JOURNAL OF COMPLEMENTARY MEDICINE RESEARCH
Journal of Complementary Medicine Research, ISSN: 2146-8397 Vol. 13, No. 3, 2022 (pp. 93-96)
RESEARCH ARTICLE
WWW.JOCMR.COM

Research of Approaches to the Treatment of Nephrotic Syndrome

[1]Zalina A. Asadulaeva, [2*]Asadula A. Asadulaev

[1,2]Saratov State Medical University named after V.I. Razumovsky,410012

ABSTRACT

The article investigates approaches to the treatment of nephrotic syndrome. Nephrotic syndrome (NS) is one of the main chronic kidney diseases, this disease is diagnosed in patients of any age. At the present stage, there is no universal treatment for this condition. NS therapy currently includes angiotensin converting enzyme inhibitors, angiotensin receptor blockers, monoclonal antibodies, steroids and immunosuppressants. Steroids continue to be the initial approach to the treatment of patients with NS and are considered the basis of therapy. In this regard, it is necessary to consider various innovative approaches to the treatment of this disease in order to increase the effectiveness of NS therapy.

Corresponding Author: asad7887@mail.ru

How to cite this article: Asadulaeva ZA, Asadulaev AA. Research of Approaches to the Treatment of Nephrotic Syndrome. Journal of Complementary Medicine Research, Vol. 13, No. 3, 2022 (pp. 93-96).

KEYWORDS:
Nephrological syndrome, Podocytes, Renal insufficiency, Treatment approaches.

ARTICLE HISTORY:
Received : Mar 24, 2022
Accepted : Apr 15, 2022
Published: Jun 27, 2022

DOI:
10.5455/jcmr.2022.13.03.20

INTRODUCTION

Worldwide and in developing countries, the prevalence of chronic kidney disease (CKD) is significantly high, with a significant number of patients requiring renal replacement therapy.[1] One of the chronic renal diseases is nephrotic syndrome (NS), which is determined by the defining signs of proteinuria, edema, hypoalbuminemia and hyperlipedemia, including podocyte loss, renal fibrosis and glomerulosclerosis. NS can be divided into several types, namely.focal segmental glomerulosclerosis, a disease with minimal changes, membranous nephropathy and IgA nephropathy, which are classified according to their main causes. NS requires continuous treatment with steroids or other immunosuppressants, angiotensin converting enzyme inhibitors and monocal antibodies, since there is still no specific targeted treatment.[2]

In most cases, patients are found to be resistant to steroids, and eventually they progress to end-stage renal failure requiring kidney transplantation or dialysis. Thus, it is extremely important to find alternative treatments that can reduce proteinuria, glomerulosclerosis and renal fibrosis associated with the condition of NS.

MATERIALS AND METHODS

When writing the study, scientific materials were analyzed in the field of determining approaches to the treatment of nephrotic syndrome, the data obtained during the analysis were processed through comparative and comparative methods.

RESULTS

Nephrotic syndrome (NS) is one of the most common kidney diseases in developing countries. This is a clinical syndrome characterized by a number of renal and extrarenal signs, such as proteinuria of more than 3.5 g per day, hyperlipidemia, lipiduria and hypercoagulation. NS is a relatively rare disease that can occur in patients of any age with a frequency of 3 patients per 100,000 patients per year.

Nephrotic syndrome can be idiopathic or occur due to various secondary causes or as a result of genetic causes involving genes such as NPHS1, NPHS2. In primary or idiopathic nephrotic syndrome (INS), the specific cause remains unknown, however, the involvement of proteins such as phospholipase A2 receptor, thrombospondin type 1 domain containing 7A, apolipoprotein 1, and a soluble urokinase-type plasminogen activator receptor has recently been revealed. Secondary main causes of NS include systemic diseases such as diabetes mellitus, lupus erythematosus, amyloidosis, viral infections and taking certain medications.[3]

Focal segmental glomerulosclerosis (FSGS) and membranous nephropathy (MN) are two common types of NS, which account for about one third of cases of primary nephrotic syndrome. Other types of NS include minimal change disease (BMI) and immunoglobulin (IgA) nephropathy.[4]

The glomerulus is the main filtration unit of the kidney, which prevents the passage of proteins. This filtration specificity is achieved due to the glomerular filtration barrier (GFB), which consists of endothelial cells, basement membrane and podocytes. In NS, GFB is damaged, primarily affecting podocytes and leading to the elimination of a large number of proteins in the urine. The condition of NS is also associated with scarring and compaction of the glomeruli, called glomerulosclerosis, and renal interstitial fibrosis due to the deposition of connective tissue in the renal parenchyma.

Currently, there is no specific and improved treatment of NS that provides complete remission, and in most cases the treatment is experimental in nature.

Traditional therapy used in NS includes angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), monoclonal antibodies and steroids. Steroids are still the initial therapeutic approach for patients with NS. The patient usually receives immunosuppressive therapy without having a clear understanding of the mechanisms involved, and therefore the condition is classified according to the reaction. Consequently, it becomes difficult to understand the underlying cause at the molecular level and, accordingly, to develop suitable treatment methods. In addition, treatment with steroids requires long-term use, accompanied by side effects, and in most cases of primary nephrotic syndrome, such as FSGS, patients show resistance to steroids. Thus, it becomes extremely important to find alternative treatments that can weaken proteinuria, glomerulosclerosis, kidney inflammation and fibrosis associated with this disease.[5]

In the recent past, histone deacetylase inhibitors (HDACi) have been widely studied in the treatment of chronic kidney diseases due to their antifibrotic, anti-inflammatory and immunosuppressive effects. Histone deacetylases (HDAC) are a class of enzymes that remove acetyl groups from the amino acid lysine on histone and thereby promote chromatin condensation and transcription repression. HDACi are chemical compounds that inhibit HDAC and alter gene transcription, causing changes in the structure of proteins in transcription factor complexes. Thus, HDACi may have significant potential in the near future. The review also highlights various therapeutic applications of HDACi in various preclinical animal models, in clinical trials and the mechanisms involved.

There are no specific recommendations for the treatment of NS, and based on the opinions of experts, individual cases and observational studies, standard treatment methods are mainly recommended. In children with NS , glucocorticoid therapy is often initiated . Subsequently, based on the response to treatment with glucocorticoids, patients are divided into steroid-resistant or steroid-sensitive. After that, with the help of biopsy, therapy is additionally directed to other immunosuppressants and the management of ACE inhibitors or ARBs.[6]

As a rule, when a patient is diagnosed with proteinuria, initial measures include treating the patient to control blood pressure. This may include conservative treatment using ACE inhibitors or ARBs for six months. If the patient has a nephrotic syndrome, therapy is continued. However, if proteinuria is in the nephrotic range, therapy includes the use of prednisone or other immunosuppressive therapy.

Adult patients may be resistant to steroids. Depending on relapses and remissions, the following therapy is determined for patients. Patients sensitive to steroids, both adults and children, continue to receive treatment with glucocorticoids, and depending on the achieved remission, the dose is reduced. Patients whose condition is prone to relapse during ongoing glucocorticoid therapy or with a slow reduction in the dose of glucocorticoids, patients are transferred to steroid-sparing agents such as cyclophosphamide, tacrolimus, cyclosporine, mycophenolate mofetil or rituximab.

When the patient is determined to be resistant to steroids, further therapy with cyclosporine or tacrolimus begins with continued treatment with ARBs or ACE inhibitors. ARBs or ACE inhibitors when used in patients with NS cause slower progression of renal failure and a more favorable renal prognosis.

However, conservative treatment with ACE inhibitors or ARBs alone in nephrotic patients does not lead to partial or complete remission and, therefore, is not satisfactory. Conservative treatment of NS may also include the use of loop diuretics, such as furosemide, to prevent the formation of edema and treatment with lipid-lowering drugs, such as statins.

For patients with NS, whether adults or children, it is vital to take additional measures that will avoid unnecessary health risks and reduce the formation of edema. These include limiting salt intake, balanced fluid intake and maintaining a healthy lifestyle appropriate to the patient's condition.[7]

Nephrotic syndrome (NS) is a common kidney disease in children, which is characterized by pronounced proteinuria, generalized edema and hypoproteinemia, with minimal change disease (BMI) and focal segmental glomerulosclerosis (FSGS), manifested as recurrent types. Before antibiotic and glucocorticoid therapy was introduced, the likely outcome of treatment of patients with NS was usually unfavorable, and mortality in children was almost 67%. However, immunosuppressive therapy in combination with kidney biopsy and histopathological diagnosis significantly reduced the mortality rate to less than 3%.

The International Study of Kidney Diseases in Children (ISKDC) showed that children aged 1 to 16 years with NS were more likely to respond to glucocorticoids when treated within eight hours. Therefore, a kidney biopsy at the initial stages is usually not performed, but postponed in those who do not respond to treatment with glucocorticoids, or in patients who have relapses after the start of glucocorticoid therapy. Thus, NS in children can initially be treated with empirical therapy with glucocorticoids.

NS in adults differs from NS in the pediatric population by numerous signs. In adults, NS is usually heterogeneous and includes both primary and secondary underlying conditions. Treatment of secondary NS mainly involves the treatment of a related primary secondary disease.

Among primary or idiopathic diseases, the most common causes are FSGS, membranous nephropathy and BMI. Therefore, an early kidney biopsy is recommended in adults in order to group the features of the development of the disease and manage the subsequent therapeutic approach.[8]

DISCUSSION

Epigenetic modifications repeatedly lead to the emergence and development of various diseases, such as cancer, viral infections, inflammatory and neurological disorders, due to the participation of epigenetic regulatory proteins, and these modifications play a crucial role by affecting transcriptionally active chromatin domains. It is noted that more than 1000 proteins can be posttranslationally modified by lysine residues by acetylation and deacetylation in human cells.

It is known that acetylation and deacetylation of histones play a predominant role in the regulation of transcription in eukaryotes. Histone acetyltransferases (HAT) and histone deacetylases (HDAC) are two important families of enzymes that regulate the acetylation of histones and non-histone proteins. The functions of HAT are to add acetyl groups to lysine, and the function of HDAC is to detach acetyl groups. The process of histone acetylation contributes to the weakening of the chromatin structure, which promotes transcription. Consequently, HDAC by deacetylation of histone proteins promote chromatin condensation and therefore act as suppressors of the transcription process. HDAC inhibitors (HDACi) modify gene transcription partly due to chromatin remodeling and due to modifications of the protein structure in transcription factor complexes.[9]

Glomerulosclerosis and fibrosis indicate chronic kidney disease and are a common pathological sign observed in NS. In chronic renal diseases, there is an aberrant expression of HDAC, which subsequently play a role in renal fibrosis and glomerulosclerosis. Thus, targeting HDAC may be a favorable therapeutic strategy for the treatment of NS.

Renal fibrosis and inflammation are closely related to NS. Epithelial-mesenchymal transition (EMF) is a process involved in the pathogenesis of renal fibrosis. EMT involves the modification of renal tubule epithelial cells into mesenchymal cells, which occurs due to several changes, such as increased synthesis and deposition of extracellular matrix (ECM), namely. fibronectin and collagen and reduction of their breakdown in renal cells, expression of smooth muscle α-actin (α-SMA). Increased synthesis of ECM can, in turn, lead to glomerulosclerosis. It is also known that the cytokine TGF-β1 plays an important role in renal fibrosis.

A study conducted on cultured epithelial cells of the proximal tubules of human kidneys showed that trichostatin A, which is a pan-HDACi that inhibits HDAC1 and HDAC2, effectively blocks EMF controlled by TGF-β1. The result demonstrated a decrease in the expression of the profibrotic extracellular matrix and the conservative expression of E-cadherin, which is the leading biomarker of epithelial identity.[10]

It is not entirely clear how HDACs control the process of fibrogenesis, however, it is assumed that they may be involved in the expression of genes that play a role in fibrosis and inflammation, as well as in the activation of cellular signaling pathways of renal fibrosis. It has been found that several molecular pathways, such as TGF-β1, MAPK, protein kinase C/B, Wnt/β-catenin, along with the inflammatory, as well as the immune system, exclusively or in combination with HDAC, play a dominant role in renal fibrogenesis. The available data show that histone acetylation plays an important role in fibrogenesis, in addition to the traditional molecular mechanisms mentioned above.

Studies have also been conducted on the potential use of HDACi after kidney transplantation. The main problem in kidney transplant recipients is transplant rejection, which makes the use of immunosuppressants that will prevent immune reactions key. CNIs have been used in kidney transplant patients and are known to reduce the incidence of acute rejection, however they have associated side effects affecting the kidneys and brain and have been reported to cause an increase in blood glucose levels and have therefore proved ineffective in preventing chronic allograft rejection. HDACs are also known to play a role in transcription of genes involved in immunological reactions. Therefore, several studies have been conducted to test the potential use of HDACi after kidney transplantation in rats. The results of studies show that HDACi can cause suppression of the immune system and thereby increase the survival of the transplant.

Also in the treatment of NSM, researchers suggest using valproic acid (VPA), which is a popular anticonvulsant and antitumor agent. It was found that this short-chain fatty acid inhibits class I and class II histone deacetylases (HDAC) and regulates cellular differentiation, apoptosis, proliferation and immunogenicity in cancer cells, thereby weakening the metastasis process.[11]

HDACi is known to exhibit its anti-inflammatory and antifibrotic effects in some organs, but their effect on the progression of renal insufficiency has been studied to a lesser extent; however, several studies have shown a positive effect of HDACi on the weakening of proteinuria and kidney damage in mouse models. Studies have shown that VPA can attenuate kidney damage and proteinuria in a model of diabetic nephropathy in rats and models with adriamycin in mice, however, the mechanisms underlying the disease and the action of the drug have not been established. clearly understood. Fully transretinoic acid (ATRA) is a natural derivative of vitamin A, which is known to play the role of an antioxidant and regulator of cellular differentiation, apoptosis and inflammation reduction. ATRA acts by binding to retinoic acid receptors (RAR). Binding of ATRA to RAR leads to relaxation of the chromatin structure through activation of RAR and thus activation of gene transcription. It is also known that it plays a protective role in some renal diseases that lead to a weakening of proteinuria.[12]

Several studies have used a combination of VPA and ATRA for the treatment of myelodysplastic syndrome and acute promyelocytic leukemia and have shown good tolerability of this combination. This particular combination has been found to be safe and is associated with the induction of DNA hypomethylation and histone acetylation. It is known that epigenetic mechanisms contribute to the progression of diseases such as cancer, inflammatory diseases, neurological diseases. In addition, epigenetic mechanisms have recently been discovered in kidney diseases accompanied by sclerosis

and fibrosis. Thus, the combined therapy of VPA and ATRA may be a new therapeutic approach to the treatment of NS.[13]

CONCLUSION

HDACs have been used in many studies, many studies have been conducted using various specific as well as general HDACs. Also, HDAC overexpression has been noted in the pathophysiology of many kidney diseases. The TGF-β signaling pathway plays a crucial role in the pathology of renal fibrosis, inflammation and glomerulosclerosis.

Numerous preclinical studies have demonstrated the positive role of HDACi in proteinuria, cell proliferation; cell growth and apoptosis through several major pathways other than TGF-β-mediated signaling, as discussed in this review. The antifibrotic, antiproteinuric effect of HDACi has been reported in many renal diseases along with their epigenetic mechanisms involved in reducing glomerulosclerosis.

Network pharmacology also plays a significant role in the further development of approaches to the treatment of NS. Drug repurposing is a strategy that the pharmaceutical industry is actively exploring. This work can contribute to understanding the complex mechanisms of NS disease. Therefore, it is advisable to assess more broadly the potential of the synergistic effect of ATRA and VPA in the treatment of NS.

Author Contributions

All authors contributed in reviewing the final version of this paper.

REFERENCES

1. A. Bagga, A. Sinha Individualizing treatment of steroid-resistant nephrotic syndrome: registries to the fore Clin. J. Am. Soc. Nephrol., 15 (7) (2020), pp. 920-922
2. G. Benoit, E. MacHuca, C. Antignac Hereditary nephrotic syndrome: A systematic approach for genetic testing and a review of associated podocyte gene mutations Pediatr. Nephrol., 25 (9) (2010), pp. 1621-1632
3. P.J. Chen, C. Huang, X.M. Meng, J. Li Epigenetic modifications by histone deacetylases: biological implications and therapeutic potential in liver fibrosis Biochimie, 116 (2015), pp. 61-69
4. M.E. Cho, et al. Open-label clinical trials of oral pulse dexamethasone for adults with idiopathic nephrotic syndrome Am. J. Nephrol., 49 (5) (2019), pp. 377-385
5. P. Chun Therapeutic effects of histone deacetylase inhibitors on kidney disease Arch. Pharm. Res., 41 (2) (2018), pp. 162-183
6. N. Duncan, et al. Treatment of focal and segmental glomerulosclerosis in adults with tacrolimus monotherapy Nephrol. Dial. Transplant., 19 (12) (2004), pp. 3062-3067
7. M. Huang, J. Zhang, C. Yan, X. Li, J. Zhang, R. Ling Small molecule HDAC inhibitors: promising agents for breast cancer treatment Bioorg. Chem., 91 (July) (2019), Article 103184
8. K. Iijima, M. Sako, K. Kamei, K. Nozu Rituximab in steroid-sensitive nephrotic syndrome: lessons from clinical trials Pediatr. Nephrol., 33 (9) (2018), pp. 1449-1455
9. P. Kumar, V.R. Gogulamudi, R. Periasamy, G. Raghavaraju, U. Subramanian, K.N. Pandey Inhibition of HDAC enhances STAT acetylation, blocks NF-kB, and suppresses the renal inflammation and fibrosis in Npr1 haplotype male mice Am. J. Physiol. - Ren. Physiol., 313 (3) (2017), pp. F781-F795
10. P. Boor, K. Šebeková, T. Ostendorf, J. Floege Treatment targets in renal fibrosis Nephrol. Dial. Transplant., 22 (12) (2007), pp. 3391-3407
11. G. Bug, et al. Clinical trial of valproic acid and all-trans retinoic acid in patients with poor-risk acute myeloid leukemia Cancer, 104 (12) (2005), pp. 2717-2725
12. G. Cimino, et al. Sequential valproic acid/all-trans retinoic acid treatment reprograms differentiation in refractory and high-risk acute myeloid leukemia
13. Cancer Res., 66 (17) (2006), pp. 8903-8911 Y. Dong, Q. Zhao, Y. Wang Network pharmacology-based investigation of potential targets of astragalus membranaceous-angelica sinensis compound acting on diabetic nephropathy Sci. Rep., 11 (1) (2021), pp. 1-16