The primary immunodeficiency disorders (PID) are a heterogeneous group of diseases resulting from inherited defects in the development and maturation of immune system which results in increased susceptibility to infection. Autoimmune manifestations are frequent and often multiple in patients with PID. In the last years, novel forms of PID have been discovered and additional pathophysiological mechanisms that account for PID and associated autoimmune symptoms have been unraveled. Recent studies have shown that there are at least three different mechanisms connecting PID with autoimmune symptoms: chronic inflammation, impaired negative regulation of immune responses and linkage between the PID gene and a gene affecting autoimmunity. In the absence of clinical trials investigating specific treatments for autoimmune complications in PID patients, most therapies are empirical. With recent advances uncovering molecular basis of PID and specific pathways responsible for the development of autoimmune complications, it is hoped that more rational treatment will evolve for these challenging patients. Careful analysis and prompt recognition of these disorders is essential for effective treatment and thus to improve survival and quality of life in patients affected with PID.

The 10 warning signs of PID developed by the Jeffrey Model Foundation are being used as a screening tool to help diagnose PID. However, a recent study showed that except for the three signs including family history, need for intravenous antibiotics and failure to thrive, the 10 warning signs are not an optimal screening for PID, particularly in daily pediatric practice (4). The early onset of multiple autoimmune disorders should be considered as highly suspicious of PID. The European Society for Immunodeficiency’s (ESID) proposed a set of warning criteria that should include inflammatory, autoimmune and lymphoproliferative features, as well as other well-established criteria to allow a better identification of PID by non-immunologists (6).

This review highlights autoimmune complications of PID and discusses recent findings that have uncovered cellular and molecular mechanisms linking PID to autoimmune disease.

**INTRODUCTION**

The primary immunodeficiency disorders (PID) are a heterogeneous group of more than 150 diseases resulting from inherited defects in the development and maturation of immune system (1, 2). Patients with PID are characterized by an increased susceptibility to infection. They are also associated with troublesome and sometimes life-threatening autoimmunocomplications (3). In the last years novel forms of PID have been discovered and additional pathophysiological mechanisms that account for PID and associated autoimmune phenomena have been disclosed. Careful analysis and prompt recognition of these disorders is vital for effective treatment and thus to improve survival and quality of life in patients affected with PID (1, 2).

**EPIDEMIOLOGY**

Autoimmune diseases occur in up to 3-5% of the general population (7, 8). Analysis of PID registry data from two neighboring pediatric centers in North-East Italy and in Slovenia conducted on a total of 175 patients showed that autoimmune symptoms were present in 14.8% of patients with PID (unpublished data). Autoimmune manifestation have been reported in 22% of patient with common variable immunodeficiency, increasing up to 50% in the subgroup of patients with chronic granulomatous disease and 70% of patients with Wiskott-Aldrich syndrome. Association with autoimmune disease in PID patient can be considered to be 100% in the group of diseases of immune dysregulation and in Omenn syndrome. Primary immunodeficiency diseases that are most frequently associated with autoimmune manifestations are presented in Table 1.

**THE BASIS OF AUTOIMMUNITY IN PRIMARY IMMUNODEFICIENCY DISEASES**

There is not a single mechanism that links autoimmune manifestations and PID. Recent studies have shown that the reare at least three different mechanisms connecting PID with autoimmune symptoms: chronic inflammation, impaired negative regulation of immune responses and linkage between the PID gene and a gene affecting autoimmunity.

**AUTOIMMUNITY AND IMMUNODEFICIENCY**

**Autoimmunity and immunodeficiency**

**Table 1**

Primary immunodeficiency diseases most frequently associated with autoimmune manifestations

<table>
<thead>
<tr>
<th>PRIMARY IMMUNODEFICIENCY DISEASE</th>
<th>AUTOIMMUNE MANIFESTATIONS</th>
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<tbody>
<tr>
<td>Combined T&amp;H cell immunodeficiencies</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<tr>
<td>Combined N&amp;H cell immunodeficiencies</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<tr>
<td>Severe combined immunodeficiency</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<tr>
<td>Težka kombinirana immunodeficijencija</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<td>Omenn syndrome</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<td>Omens syndrom</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<tr>
<td>&quot;Atypical&quot; severe combined immunodeficiency</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<td>&quot;Ateipena&quot; težka kombinirana immunodeficijencija</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<tr>
<td>CD40 ligand deficiency</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<td>Deficienca CD40 iglanda</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<td>Predominantly antibody deficiencies</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<td>Common variable immunodeficiency</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<tr>
<td>Uobičajene varijabilne immunodeficijencije</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<td>Other well-defined immunodeficiency syndromes</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<td>Drug-resistant, autoimmunedeficient syndromi</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<td>Wiskott-Aldrich syndrome</td>
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<td>Wiskott-Aldrichov syndrom</td>
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<td>DiGeorge syndrome</td>
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<tr>
<td>Diseases of immune dysregulation</td>
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<td>Bečeli s poremećajima immunoregulacije</td>
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<td>Autoimmune lymphoproliferative syndrome</td>
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<td>Autoimmun linfoproliferativni sindrom</td>
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<td>Autoimmune polyendocrinopathy with candidiasis and ecotdermal dystrophy</td>
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<td>Autoimuna polyendocrinopatija s kandidijazom i ekotdermalnom dystrofijom</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<td>Immune dysregulation, polyendocrinopathy, enteropathy, X-linked</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<td>Immunodegresijalne, polyendocrinopatija, enteropatija, X-vezana</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
</tr>
<tr>
<td>Congenital defects of phagocyte number, function, or both</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<tr>
<td>Kongenitali poremećaji broja fagocita, funkcije, ili obje</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<tr>
<td>Chronic granulomatous disease</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
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<tr>
<td>Kronična granulomazna</td>
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</tr>
<tr>
<td>Leukocyte adhesion molecule deficiency</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
</tr>
<tr>
<td>Deficienca alatačkih molekula na leucocitima</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
</tr>
<tr>
<td>Complement deficiencies</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
</tr>
<tr>
<td>Deficienca komplementa</td>
<td>autoimmune cytopenias, autoimmune colitis, etc.</td>
</tr>
</tbody>
</table>

**Review**


**Table 1.**

Primary immunodeficiency diseases most frequently associated with autoimmune manifestations

**References:**

1. Department of Allergology, Rheumatology and Clinical Immunology, University Children's Hospital, University Medical Center Ljubljana
independent of any known infection, because the underlying immunodeficiency directly alters the involvement or self-reactive B and T cells and favor the occurrence of autoimmune manifestations (10). Although a strong case can be made for a cause-effect relationship between primary PID and autoimmune disease, this association is much less clear in other cases, and the possibility remains that some of the apparent correlation is a spurious association due to a special connection between the PID gene and a gene affecting autoimmunity (11).

**SPECIFIC PRIMARY IMMUNODEFICIENCY DISEASES ASSOCIATED WITH AUTOIMMUNITY**

Combined T and B cell immunodeficiency’s

**Severe combined immunodeficiency**

Severe combined immunodeficiency (SCID) is a genetic form of primary immunodeficiency, caused by mutation in genes involved in lymphocyte development and function. In their first year of life, children with SCID present with high susceptibility to bacterial, viral and fungal infections, which are often associated with protracted diarrhea and failure to thrive. Engraftment of maternal T cells can lead to symptoms of graft versus host disease, such as severe erythematous skin rash or chronic liver disease. Without bone marrow transplantation (BMT), the disease usually lethal within the first year of life. Over 20 different molecular defects can result in the clinical syndrome of SCID (12). Severe autoimmune complications can develop in patients with SCID.

Omenn syndrome is a SCID subtype associated with a number of specific autoimmune complications. This syndrome is characterized by severely decreased circulating T and B cells (9). The disorder is caused by mutations in recombination-activating genes (RAG) 1 and 2, which are involved in immunoglobulin and T-cell receptor gene recombination and thus the generation of immune diversity (5).

Association with autoimmune disease can be considered to be primarily as a result of the involvement or self-reactive T cells. The autoimmune diseases are consistently organ specific and usually involve both the skin and the intestine (13). Autoimmune complications include lymphoplasmaud, splenomegaly, erythromderaemia, autoimmune hepatic dysfunction or failure and encephalopathy (3). These complications are associated with neonatal meningitis, esophagitis and elevated IgE, suggesting involvement of the Th2 subset of T cells that produces IL-4, IL-6 and other cytokines that drive pathogenic IgE synthesis (14). Patients with these complications have been treated with high-dose steroids, antithymocyte globulin and cyclosporine A, however BMT remains the only definitive treatment (9).

The clinical presentation and the immunological phenotypes of SCID and Omenn syndrome are well defined and there are clear concepts for three disorders. Diagnosis and treatment is much less clear for patients with mutations in the SCID-1 pathway (10) and in the SCID-4 pathway (11). A recent study performed in 73 patients with SCID suggests that the SCID-1 pathway is more common. Systemic review of the clinical and immunological presentations was recently performed in 73 patients with "atypical" SCID. In this study "atypical" SCID was defined as an immunodeficiency disease due to mutations in SCID-causing genes in patients with a presentation different from typical SCID and Omenn syndrome and T cells above 100/μl. This study revealed that the clinical presentation of "atypical" SCID is not limited to infection susceptibility, but also includes disorders of immune regulation. In particular, immune dysregulation can be a leading clinical manifestation of "atypical" SCID. In at least 10 out of 73 patients autoimmune cytopenias, granulomatous colitis or colitis were the first and in 3 patients the only disease manifestation before molecular diagnosis was established. The most features of immune dysregulation affected predominantly patients with a mutation affecting antigen receptor recombination and patients with adenosine deaminase deficiency. Antibody mediated autoimmunity was almost exclusively observed in patients with SCID variants affecting B cell development (12).

**CD40 ligand deficiency**

CD40 ligand deficiency or hyper-IgM syndrome is a primary immunodeficiency from a genetic defect in the CD40 ligand pathway or in other proteins required for immunoglobulin class switch recombination (9). Consequently, patients with hyper-IgM syndrome have normal or high levels of serum IgM and low IgG, IgA and IgE levels associated with sinusopulmonary infections. A principal cause of death in these patients is liver failure due to sclerosing cholangitis. The mechanism for this organ-specific auto-immune phenomenon has been described. Cryptosporidium gastroenteritis is common in these patients, and Cryptosporidium is able to infect the biliary tree and induce bile duct epithelium. The inability of T lymphocytes to induce destruction of infected cells results in persistence of Cryptosporidium, cryptogenic inflammation and, consequently, sclerosing cholangitis (3). Other autoimmune complications include autoimmune cytopenias, inflammatory bowel disease, monocytosis, seborrheic dermatitis, arthritis and pernicious anemia (9, 11).

**Inflammatory bowel disease associated with chronic diarrhea and sometimes malabsorption, failure to thrive, or protein-losing enteropathy occurs in about 30% of patients and most often affects the small intestine but can affect the stomach or small bowel. If the stomach is involved, associated atrophic gastritis and pernicious anemia may occur. The inflammatory bowel disease may have histological features of celiac disease or Crohn’s disease. About 10% of patients with hyper-IgM syndrome have multitys, nonaceseing granulomatous disease.**

**CVID-associated granulomatous disease** is a rare X-linked immunodeficiency disorder caused by a maturational defect affecting both lymphocytes and platelets. The mutated gene in WAS encodes a multidomain protein called Wiskott-Aldrich syndrome protein (WASP). WASP is expressed exclusively in cells of the hematopoietic lineage and is critical for cytokine remodeling via actin polymerization. WASP deficiency can affect N and T cell cytolic function and T cell help for B cells. WAS patients have reduced antibody responses to polysaccharide vaccines and increased susceptibility to a wide variety of bacterial, viral and fungal infections. WAS is associated with a remarkably high prevalence of autoimmunity, as high as 70% in retrospective cohorts with some patients developing multiple autoimmune manifestations. WASP deficient T cells are defective in their production of IL-12, a cytokine that is required for the survival of regulatory T cells, which are essential in the control of T-cell mediated autoimmunity. The most common autoimmune problems are AIHA and vasculitis, followed by renal disease and arthritis (3, 9). WASP deficient mice were found to develop immune-mediated colitis and other autoimmune manifestations. Recent findings illustrate that even in a single-gene PID, multiple mechanisms may contribute to autoimmune disease. Recent work established that regulatory T cells, defective production of Fas ligand or defective clearance of apoptotic cells (9).

**DiGeorge syndrome**

DiGeorge syndrome is a congenital immunodeficiency characterized by absent parathyroids, congenital heart defects, hypoparathyroidism with hypocalcemia and a hypothyroid phenotype. DiGeorge syndrome is caused by a microdeletion in chromosome band 22q11. The most frequent complications of DiGeorge syndrome have been specified as autoimmune disease, and patients often present with one or more autoimmune manifestations. Other well defined immune deficiencies are present in approximately 1 percent of patients with DiGeorge syndrome. A few reports have described autoimmune phenomena in patients with 22q11 deletions including autoimmune cytopenias, arthritis and autoimmune thyroid disease (3).

**Diseases of immune dysregulation**

In the following group of diseases there is primary deficiency on the level of immune regulations mechanisms causing autoimmune diseases such as genetic defects and occurrence of autoimmune manifestations. Moreover, this group of PID is defined by the occurrence of autoimmune manifestations.

**Autoimmune lymphoproliferative syndrome**

Autoimmune lymphoproliferative syndrome (ALPS) is characterized by the occurrence of lymphopenopathy, splenomegaly and lymphocytosis with circulating CD4+CD8+ double negative T cells. Patients with ALPS type I have a deficiency in Foxa, a member of the tumor necrosis factor (TNF) superfamily. Patients with ALPS type II have a mutation in caspase 10, another cellular component of the same apoptotic pathway. The principal clinical features are chronic benign lymphoproliferation and autoimmune disease (3). Autoimmune manifestations occur in 50 to 70% of the cases, mainly in the form of autoimmune cytopenias (AIHA, ITP and autoimmune neutropenia) and autoimmune hepatitis (AIH). Other autoimmune manifestations of proven or suspected autoimmune mechanisms have been reported less commonly: gonorheumonitis, optic neuritis, Guillain-Barré syndrome, arthritis, cutaneous vasculitis, primary biliary cirrhosis and autoimmune hepatitis (10).

**Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy**

Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APECED) is a recessive autosomal disease defined by at least two of
the following symptoms: chronic cuta-
neous mucous candidiasis, hypoparathyroid-
ism and Addison’s disease. Candidiasis is
usually the first clinical manifestation of
the disease, occurring around the age of
5, followed in most cases by hypopara-
thyroidism before the age of 10 and adeno-
cretal failure before the age of 15.

Other organ-specific autoimmune
manifestations encountered in this con-
dition include hypothyroidism, hypogo-
nadism, type 1 diabetes mellitus, auto-
immune hepatitis, pernicious anemia, vi-
tiligo, alopecia, primary biliary cirrhosis
and ectodermal dystrophy (10). APECED
results from a defect in the autoimmune
regulator (AIRE) gene which is involved in
the negative selection or anergy induc-
tion of self-reactive lymphocytes in the
thymus (3). Developing thymocytes with
a T-cell receptor that recognize tissue-
specific antigens (9). Mice deficient in
AIRE also showed evidence of sponta-
neous organ-specific autoimmunity (3).

Clinical features include early onset type
of granulomas and severe inflammatory
bowel disease occurring in 50% of pa-
ients (9). Inflammation can occur anywhere
from mouth to anus. Widespread granu-
lofoma formation and fibrosis may result in
stomatitis and oral ulcers; esophagitis
associated with dysphagia, dysmotility,
and obstruction; gastric outlet obstruc-
tion and eosinophilic gastritis; intesti-
nal villous atrophy or granulomatous
colitis; and liver fibrosis and cirrhosis.
Gastrointestinal symptoms of abdomi-
nal pain, diarrhea, and malabsorption
respond variably to immunomodulatory
agents (prednisolone, cimetidine A, and
interferon-7), but there is an in-
creasing risk of reactivating latent infection.

Besides, the above-mentioned symptoms
are similar for the Crohn’s disease which
further aggravates the therapeutic di-
lemma. Chronic inflammation in other
systems, such as the lung, may produce fibrosis
and cor pulmonale. These pa-
ients have poor long-term prognosis and
early BMT is recommended (3).

Leukocyte adhesion molecule
deficiency

Leukocyte adhesion molecule defici-
cy (LAD) is due to defects in integrin
family adhesion molecules (CD18) that
are essential for binding of neutrophils
to the endothelial surface and extra-
vasion from blood vessels. Consequently,
patients with LAD have high circulating
neutrophil counts which may produce
a persistent leukocytoclastic vasculitis.
Patients with LAD have high circulating
neutrophil counts which may produce
a persistent leukocytoclastic vasculitis.

Deficiencies in components of com-
plement are rare, with the most common
being a deficiency in C2 that occurs in
1 in 20000 people. Only deficiencies in
the earlier components of the classical
pathway (Clq, C1r, C1s, C2 and C4) have
been linked to autoimmune diseases.
Among these patients, systemic lupus erythematous (SLE) tends to be more
severe with earlier age of onset and pre-
ponderance for male patients. A defici-
ency of mannose-binding protein, which
cleaves C4 and C2 when bound to anti-
body in the same way as activated C1s,
has been linked to an increase in auto-
immune disorders (arthritis, ITP, ente-
ropathy, pernicious anemia, and vitiligo)
when associated with CVID. The exact
mechanism by which complement defici-
cy causes autoimmunity is unknown.
The fact that it is Clq that binds to Fc
receptors of granulocytes and platelets
suggests that the lack of interacti-
on of complement with immunoglobulin
and apoptotic cells may prevent the clea-
ning of damaged cells thereby leading to
production and buildup of circulating autoanti-
odies (3, 11).

THERAPY OF AUTOIMMUNE
COMPLICATIONS IN PATIENTS WITH PID

PID patients are by definition immu-
 nocompromised and a thorough exclu-
sion of infections coincident with or possi-
 bly causative of autoimmune complica-
tions should be undertaken before initia-
ing specific treatments for autoimmune
complications. In the absence of clinical
trials investigating specific treatments for
autoimmune complications in PID patients,
most therapies are empirical. A recom-
ended approach is to consider the clinical
severity of particular autoimmune
complication and need for treat-
ment, similarly as in a patient without
underlying immunodeficiency. Specific
therapy should then be adjusted to avoid
those known to predispose to infecti-
ons to which a patient may already be
susceptible given the specific immuno-
deficiency involved. If applicable, non-
immunosuppressive therapies such as
intravenous immunoglobulin would be
preferable. Targeted therapies that affect
specific immune cell subsets may be pre-
ferrable over the broad immunosuppressi-
ve efficacy of glucocorticoids. With the
recent advances uncovering molecular basis of PID and specific pathways respon-
sible for the development of auto-
immune complications, it is hoped that
more targeted treatments will evolve (9).

CONCLUSION

PID is a diverse and complex group
of diseases that includes not only unusual
or recurrent infections but also common
infections as well as autoimmune mani-
festations (5). Autoimmune manifesta-
tions are frequent and often multiple in pa-
ients with PID and can also importantly
contribute when considering the diagno-
sis of PID. The diagnosis of PID should
be made as early as in disease evolution
as possible since it may considerably influ-
ence the therapeutic strategy (10). Early
diagnosis ensures a 95% chance of cure
and long-term survival for many pa-
tients with PID (5). The ongoing studies
should contribute to development and
establishment of a set of comprehensi-

Primarne imunodeficijencije su heterogena skupina bolesti nastale kao posljedica prirodnog poremećaja razvoja i sazrijeva-
ja imunološkog sustava što dovodi do pojačane osjetljivosti na infekcije. U pacijentima s primarnom imunodeficijencijom često su
prerađeni i autonemi poremećaji. U zadnjih nekoliko godina otkrivene su nove forme primarnih imunodeficijencija i razjašnjeni
su patofiziološki mechanismi koji se povezuju s autoimunim sindromima. Najnovija istraživanja dokazuju da su barem tri različita
mehanizma odgovorni za razvoj autoimunih sindromi: kronična upala, poremećena negativna regulacija imunogogova
i povezovatnost između gena koji su odgovorni za pojavu primarnih imunodeficijencija i gena koji utječu na autoimmunost. S obzirom
na nedovoljno klinička istraživanja na području specifične terapije za autoimunne komplikacije, većina terapijskih pogleda je
impurišan. Međutim, sve veći broj istraživačkih studija može pokazati da su postojale za razvoj autoimunnih sindromi
koji su radi odgovora na posljedice primarne i sekundarne autoimunne komplikacije, doprinijeli je racionalnoj terapiji. Pravovremeno
prepoznavanje i djelovanje primarne i sekundarne autoimunne komplikacije je neophodno za to ranije primijeniti odgovor je
terapije što poboljšava preživljavanje i kvalitetu života pacijenata s primarnom imunodeficijencijom.

Ključne riječi: Primarne imunodeficijencije, Autoimmunne kompleksne poremećaje, autoimunne komplikacije

Sažetak

Slovenščina

Primarne imunodeficijencije su heterogena skupina bolesti nastale kao posljedica prirodnog poremećaja razvoja i sazrijeva-
ja imunološkog sustava što dovodi do pojačane osjetljivosti na infekcije. U pacijentima s primarnom imunodeficijencijom često su
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