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The Latest Treatment Strategies for Henoch-Schönlein Purpura Nephritis: Application of Immunosuppressants

Baichi Chen [1], Manqiong Yang [2], Yaoxue Zeng [1], Hao Feng [1, *]

[1] Department of Dermatology, Hunan Provincial People's Hospital (The First Affiliated Hospital of Hunan Normal University), Changsha, Hunan, China
[2] Department of Pediatric, Hunan Provincial People's Hospital (The First Affiliated Hospital of Hunan Normal University), Changsha, Hunan, China

*** Corresponding author:** Hao Feng

Abstract: Henoch-Schönlein purpura (HSP) is a common vasculitis in children, primarily characterized by skin purpura, abdominal pain, joint pain, and kidney involvement. In recent years, immunosuppressants have gained increasing attention in treating HSP nephritis, especially for severe cases and patients with persistent symptoms. This review summarizes the current applications, efficacy assessments, and potential side effects of immunosuppressants in patients with HSP nephritis, aiming to provide a reference for clinical treatment.

Keywords: Henoch-Schönlein Purpura; Immunosuppressants; Clinical Treatment; HSP Nephritis.

1. Introduction

Henoch-Schönlein purpura (HSP) is a type of vasculitis primarily characterized by skin purpura, joint pain, abdominal pain, and kidney damage. Although HSP mainly affects children, adults can also develop the condition[1]. Its pathogenesis is associated with abnormal immune responses, endothelial damage, and inflammation in small blood vessels. Epidemiological studies indicate that HSP has a higher incidence in children, typically between the ages of 4 and 7, with boys being more frequently affected than girls. Some data suggest that the annual incidence of HSP is approximately 10–20 cases per 100,000 people, with peaks during the influenza season and following upper respiratory infections[2]. The etiology of HSP remains incompletely understood, though various factors, such as infections, drug allergies, and food allergies, may trigger the disease[3].

The prognosis for pediatric HSP is generally favorable, though serious complications, especially kidney involvement, can occur. Up to 20% of affected children may progress to end-stage renal disease within 20 years post-diagnosis, presenting a substantial public health concern[4, 5]. Commonly used medications include corticosteroids (CS), immunosuppressants, and biological agents. CS have potent anti-inflammatory effects and can help slow the progression of Henoch-Schönlein purpura nephritis (HSPN) to some extent. However, long-term corticosteroid therapy may lead to adverse effects, including growth suppression, osteoporosis, diabetes, adrenal suppression, and Cushing's syndrome. More importantly, a significant proportion of patients do not respond to CS or experience worsening symptoms and steroid resistance. For patients with moderate to severe HSP nephritis who respond poorly to long-term corticosteroid therapy, additional immunosuppressants are often prescribed. However, no consensus exists on the choice of immunosuppressants. Studies indicate that combining immunosuppressants with CS, angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin II receptor blockers (ARBs) can significantly improve treatment outcomes. This review examines current research on immunosuppressive treatments for HSPN, providing an updated overview of the field.

2. Common Immunosuppressants

2.1. Cyclophosphamide

Cyclophosphamide (CYC) is an immunosuppressant widely used to treat autoimmune diseases and malignancies. It functions by inhibiting B cell proliferation and antibody production, thereby reducing the deposition of abnormal IgA and associated immune complexes in the glomeruli. Additionally, CYC decreases T cell activation, further alleviating inflammatory responses[6]. CYC has garnered global recognition among researchers for its effectiveness in treating Henoch-Schönlein purpura nephritis (HSPN). The 2021 KDIGO Glomerular Disease Management Guidelines recommend that patients with rapidly progressive primary HSPN (defined as a ≥50% decline in GFR within three months) be treated with CYC and corticosteroids (CS) following the protocol for ANCA-associated vasculitis[7]. CS combined with CYC is the mainstream immunosuppressive therapy for pediatric HSPN. In a retrospective study by Wang et al., involving 356 pediatric HSPN patients treated with corticosteroids and CYC, results indicated a complete remission rate (defined as a negative proteinuria test or 24-hour urinary protein <0.15 grams) of 34.6% within six months and 67.7% within twelve months. The study also highlighted adverse effects associated with CYC treatment, including gastrointestinal discomfort (16.0%), liver function impairment (9.2%), bone marrow suppression (14.5%), and hair loss (9.0%) [8]. In conclusion, as an effective immunosuppressant, CYC shows good efficacy in HSPN patients; however, due to its potential side effects, careful patient selection and close monitoring are essential to ensure treatment efficacy and safety. Further research is needed to optimize CYC usage regimens and to improve understanding and management of HSPN.

2.2. Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid (MPA), which is metabolized in the body into the active compound MPA. MPA inhibits inosine monophosphate dehydrogenase (IMPDH), interfering with the purine synthesis pathway and thereby inhibiting T and B cell proliferation and differentiation. This action effectively reduces the production of IgA and other antibodies, mitigating kidney damage [9]. In China, experts recommend combining corticosteroids (CS) with immunosuppressants for treating severe Henoch-Schönlein purpura nephritis (HSPN) in children [10]. The recommended regimen for MMF combined with CS is MMF at 20-30 mg/kg/day in two doses, with gradual tapering after 3-6 months over a total treatment duration of 12-24 months[11].A retrospective analysis by Wang et al. evaluated the efficacy and safety of MMF for pediatric HSPN, comparing it with cyclophosphamide (CYC) in 319 patients. Results showed a complete remission rate of 43.9% within six months and 79% within twelve months for MMF combined with CYC. The study also reported adverse reactions with MMF treatment, including gastrointestinal discomfort (6.3%), liver function impairment (2.6%), bone marrow suppression (1.4%), and hair loss (1.0%). This analysis demonstrated that MMF combined with CYC achieved a higher remission rate in pediatric HSPN than CYC alone, with a better safety profile [8]. Although the KDIGO guidelines remain cautious about immunosuppressants and only recommend CYC, MMF may be considered a second-line treatment for pediatric HSPN and an option for moderate cases. Given the adverse reactions associated with CYC, MMF is recommended as maintenance therapy following induction treatment with CYC in severe HSPN cases[12] .

2.3. Azathioprine

Azathioprine (AZA) is a purine analog that exerts immunosuppressive effects primarily by inhibiting lymphocyte proliferation. Both MMF and AZA are generally considered equally effective immunosuppressants for treating Henoch-Schönlein purpura nephritis (HSPN). Once metabolized, AZA converts to 6-mercaptopurine, which interferes with DNA and RNA synthesis by disrupting purine nucleotide formation. This inhibition of nucleic acid synthesis suppresses T and B lymphocyte proliferation, reducing antibody production and moderating the immune response[13]. The recommended dose of AZA in combination with corticosteroids (CS) is 2 mg/kg/day for a duration of 8 to 12 months. AZA is considered a second-line treatment option for mild HSPN and may serve as a first- or second-line treatment for moderate cases[12].A retrospective study analyzed the effects of AZA on 67 HSP patients with kidney involvement. The study found that most renal-involved patients were female, with an average onset age of 7.3 years; 79.1% had kidney involvement at the early stage, presenting primarily with hematuria and proteinuria, and some exhibited nephrotic-range proteinuria and systemic hypertension. AZA was administered to 13 patients with severe kidney damage, and after six months, abnormal urinary findings improved in most, indicating a positive role for an AZA combined with CS and ACEI treatment regimen in early proteinuria control. Although AZA shows promise in HSPN treatment, multicenter prospective studies are necessary to further validate its efficacy[14].The most common side effect of AZA is bone marrow suppression, which manifests as reductions in white blood cells, red blood cells, and platelets, increasing the risk of infection and bleeding[15]. During AZA treatment, regular blood count monitoring is essential to detect and manage bone marrow suppression early, ensuring patient safety.

2.4. Cyclosporine A

Cyclosporine A (CyA) is a classic immunosuppressant widely used to prevent organ transplant rejection and treat various autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus. Its primary mechanism of action involves inhibiting calcineurin activity, which suppresses the synthesis and release of interleukin-2 (IL-2), thereby preventing T-cell activation and proliferation and achieving an immunosuppressive effect[16].In Finland, Koskela et al. conducted a study comparing the long-term prognosis of 62 pediatric Henoch-Schönlein purpura nephritis (HSPN) patients treated with methylprednisolone (MP) or CyA between 1996 and 2011, with an average follow-up of 10.8 years. Results showed that the CyA group had more sustained effects in reducing proteinuria and improving renal function, and the need for additional immunosuppressive therapy was significantly lower than in the MP group. In the MP group, 38% of patients switched to CyA due to poor response, whereas only 10% of the CyA group required a switch to MP. The study suggested that children with a poor response to MP may benefit from long-term CyA therapy to prevent HSPN progression[17].Hyung-Seok Ihm and colleagues conducted a retrospective study analyzing data from 37 patients treated with low-dose CyA plus steroids (C+P) and 49 patients treated with high-dose steroids alone (P). Their findings indicated that low-dose CyA combined with steroids achieved comparable improvements in proteinuria and hematuria in adult HSPN patients to high-dose steroid monotherapy, with approximately 51% of patients reaching a proteinuria/creatinine ratio (PCR) <0.5 within six months. Over a two-year follow-up, there was no significant difference in estimated glomerular filtration rate (eGFR) changes between the two groups, suggesting a similar effect on renal function preservation. The infection rate was significantly lower in the C+P group, and no cases of acute kidney injury were reported, highlighting a potential advantage of this regimen in reducing side effects. Thus, low-dose CyA combined with steroids may offer a safer alternative to high-dose steroids for HSPN patients with relatively normal renal function and proteinuria >0.5 g/g[18].CyA has several side effects, including nephrotoxicity, hypertension, neurotoxicity, hepatotoxicity, gingival hyperplasia, hirsutism, gastrointestinal discomfort, and an increased risk of infection, with particular risks for renal and liver toxicity. Close monitoring of CyA levels and renal and hepatic function is essential, and dose adjustment and combination therapy are recommended to minimize adverse effects[19]. Due to limited evidence from small case studies, current guidelines do not routinely recommend CyA for moderate HSPN. However, CyA may be considered for patients who are corticosteroid-resistant, have failed other treatments, or have relapsed with other immunosuppressants.

3. Other Immunosuppressants

3.1. Tacrolimus

Tacrolimus (TAC) is an immunosuppressive drug commonly used in organ transplantation and for treating autoimmune diseases. Its primary mechanism involves

inhibiting calcineurin, which blocks T-cell activation and reduces immune responses[20].A prospective cohort study compared the efficacy and safety of TAC versus full-dose corticosteroids (CS) in treating Henoch-Schönlein purpura nephritis (HSPN) patients. Fifty HSPN patients were randomly assigned to either the TAC or CS group, and complete remission rates were observed over six months. Results showed no significant difference in proteinuria remission between the groups, with complete remission rates of 35% and 40%, respectively (P=0.7), suggesting that TAC was not inferior to full-dose CS. However, serum creatinine levels significantly increased in the TAC group, indicating potential renal impairment. The study suggests that TAC could be a viable alternative for patients intolerant to CS, with careful monitoring for renal impact[21].In another study, Wu et al. evaluated the efficacy and safety of TAC combined with CS for pediatric HSPN. This study involved 87 HSPN patients with 24-hour urinary protein levels ≥0.75g, randomly divided into three groups: TAC, cyclophosphamide (CYC), and mycophenolate mofetil (MMF). Observations included proteinuria, hematuria, renal function, and adverse effects. After a two-month follow-up, the TAC group showed an overall efficacy rate of 93.3%, significantly higher than the CYC (83.9%) and MMF (61.5%) groups. TAC markedly reduced 24-hour urinary protein levels, with most patients reaching normal levels by the end of the two-month treatment. The TAC and CYC groups also demonstrated a significant reduction in urinary red blood cells, whereas the MMF group showed no noticeable change. TAC was additionally effective in reducing urinary β2-microglobulin and microalbumin, which helps mitigate tubulointerstitial damage. TAC's side effects were relatively mild, primarily minor hand tremors and hirsutism, with a lower infection rate than that observed in the MMF group. The authors concluded that TAC is more effective in reducing proteinuria and hematuria, improving renal function, and has relatively mild side effects in treating pediatric HSPN[22].

3.2. Mizoribine and leflunomide

Mizoribine (MZB) is an immunosuppressant that primarily inhibits inosine monophosphate dehydrogenase (IMPDH), thereby reducing guanine nucleotide production. This mechanism is particularly effective on rapidly proliferating lymphocytes, lowering T and B cell activity, reducing antibody production, and dampening immune responses[23].A retrospective study analyzed five adult patients with Henoch-Schönlein purpura (HSP) treated with MZB (150 mg daily) in combination with prednisolone (initial dose 30-50 mg/day). Results showed significant improvement in proteinuria and microscopic hematuria in all subjects, with no notable adverse reactions. The study suggested that MZB reduces the required prednisolone (PSL) dosage by inhibiting B and T cell proliferation, reducing IgA immune complexes, and possibly enhancing glucocorticoid efficacy through heat shock protein 60 (HSP60) interaction with platelet-derived growth factor (PDGF). The conclusion was that MZB combined with PSL might be an effective option for treating HSP nephritis (HSPN), especially for patients needing lower CS doses[24].A clinical trial using MZB as an adjunct to PSL monotherapy for HSPN indicated that MZB might help prevent relapse in high-risk patients[25]. MZB is well-tolerated in pediatric HSPN, with no significant adverse reactions, including bone marrow suppression, suggesting it as a potential therapeutic option for children with HSPN[13].In clinical practice, some patients and families are hesitant about CYC therapy due to its gonadotoxicity, while the high cost of MMF can influence treatment choices[13]. Leflunomide (LEF), a newer immunosuppressant, has recently been used to treat HSP with nephritis. Although its efficacy in adult HSP-related nephropathy has been documented, data for pediatric patients remain limited. One study reported favorable outcomes in five pediatric patients with biopsy-confirmed tubulointerstitial lesions and proteinuria up to 50 mg/kg following intravenous steroid treatment, with four patients achieving complete remission on LEF combined with CS [26]. LEF primarily works by inhibiting pyrimidine synthesis, thereby reducing T cell proliferation and activation. Additionally, it has anti-inflammatory effects, reducing pro-inflammatory cytokine production and alleviating tissue damage[27]. These mechanisms support LEF's potential application in autoimmune diseases. In HSPN, it may help modulate immune response and alleviate renal inflammation. However, further research is necessary to clarify its precise mechanisms and long-term efficacy to guide clinical practice.

3.3. Rituximab

Rituximab (RTX) is a monoclonal antibody drug that targets B cells by binding to the CD20 antigen, inhibiting B-cell activity. It is commonly used to treat autoimmune diseases and certain lymphomas. In treating Henoch-Schönlein purpura (HSP), RTX has shown potential in reducing autoantibody production and modulating abnormal immune responses. Its mechanism includes depleting B cells, which reduces immune inflammation and helps slow disease progression[28].A systematic review of RTX's efficacy and safety in HSP patients analyzed 35 cases of refractory HSP that were unresponsive to other immunosuppressants, including 16 pediatric cases. All patients exhibited purpura, and 88.6% had renal involvement. RTX was primarily administered due to resistance or intolerance to corticosteroids (CS) and other immunosuppressants, with some patients opting for RTX to avoid adverse reactions from other treatments. Among those treated with RTX, 94.3% showed clinical improvement, with 74.3% achieving sustained remission. Relapse occurred in 37.1% of cases, but these patients responded well to additional RTX treatment. RTX notably improved skin, joint, and gastrointestinal symptoms while maintaining stable renal function. After RTX therapy, the need for CS and other immunosuppressants significantly decreased, suggesting RTX may reduce dependency on prior therapies. RTX has shown good efficacy and safety in refractory or relapsing HSP nephritis (HSPN), making it a promising alternative to traditional therapies when steroids or other immunosuppressants are contraindicated. However, small sample sizes and data variability in studies limit the current evidence, and further randomized controlled trials are needed to confirm RTX's role in HSP treatment[29].A separate study assessed RTX's efficacy and safety in patients with severe HSP and aggressive glomerulonephritis, including 12 adults followed for an average of 33.7 months. Patients received weekly RTX treatment, and 91.7% achieved a clinical response within six months; 10 patients reached complete remission, while one patient achieved partial remission, later converting to complete remission with additional RTX. RTX treatment significantly reduced BVAS scores and 24-hour proteinuria levels while maintaining stable renal function. Overall, RTX

was well tolerated, with no severe adverse events reported. The authors concluded that RTX is effective and safe for inducing and maintaining long-term remission in severe HSP with aggressive renal involvement, suggesting it may be used not only for refractory cases but also as a first-line treatment[30].As an emerging therapy, RTX offers new hope for patients with refractory HSP. While initial results are promising, further high-quality clinical trials are needed to confirm its efficacy and safety across diverse populations and to establish clearer treatment guidelines.

4. Summary and Outlook

We reviewed the latest treatment strategies for Henoch-Schönlein purpura (HSP), particularly for patients with renal involvement, focusing on the role of immunosuppressants. Current studies indicate that immunosuppressants such as cyclophosphamide, mycophenolate mofetil, azathioprine, cyclosporine, and emerging monoclonal antibodies like rituximab can alleviate renal damage in HSP patients to some extent. However, there is no consensus on the optimal use of these immunosuppressants, and concerns remain regarding their side effects and long-term efficacy. Thus, selecting an appropriate immunosuppressant regimen requires careful consideration of the patient's specific condition, the potential side effects, and cost factors. Future research should prioritize the following areas: first, further optimization of immunosuppressant regimens to minimize side effects and enhance efficacy. Second, an in-depth exploration of personalized treatment approaches is needed, including the use of biomarkers to predict patient responses to various immunosuppressants and to guide the selection of the most suitable therapy. Additionally, the efficacy of combination therapy with immunosuppressants warrants further investigation, particularly regarding synergistic effects among different agents. Finally, the development of new immunosuppressants should prioritize specific targeting and improved safety profiles to provide safer and more effective treatment options for HSP patients.

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