing cholangitis [41, 45, 58–60].

8.7. Autoimmune hepatitis

Autoimmune hepatitis (AIH), chronic liver inflammation is described as AIH type-1 and AIH type-2 based on profile of autoantibodies, time of onset and response to therapy. Aetiology of autoimmune hepatitis, like other autoimmune diseases, is unknown. Moreover, the precise role of autoantibodies in given types of hepatitis, relations between types of antibodies (e.g. combination ANA/SMA), pathomechanisms leading to good response or resistance to therapy and aggressiveness of course are far from description. AIH type 1 is specified by antinuclear (ANA), anti-smooth muscles (SMA) and anti-actin antibodies. In type 2 antibodies to liver microsomal antigen (LKMA-1) and liver cells cytosol antigens (LC-1) are significant. AIH type-1 is more frequent (>80%) than AIH type-2, observed in young people (majority of patients in age below 30 years) with very good response to therapy (mostly steroids). AIH type-2 is frequently noted in children with more aggressive course, resistance to therapy with cirrhosis in about 80% of patients. The serological diagnosis is clinical significant for the estimation of therapy strategy and prognosis for patient. Some of antibodies are related to course of disease and response to therapy, e.g. anti-actin antibodies are associated with higher frequency of liver failure and patients’ death, suggesting liver transplantation as life-saving procedure [59]. The presence of different profile of antibodies are seen in overlapping syndromes e.g. AIH and sclerosing cholangitis—ASC and hepatitis associated with viral infection e.g. in HCV. Difference between AIH and HCV with autoantibodies—ANA, SMA and LKMA—is histological—in HCV the tissue infiltrations containing plasma cells are absent. The occurrence of LKMA in HCV is probably the result of molecular mimicry of cytochrome 4502D6.
and viral genome [46]. Another typical combination of autoimmune diseases involving liver
is AIH and PBC resembled by presence of pANCA and AMA simultaneously. However, lon-
gitudinal study did not show the poorer prognosis of AIH patients with AMA compared to
AIH patients without AMA in serum [46]. The combination of AIH and sclerosing cholangitis
is sometimes classified as autoimmune sclerosing cholangitis—ASC [61].

Antibodies seen in AIH-1, AIH-2 and PBC are shown in Table 2.

8.8. Other diseases: autoimmune enteropathy

Autoimmune enteropathy (AE) is a rare disease noted in infants and young children. Clinical
symptoms included severe and protracted diarrhoea followed with weight loss, malabsorp-
tion syndrome. Pathomechanism is typical for autoimmune disease with the central role of
anti-epithelial antibodies. Expression of HLA class II determinants on the surface of epithe-
lial cells in case of AE is facilitating recognition of autoantigen and stimulation of immune
response with activated CD4 T lymphocytes [61]. Role of HLA class II determinants in AE
was supported by observation of aberrant expression on epithelial cell from the crypts and
overexpression by enterocytes suggesting local induction of autoimmune reaction with acti-
vation of intestinal T lymphocytes [62]. Clinical symptoms of AE are associated with autoim-
mune process against other organs and tissues. Besides autoantibodies against enterocytes,
in AE antibodies toward gastric parietal cells, pancreatic islets cells, insulin, GADA, goblet
cells, smooth muscles antigens, thyroid are noted. Combination of AE symptoms with auto-
imune polyendocrinopathy and skin manifestation is observed in IPEX syndrome [62, 63].
In biopsy of jejunum severe villi atrophy, inflammatory infiltrations with destruction of crypt
structure and depletion of goblet cells (in cases with anti-goblet cells antibodies) are observed.
In majority of patients increased apoptosis of epithelial crypts is seen as typical feature [63].
Inflammatory changes are noted not only in jejunum, but in large bowel and stomach also,
what indicate diffuse autoimmune disorder more difficult to control and release symptoms.
Management of these patients include immunosuppression (e.g., steroids, azathioprine,
cyclosporine, tacrolimus, MMF) and adequate nutritional support with correction of malab-
sorption effects, e.g., vitamins, calcium, proteins deficiency [62, 63]. In patients with poor
response to therapy, monoclonal antibodies to TNF and immunoglobulins in high dose were
introduced, but without breathtaking results. The good results on monotherapy were noted
with cyclophosphamide [62].

9. Therapy of autoimmune diseases of gastrointestinal tract

9.1. Microbiota correction and diet

The use of selected bacterias for modification of dysbiosis in inflammatory bowel diseases is
known from 1907 when consumption of fermented milk products containing Lactobacillus
bulgaricus were used and associated with ‘longevity and good health’ [64]. Now, three dif-
ferent preparations are used—probiotics means live microorganisms with beneficial effect
on host health when administered in adequate amount, prebiotics defined as selectively fermented ingredient that allows changes in composition and/or activity in gastrointestinal microflora and the last—synbiotics when probiotics and prebiotics are used simultaneously [64]. List of probiotics contains different strains of Lactobacillus, e.g., casei, rhamnosus, gas- seri, Bifidobacterium, Saccharomyces boulardii and others. List of prebiotics is shorter and contains inulin, xylooligosaccharide, oligofructose and fructooligosaccharide [64, 65]. Results of probiotics, synbiotics therapy are noted as mildering course of disease (e.g., ulcerative colitis), than clinical remission or real corrections of dysbiosis [64, 65]. The effects and mechanisms of used probiotic activity in patients with IBD are shown in Table 5.

Faecal microbial transplantation (FMT) is now a new approach to chronic microbial dysbiosis. The idea is to reintroduce and re-establish stable physiological bacterias from healthy donor supplanting dysbiotic microbiota. The first recognised successful use of this therapy was noted in patients with Clostridium difficile infection and dysbiosis in follow. In 2 weeks and 1 month after this procedure the composition of faecal bacterial containing bacterias derived mainly from donor. In spectrum of gastrointestinal disease, it seems that correction of microbiota homeostasis is indicated in Crohn's disease. According to observations and hypothesis about the role of microbial homeostasis, the bacterial dysbiosis noted in Crohn's disease is common and associated with severity of symptoms. The correction of microbiota homeostasis in these patients leads to resolving of some symptoms and help in normalisation of jejunal function [64, 66].

9.2. Classical immunosuppression

Steroids were first in autoimmune diseases therapy and up to now, there are common as first line treatment. In refractory celiac disease, autoimmune liver and biliary tract disease and IBD steroids are used to release syndromes in acute stage of disease and as maintenance therapy in remission. In CD remission was obtained with steroid in about 80% of patients in first 30
days of therapy [55]. Decrease of steroids dose, due to accumulation of side effects, is possible, when azathioprine or other classical immunosuppressant is added to therapy. Steroids are used as systemic with risk of accumulative side effects or enteral active budesonide acting in intestinal lumen with low absorption [55]. In CD, at the beginning of therapy, antibiotics were used very often, as in UC—5-aminosalicylates. Classical immunosuppression included azathioprine, methotrexate, cyclosporine A, tacrolimus and others. In children, in CD therapy, good results are obtained with cyclosporine A, but severe side effects are very often the limitation of therapy. Prolong therapy with immunosuppressant in children is resulting with inhibition of growth, puberty, cytopenias (leukopenia, neutropenia, thrombocytopenia, anaemia) and list of steroids side effects—osteopenia/osteoporosis, obesity, diabetes. Another limitation is long perspective of therapy, so accumulation of side effects is serious problem, especially for children. In UC classical immunosuppression is less effective than in CD. However, good results in UC were noted, when tacrolimus (calcineurin inhibitor) was used in therapy schedule. The target for tacrolimus and cyclosporine A is inhibition of TCR signalling, what resulted in blocking of T cell activation [14]. However, explanation why cyclosporine A is associated with good effects in CD, in opposite to UC when similar effects are obtained with tacrolimus is unknown. It maybe, that different profile of cytokines produced by given subpopulation of T lymphocytes mediating process of autoimmunity is a background for these observations. In autoimmune liver diseases steroids are used in first line of therapy together with azathioprine to reduce steroids dose and avoid side effects. In majority of AIH patients the response to this therapy in good (in about 90% of patients level of serum immunoglobulins and liver enzymes decreased to normal value). However, relapses are noted in 50–86% of patients within 6 months of remission. For these patients the second line of therapy is advice—cyclosporine A, tacrolimus, mycophenolate mofetil with success in majority of AIH patients [59].

9.3. Biological therapy

The use of monoclonal antibodies is indicated as second line of therapy after poor response to steroids and classical immunosuppression. Celiac disease is included into diseases treated with monoclonal antibodies only in the case of GFD resistance and progression of malabsorption syndrome [28, 52]. The good effect of elimination of TNF is noted only in refractory celiac disease type 1. In refractory celiac disease type 2 with T lymphocytes responsible for process and resistance to immunosuppressive therapy, infliximab is not effective. For these patients, only HSCT procedure is curative [28].

A discovery of the crucial role of TNF in regulation of pro-inflammatory cytokines production and supporting of inflammation was based on the idea of elimination of this cytokine as possible therapy. After good results observed in rheumatoid arthritis, ankylosis spondylitis patients, IBD was the next group of autoimmune diseases with successful anti-TNF therapy. In CD, anti-TNF therapy was used in refractory fistula sign form leading to surgery and disability of patients. Now, anti-TNF therapy is used in all patients with CD with indications for biological therapy, e.g. steroid refractory or steroid dependent form of disease, acute stage with severe clinical symptoms, even life-threatening, lack of remission with chronic, stable symptoms of disease. In children with CD, anti-TNF therapy is used early in disease course, often in active, severe stage, without prolonged immunosuppressive therapy carrying high risk of side effects.
for these patients [54, 55]. Proposition of sequential (step-by-step) therapy of CD included antibiotics and budesonide in first line, steroids and classical immunosuppression (azathioprine, methotrexate, 6-mercaptopurine) as second line and biological therapy as last line. This step-up therapy schedule maybe used as step-down after success with biological therapy, in maintaining of clinical remission. The effect of monoclonal antibodies is better, when anti-TNF antibody is used with other therapeutic, e.g., azathioprine [55]. Infliximab as anti-TNF therapy was introduced into schedule of UC therapy in 2005 year after good results of anti-TNF therapy in CD since 1998 year. Similar to CD, in UC monoclonal antibodies are used as last, third line of therapy after steroids and immunosuppression [54, 55]. In CD and UC as chronic diseases, anti-TNF therapy, like other therapy schedules, should be individualised ("patient tailored therapy"). The choice of anti-TNF antibody from, e.g., infliximab to adalimumab depends on expected effects on given symptoms of patient. The lack of effect or severe side effects contraindicated continuing therapy suggests use of monoclonal antibody against other mediator of autoimmune process, e.g., natalizumab [54]. Natalizumab is recombinant, humanised IgG4 monoclonal antibodies to α4-integrin with function of blocking this integrin. In consequence the migration of leukocytes into the intestine wall from blood is inhibited. Effect of this inhibition is noted as increase of leukocytes number in peripheral blood due to block of adhesion and transmigration out [54]. However, the fatal progressive multifocal leukoencephalopathy (PML) after natalizumab in three patients was concerned as severe side effects followed by withdrawing of this antibody from the market. Now, natalizumab is available, but for patients without other possible effective therapy [54]. Vedolizumab is used in CD and UC, but the effects of therapy are rather low. Summarising vedolizumab use is indicated in moderate-severe CD, not for UC [53]. Briakinumab was very effective in rheumatoid arthritis but without good results in CD patients. Ustekinumab as inhibitor of p40 subunit blocking IL-12 and IL-23 preventing activation of Th1, Th17 and APC (antigen presenting cells) was used with success in CD patients after anti-TNF therapy without good effect. Moreover, this antibody helps in healing of perianal symptoms of CD. Other antibodies (anti-IL-13—Dectrekumab, anti JAK inhibitors—Tofacitinib, anti-IL-6—Tocilizumab) are under clinical trials and pilot studies [53].

New promising biological therapies are directed against different molecules, including cytokines produced by autoreactive T lymphocytes mediating chronic inflammation. Monoclonal antibodies against interleukins, interleukins receptors, integrins, IFN are used in different clinical trials in CD and UC [54]. List of antibodies used in biological therapy is shown in Table 4.

9.4. Haematopoietic stem cell transplantation procedure

In celiac disease and IBD indications of HSCT procedure are associated with co-existent disease, e.g., haematological or severe course, resistant to therapy or diet with progression of malabsorption syndrome. Decision of HSCT is difficult, because patients resistant to therapy with progress of disease, are usually on total parietal nutrition, with recurrent, prolong or opportunistic infections, malabsorption syndrome with high risk of death after HSCT procedure. Another therapy proposed is mesenchymal cell application (MSC)—used intraperitoneally, intravenously. However, the results are not conclusive, although a decrease of pro-inflammatory cytokines in mucous biopsy was noted [51, 52].
10. Conclusions

Certain gastrointestinal tract diseases are classified as autoinflammatory/autoimmune due to chronic course with remissions and exacerbations, histological and serological features, good response to immunosuppressive treatment. Therapy is based on inhibition of immune system activation, reduction of inflammatory process, decrease of antibody production and complexes formation. Steroids are commonly used to obtain and, in small doses, to maintain remission. However, severe side effects or steroid resistance implicate the usage of classical immunosuppressive drugs. Classification of gastrointestinal tract diseases as autoimmune opened the opportunity for analagous treatment with other autoimmune diseases including monoclonal antibodies. Moreover, for progressive cases with poor prognosis haematopoietic stem cell, transplantation is proposed with encouraging results.

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