THERAPEUTIC STRATEGIES FOR WILSON'S DISEASE: CURRENT STATE AND PROSPECTS

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Wilson's disease is a rare hereditary disorder caused by the *ATP7B* gene mutations that leads to copper metabolism disturbances and toxic copper accumulation in the liver, brain, and other organs. The main manifestations include liver damage, neurological and psychiatric symptoms. The use of advanced treatment methods (D-penicillamine, trientine, zinc salts) improves the outcome, but is limited by side effects and complexity of adherence to therapy. Liver transplantation is used in severe forms, but it is limited by the donor shortage and the need for immunosuppression. In our opinion, promising areas include gene therapy involving the use of AAV vectors and CRISPR/Cas9, mRNA platforms, and cell technologies. However, these approaches require further research for the efficacy, safety, and accessibility improvement.

Keywords: Wilson's disease, monogenic disorder, ATP7B, copper overload, gene therapy, cellular therapy

Funding: the study was supported by the Russian Science Foundation grant (RSF grant No. 24-74-10106).

Author contribution: Ivanenko AV, Starodubova VD — manuscript writing; Shokhina AG — developing the concept, manuscript writing and editing, obtaining funding.

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Received: 02.04.2025 **Accepted:** 20.04.2025 **Published online:** 28.04.2025

DOI: 10.24075/brsmu.2025.022

ТЕРАПЕВТИЧЕСКИЕ СТРАТЕГИИ ДЛЯ ЛЕЧЕНИЯ БОЛЕЗНИ ВИЛЬСОНА–КОНОВАЛОВА: СОВРЕМЕННОЕ СОСТОЯНИЕ И ПЕРСПЕКТИВЫ

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Болезнь Вильсона-Коновалова — редкое наследственное заболевание, вызванное мутациями гена *ATP7B*, приводящее к нарушению метаболизма меди и ее токсическому накоплению в печени, мозге и других органах. Основные проявления — поражение печени, неврологические и психиатрические симптомы. Применение современных методов лечения (D-пеницилламин, триентин, соли цинка) улучшает прогноз, но ограничено побочными эффектами и сложностью соблюдения терапии. Трансплантацию печени применяют при тяжелых формах, однако она ограничена дефицитом доноров и необходимостью иммуносупрессии. Перспективные направления, на наш взгляд, включают генную терапию с использованием AAV-векторов и CRISPR/Cas9, мРНК-платформы и клеточные технологии, однако эти подходы требуют дальнейших исследований для повышения эффективности, безопасности и доступности.

Ключевые слова: болезнь Вильсона–Коновалова, моногенное заболевание, ATP7B, перегрузка медью, генная терапия, клеточная терапия

Финансирование: работа поддержана денежными средствами гранта Российского научного фонда (грант РНФ №24-74-10106).

Вклад авторов: А. В. Иваненко, В. Д. Стародубова — написание статьи; А. Г. Шохина — разработка концепции, написание и редактирование статьи, получение финансирования.

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Статья получена: 02.04.2025 **Статья принята к печати:** 20.04.2025 **Опубликована онлайн:** 28.04.2025

DOI: 10.24075/vrgmu.2025.022

Wilson's disease (WD) is a rare autosomal recessive disorder caused by the *ATP7B* gene mutations that leads to copper metabolism disturbances and toxic copper accumulation in the liver, brain, and other organs. Clinical manifestations include primarily liver damage (hepatitis, cirrhosis, acute liver failure), neurological symptoms (tremor, dystonia, parkinsonism), and mental disorders (depression, mood swings). The diagnosis is based on the combination of clinical data, laboratory tests (ceruloplasmin levels, copper in blood and urine), and molecular genetic testing. The use of advanced treatment methods significantly improves the patients' outcomes, but it is still limited by side effects, complexity of adherence to treatment regimen, and insufficient symptom control efficacy. The paper considers evolution of therapeutic approaches to treatment of WD: from conventional pharmacological methods to promising genetic and cell technologies.

Advanced pharmacological approaches: copper overload control

D-penicillamine (DPA) and trientine are the major chelating agents that enhance urinary copper excretion and return blood free copper levels back to normal after 1–2 years or 6–48 months of therapy, respectively [1]. However, DPA causes severe side effects, such as immune-mediated nephritis and neurological deterioration in 14–21% of patients having neurological symptoms. Trientine is a safer alternative, but it is also associated with the risk of neurological complications [2].

Zinc salts inhibit copper absorption through induction of metallothionein expression in enterocytes. Despite the fact that the method is relatively safe, several months of zinc therapy are needed to achieve the effect, and zinc therapy is not suited for

acute conditions [3]. Furthermore, there are cohorts of patients that do not respond to zinc salt therapy.

Tetrathiomolybdate (TTM) and methanobactins represent innovative exprerimental agents that have shown promising results in pre-clinical trials [4, 5]. However, the development of TTM was terminated during the phase III clinical trial due to mixed efficacy and side effects (anemia, neutropenia) [6]. Pre-clinical and clinical trials of methanobactin have not yet been completed.

Transplantation: radical but limited approach

Liver transplantation is a radical treatment method for patients with WD suffering from acute liver failure or not responding to drug therapy. However, the use of this method is limited by the donor organ shortage, perioperative risk, and the need for lifelong immunosuppression. Immunosuppression increases susceptibility to infections and malignant tumors, which makes transplantation an extreme measure.

Hepatocyte transplantation represents a minimally invasive alternative, in which isolated donor cells are injected into the hepatic portal vein. The animal model studies have shown the decrease in copper levels and improved survival rate [7, 8]. However, such problems, as low cell engraftment effectiveness, immune rejection, and disturbed liver repopulation, limit the clinical use.

Gene therapy: addressing the root cause

Gene therapy is aimed at restoring the *ATP7B* function through functional gene delivery in hepatocytes. The use of recombinant adeno-associated viruses (rAAV) has shown promising results in pre-clinical and early clinical trials: tATP7b (UX701) (truncated *ATP7B* variant delivered via AAV8) has shown a persistent therapeutic effect in mice; it is currently through phase I/II/III clinical trials [9]. MiniATP7B (VTX-801) represents one more truncated variant that has shown dose-dependent efficacy in mice and is tested in phase I/II clinical trials [10].

The CRISPR/Cas9 method provides an opportunity to ensure the directed correction of mutations. However, the use of the method faces such problems, as low editing effectiveness in non-dividing hepatocytes and potential off-target effects [11]. Base editors and prime editors expand the possibilities of adjustment without creating double-strand breaks, but require further optimization for clinical use.

mRNA technologies represent a promising approach of Wilson's disease treatment. In contrast to viral vectors (such as AAV), mRNA does not integrate into the genome, which minimizes the risk of insertion mutagenesis. Lipid nanoparticles (LNPs) used to deliver mRNA show tropism for the liver. Despite the fact that direct trials of mRNA therapy for WD are yet to be launched, advances in treatment of other liver diseases using mRNA platforms (for example, transthyretin amyloidosis) confirm their performance [12]. In particular, the NTLA-2001 therapy based on CRISPR has already shown promising results [13].

Stem cell-based therapy: liver function restoration

Induced pluripotent stem cells (iPSCs) can be differentiated into hepatocytes for autologous stem cell transplantation, which potentially eliminates the risk of immune rejection. However, the current protocols allow to create immature hepatocyte-like cells with reduced functionality compared to mature cells of the mature organism [14]. 3D cell culture is the main area which, in the long term, will improve cell maturation and engraftment effectiveness [15].

Combining gene therapy with the stem cell-based technologies can ensure a renewable source of the genetically adjusted hepatocytes for transplantation, thereby solving the problem of genetic defects, and the need for liver regeneration.

CONCLUSION

Therapeutic approaches of Wilson's disease treatment evolve rapidly from symptomatic management to potentially radical methods aimed to eliminate the genetic cause of the disease. Despite the fact that conventional methods remain important for ongoing treatment, innovations in gene therapy, genome editing, and stem cell-based technologies have serious potential for long-term management of the disease and its complete cure.

Further research is needed to optimize these methods in order to ensure clinical use, safety, efficacy, and accessibility for all patients suffering from this severe disorder.

References

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Wilson's disease. Journal of Hepatology. 2012; 56 (3): 671–85. DOI: 10.1016/j.jhep.2011.11.007.
2. Weiss KH, et al. Zinc Monotherapy Is Not as Effective as Chelating Agents in Treatment of Wilson Disease. Gastroenterology. 2011; 140 (4): 1189–98.e1. DOI: 10.1053/j.gastro.2010.12.034.
3. Munk DE, et al. Effect of oral zinc regimens on human hepatic copper content: a randomized intervention study. Sci Rep. 2022; 12 (1): 14714. DOI: 10.1038/s41598-022-18872-8.
4. Solovyev N, Ala A, Schilsky M, Mills C, Willis K, Harrington CF. Biomedical copper speciation in relation to Wilson's disease using strong anion exchange chromatography coupled to triple quadrupole inductively coupled plasma mass spectrometry. Analytica Chimica Acta. 2020; 1098: 27–36. DOI: 10.1016/j.aca.2019.11.033.
5. Snijders RJALM, et al. An open-label randomised-controlled trial of azathioprine vs. mycophenolate mofetil for the induction of remission in treatment-naive autoimmune hepatitis. Journal of Hepatology. 2024; 80 (4): 576–85. DOI: 10.1016/j.jhep.2023.11.032.
6. Medici V, Sturniolo GC. Tetrathiomolybdate, a copper chelator for the treatment of Wilson disease, pulmonary fibrosis and other indications. IDrugs. 2008; 11 (8): 592–606.
7. Fujiyoshi J, et al. Therapeutic potential of hepatocyte-like-cells converted from stem cells from human exfoliated deciduous teeth in fulminant Wilson's disease. Sci Rep. 2019; 9 (1): 1535. DOI: 10.1038/s41598-018-38275-y.
8. Sauer V, et al. Repeated transplantation of hepatocytes prevents fulminant hepatitis in a rat model of Wilson's disease. Liver Transplantation. 2012; 8 (2): 248–59. DOI: 10.1002/lt.22466.
9. Leng Y, et al. Long-Term Correction of Copper Metabolism in Wilson's Disease Mice with AAV8 Vector Delivering Truncated ATP7B. Human Gene Therapy. 2019; 30 (12): 1494–504. DOI: 10.1089/hum.2019.148.
10. Murillo O, et al. Liver Expression of a MiniATP7B Gene Results in Long–Term Restoration of Copper Homeostasis in a Wilson Disease Model in Mice. Hepatology. 2019; 70 (1): 108–26. DOI: 10.1002/hep.30535.
11. Pöhler M, et al. CRISPR/Cas9-mediated correction of mutated copper transporter ATP7B. PLoS ONE. 2020; 15 (9): e0239411. DOI: 10.1371/journal.pone.0239411.
12. Fontana M, et al. Vutrisiran in Patients with Transthyretin

Amyloidosis with Cardiomyopathy. N Engl J Med. 2025; 392 (1): 33–44. DOI: 10.1056/NEJMoa2409134.
13. Gillmore JD, et al. CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis. N Engl J Med. 2021; 385 (6): 493–502. DOI: 10.1056/NEJMoa2107454.
14. Baxter M, et al. Phenotypic and functional analyses show stem cell-derived hepatocyte-like cells better mimic fetal rather than adult hepatocytes. Journal of Hepatology. 2015; 62 (3): 581–9. DOI: 10.1016/j.jhep.2014.10.016.
15. Suominen S, et al. Improvements in Maturity and Stability of 3D iPSC-Derived Hepatocyte-like Cell Cultures. Cells. 2023; 12 (19): 2368. DOI: 10.3390/cells12192368.

Литература

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Wilson's disease. Journal of Hepatology. 2012; 56 (3): 671–85. DOI: 10.1016/j.jhep.2011.11.007.
2. Weiss KH, et al. Zinc Monotherapy Is Not as Effective as Chelating Agents in Treatment of Wilson Disease. Gastroenterology. 2011; 140 (4): 1189–98.e1. DOI: 10.1053/j.gastro.2010.12.034.
3. Munk DE, et al. Effect of oral zinc regimens on human hepatic copper content: a randomized intervention study. Sci Rep. 2022; 12 (1): 14714. DOI: 10.1038/s41598-022-18872-8.
4. Solovyev N, Ala A, Schilsky M, Mills C, Willis K, Harrington CF. Biomedical copper speciation in relation to Wilson's disease using strong anion exchange chromatography coupled to triple quadrupole inductively coupled plasma mass spectrometry. Analytica Chimica Acta. 2020; 1098: 27–36. DOI: 10.1016/j.aca.2019.11.033.
5. Snijders RJALM, et al. An open-label randomised-controlled trial of azathioprine vs. mycophenolate mofetil for the induction of remission in treatment-naive autoimmune hepatitis. Journal of Hepatology. 2024; 80 (4): 576–85. DOI: 10.1016/j.jhep.2023.11.032.
6. Medici V, Sturniolo GC. Tetrathiomolybdate, a copper chelator for the treatment of Wilson disease, pulmonary fibrosis and other indications. IDrugs. 2008; 11 (8): 592–606.
7. Fujiyoshi J, et al. Therapeutic potential of hepatocyte-like-cells converted from stem cells from human exfoliated deciduous teeth in fulminant Wilson's disease. Sci Rep. 2019; 9 (1): 1535. DOI: 10.1038/s41598-018-38275-y.
8. Sauer V, et al. Repeated transplantation of hepatocytes prevents fulminant hepatitis in a rat model of Wilson's disease. Liver Transplantation. 2012; 8 (2): 248–59. DOI: 10.1002/lt.22466.
9. Leng Y, et al. Long-Term Correction of Copper Metabolism in Wilson's Disease Mice with AAV8 Vector Delivering Truncated ATP7B. Human Gene Therapy. 2019; 30 (12): 1494–504. DOI: 10.1089/hum.2019.148.
10. Murillo O, et al. Liver Expression of a MiniATP7B Gene Results in Long–Term Restoration of Copper Homeostasis in a Wilson Disease Model in Mice. Hepatology. 2019; 70 (1): 108–26. DOI: 10.1002/hep.30535.
11. Pöhler M, et al. CRISPR/Cas9-mediated correction of mutated copper transporter ATP7B. PLoS ONE. 2020; 15 (9): e0239411. DOI: 10.1371/journal.pone.0239411.
12. Fontana M, et al. Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy. N Engl J Med. 2025; 392 (1): 33–44. DOI: 10.1056/NEJMoa2409134.
13. Gillmore JD, et al. CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis. N Engl J Med. 2021; 385 (6): 493–502. DOI: 10.1056/NEJMoa2107454.
14. Baxter M, et al. Phenotypic and functional analyses show stem cell-derived hepatocyte-like cells better mimic fetal rather than adult hepatocytes. Journal of Hepatology. 2015; 62 (3): 581–9. DOI: 10.1016/j.jhep.2014.10.016.
15. Suominen S, et al. Improvements in Maturity and Stability of 3D iPSC-Derived Hepatocyte-like Cell Cultures. Cells. 2023; 12 (19): 2368. DOI: 10.3390/cells12192368.