Therapies of the Immune-Mediated Kidney Diseases

Subjects: Pharmacology & Pharmacy

Contributor: Ryszard Grenda

Therapy of immune-mediated kidney diseases has evolved during recent decades from the non-specific use of corticosteroids and antiproliferative agents (like cyclophosphamide or azathioprine), towards the use of more specific drugs with measurable pharmacokinetics, like calcineurin inhibitors (cyclosporine A and tacrolimus) and mycophenolate mofetil, to the treatment with biologic drugs targeting detailed specific receptors, like rituximab, eculizumab or abatacept. Moreover, the data coming from a molecular science revealed that several drugs, which have been previously used exclusively to modify the upregulated adaptive immune system, may also exert a local effect on the kidney microstructure and ameliorate the functional instability of podocytes, reducing the leak of protein into the urinary space. The innate immune system also became a target of new therapies, as its specific role in different kidney diseases has been de novo defined. Current therapy of several immune kidney diseases may now be personalized, based on the detailed diagnostic procedures, including molecular tests. However, in most cases there is still a space for standard therapies based on variable protocols including usage of steroids with the steroid-sparing agents. They are used as a first-line treatment, while modern biologic agents are selected as further steps in cases of lack of the efficacy or toxicity of the basic therapies. In several clinical settings, the biologic drugs are effective as the add-on therapy.

Keywords: immune mediated kidney diseases ; evolutions of therapies ; biologic drugs ; local mechanisms of immunosuppressive drugs

1. Introduction

There are a variety of immune-mediated kidney diseases diagnosed in children from early childhood to adolescence. Most of them are presented as one of the clinical forms of isolated glomerulonephritis, while the other ones as a vasculitis-related nephritis or a systemic disease with renal involvement. Nevertheless, the clinical pattern, the innate and/or adaptive immune system is upregulated in most cases and several specific mechanisms of immune dysfunction are involved, as an underlying cause. The typical clinical characteristics of nephrotic glomerulopathies are related to the frequent relapses and the remission dependence from several drugs (as the dose reduction or drug withdrawal results in a relapse of the disease). The hypocomplementemic kidney diseases are often resistant to the standard therapies. The scientific knowledge and clinical experience regarding the relevant therapies have evolved over time. The adaptive immune system was a general target of steroids, which has been the first-line therapy for decades [1][2][3][4][5]. The steroid-related toxicity, especially important in the long-term treatment, was a reason for introducing the steroid-sparing, primarily non-selective antiproliferative drugs, including cyclophosphamide (CYC) and azathioprine (AZA) [5][6][7][8][9]. Treatment with these drugs was not routinely followed by therapeutic drug monitoring (TDM), which precisely evaluates the exposure to the native drugs or its active metabolites This monitoring possibility has appeared more recently (for CYC and AZA) [10], however, it is not frequently used in clinical practice. The next step in specific pharmacotherapy was related to the wider availability of calcineurine inhibitors—cyclosporine A (CsA) and tacrolimus (TAC) [11][12][13][14][15]—and the selective antiproliferative drug mycophenolate mofetil (MMF) [16][17]. The exposure to all of them is easily measurable with TDM. The next step of progress was associated with introduction of the biologic drugs, targeting specific receptors or narrow pathways of the innate and/or adaptive immune system, important for the variable mechanisms of a specific kidney disease [18][19][20][21]. The final issue in the therapy of immune-mediated kidney diseases was the discovery of local mechanisms of specific drugs, targeting podocytes in glomeruli, independently of the impact on the immune system [22][23]. Evolution of the management of pediatric immune-mediated kidney diseases is presented in **Figure 1**.

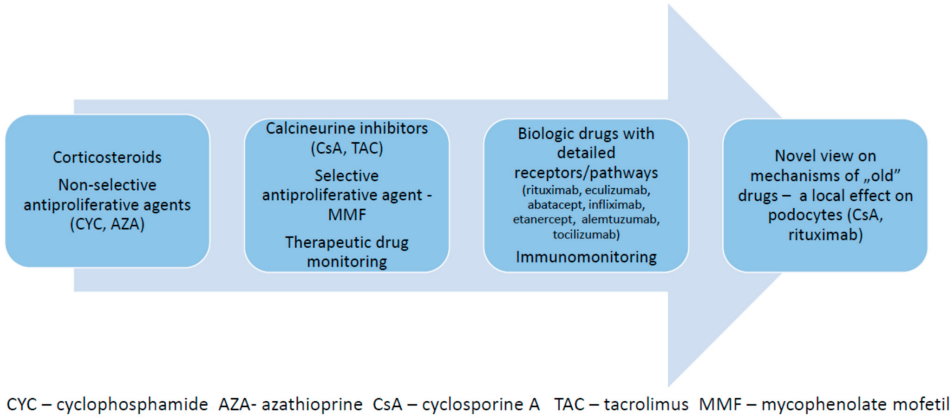

Figure 1. Evolution of therapies used in pediatric immune-mediated kidney diseases.

2. Biologic Drugs in Pediatric Systemic Vasculitis

Systemic vasculitis is a family of diseases characterized by the presence of vascular wall inflammation and involving multiorgan symptoms. Despite the low incidence in children (mainly adolescents), this group of diseases, and particularly ANCA-associated vasculitis (AAV)), has gained an access to several biologic agents, targeting the underlying mechanisms. The pathogenesis of AAV is multifactorial and genetic/epigenetic factors interact with different external triggers. Dysregulation of B cells and lack of balance between T helpers and T effectors lead to the production of ANCA (anti-neutrophil cytoplasmic antibody), activation of neutrophils, and further damage of vessel walls with the late multiorgan consequences [24]. The relevant biologic agents, preliminarily described in case reports, then evaluated in several clinical trials enrolling adult and (in some projects) also pediatric and adolescent patients, include rituximab (anti-B CD_{20} moab), infliximab (anti-TNFα moab), etanercept (TNFα-receptor blocker), abatacept (CTLA-4 Ig Fc fusion protein), alemtuzumab (humanized anti-CD52 moab) and tocilizumab (anti-IL6 moab) [25]. The use of rituximab is aimed to block B-cell dependent T-cell activation, causing the overproduction of several interleukins (like IL-5). A pediatric trial (among several others enrolling only adult patients), in which children with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) received four doses of rituximab, has demonstrated a positive effect, as the remission (verified with the Pediatric Vasculitis Activity Score) was achieved in 56%, 92%, and 100% of patients at months 6, 12, and 18, respectively [26]. The idea of using TNFα blockers is based on the mechanism, in which inhibition of TNFα decreases the formation of granuloma, as a result of the TNFα-mediated activation of neutrophils that enhances the ability of ANCA to stimulate degranulation of neutrophils, is a which important factor in a process of the vascular wall damage [25]. The research named WGET (Wegener's Granulomatosis Etanercept Trial), which enrolled adult patients, did not prove a clinical benefit in terms of achieving remission, as compared with the placebo group (notably, both groups also received standard care drugs, including steroid and cyclophosphamide or methotrexate [27]. Abatacept was used as a T-cell activation blocking agent in adult patients with GPA (granulomatosis with polyangiitis). Overall, 80% of enrolled patients achieved remission, and in 78% of cases a complete steroid withdrawal was possible [28]. Alemtuzumab, a depleting moab against CD52, the receptor expressed by the several cells (T lymphocytes, monocytes, macrophages), was used in adult AAV patients. The remission was achieved in two thirds of patients at six months, and was maintained to twelve months in one third of them [29].

The clinical view on the real success rate in several trials, comparing the efficacy and safety of modern biologic agents with "traditional" drugs, is complex, as in several cases the interpretation of final outcome and safety was difficult and not always in favor of the use of particular biologics, which have been used as the add-on therapy.

3. Biologic Drugs in Systemic Lupus Erythematosus with Renal Involvement

Several specific mechanisms relevant for the lupus erythematosus with renal involvement have been currently targeted by narrow biologic agents, evaluated in clinical trials. One of them is B-cell activating factor (BAFF). The agents used in this setting included blisibimod (A-623, AMG 623), a fusion protein, built of tetrameric BAFF binding domain fused to human IgG1 Fc region and belimumab (a monoclonal antibody). Clinical data on blisibimod from CHABLIS-SC1, randomized, double-blind, placebo-controlled clinical trial, conducted in adult patients, treated previously with variable drugs (including steroids, MMF, methotrexate, AZA or antimalarian agents), showed that the primary end-point (week 52 SLE Responder Index-6) was not achieved; however, the use of blisibimod was associated with decreased proteinuria, successful reduction of exposure to steroids, and a positive response of the relevant biomarkers [30]. Several clinical trials have been

conducted in adults and children with SLE, evaluating the efficacy and safety of belimumab. Overall, in children, belimumab reduced the risk of severe flares by 64% (versus standard therapy), which was more pronounced than in the adult studies (23–50%, respectively) [31]. Atacicept is a recombinant fusion protein consisting of the binding portion of transmembrane activator and CAML interactor (TACI; also known as tumor necrosis factor receptor superfamily member 13B), that binds to BLyS (B lymphocyte stimulator) and APRIL (a proliferation-inducing ligand), inhibiting interactions with their specific receptors. An adult trial with extended follow-up showed a reduction of the incidence of severe SLE flares and prolongation of time to the occurrence of severe flares with a high dose of the drug, as compared to the placebo [32]. Blisibimod and atacitept have also been evaluated in adult patients with IgA nephropathy-related persistent proteinuria >1 g (NCT02062684; NCT02808429); however, (published) results are not available. In general, the role of these kind of narrow-targeted therapies may be regarded mainly as add-on treatments, ameliorating the clinical course of the disease and acting as the steroid-sparing drugs. Anyway, the direction towards the use of “therapeutic arrows” [33], drugs and agents designed based on increasing molecular knowledge on the mechanisms of immune-mediated kidney diseases is a promising clinical approach, with prospects for the future.

4. Summary

- Upregulation of the innate and/or adaptive immune system leads to the development of a variety of immune-mediated kidney diseases in children.
- There is an ongoing progress in pharmacotherapy of immune kidney diseases, based on scientific knowledge, which defines detailed, variable underlying disease-related mechanisms.
- The adaptive immune system is a target of steroids, antiproliferative drugs, calcineurin inhibitors and several receptor-specific biologic agents.
- The innate immune system is a target of specific monoclonal antibodies.
- Surveillance of the current therapies is based on therapeutic drug monitoring and/or immunomonitoring.
- Apart from the effect on the immune system, specific drugs (calcineurin inhibitors, rituximab, abatacept) also exert a local effect on the microstructure of the podocyte cytoskeleton, which may be clinically relevant in selected cases.

References

1. Coutinho, A.E.; Chapman, K.E. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Mol. Cell. Endocrinol. 2011, 335, 2–13.
2. Yoshikawa, N.; Nakanishi, K.; Sako, M.; Oba, M.S.; Mori, R.; Ota, E.; Ishikura, K.; Hataya, H.; Honda, M.; Ito, S.; et al. A multicenter randomized trial indicates initial prednisolone treatment for childhood nephrotic syndrome for two months is not inferior to six-month treatment. Kidney Int. 2015, 87, 225–232.
3. Lombel, R.M.; Gipson, D.S.; Hodson, E.M. Treatment of steroid-sensitive nephrotic syndrome: New guidelines from KDIGO. Pediatric Nephrol. 2012, 28, 415–426.
4. Haun, M.W.; Estel, S.; Rucker, G.; Friederich, H.C.; Villalobos, M.; Thomas, M.; Hartmann, M. Early palliative care for adults with advanced cancer. Cochrane Database Syst. Rev. 2017, 6, CD011129.
5. Yoshikawa, N.; Honda, M.; Iijima, K.; Awazu, M.; Hattori, S.; Nakanishi, K.; Ito, H. Steroid Treatment for Severe Childhood IgA Nephropathy: A Randomized, Controlled Trial. Clin. J. Am. Soc. Nephrol. 2006, 1, 511–517.
6. Moore, M.J. Clinical Pharmacokinetics of Cyclophosphamide. Clin. Pharmacokinet. 1991, 20, 194–208.
7. Tejani, A.; Phadke, K.; Nicastri, A.; Adamson, O.; Chen, C.; Trachtman, H.; Tejani, C. Efficacy of Cyclophosphamide in Steroid-Sensitive Childhood Nephrotic Syndrome with Different Morphological Lesions. Nephron Exp. Nephrol. 1985, 41, 170–173.
8. Zagury, A.; de Oliveira, A.L.; de Moraes, C.A.P.; Montalvão, J.A.D.A.; Novaes, R.H.L.L.; de Sá, V.M.; Carvalho, D.D.B.M.D.; Matuck, T. Long-term follow-up after cyclophosphamide therapy in steroid-dependent nephrotic syndrome. Pediatric Nephrol. 2011, 26, 915–920.
9. Kamei, K.; Nakanishi, K.; Ito, S.; Saito, M.; Sako, M.; Ishikura, K.; Hataya, H.; Honda, M.; Iijima, K.; Yoshikawa, N.; et al. Long-Term Results of a Randomized Controlled Trial in Childhood IgA Nephropathy. Clin. J. Am. Soc. Nephrol. 2011, 6, 1301–1307.

10. Mircheva, J.; Legendre, C.; Soria-Royer, C.; Thervet, E.; Beaune, P.; Kreis, H. Monitoring of azathioprine-induced immunosuppression with thiopurine methyltransferase activity in kidney transplant recipients. Transplantation 1995, 60, 639–642.
11. Plank, C.; Nephrologie, F.A.F.P.; Kalb, V.; Hinkes, B.; Hildebrandt, F.; Gefeller, O.; Rascher, W. Cyclosporin A is superior to cyclophosphamide in children with steroid-resistant nephrotic syndrome—A randomized controlled multicentre trial by the Arbeitsgemeinschaft für Pädiatrische Nephrologie. Pediatric Nephrol. 2008, 23, 1483–1493.
12. Kemper, M.J.; Kuwertz-Broeking, E.; Bulla, M.; Mueller-Wiefel, D.E.; Neuhaus, T.J. Recurrence of severe steroid dependency in cyclosporin A-treated childhood idiopathic nephrotic syndrome. Nephrol. Dial. Transplant. 2004, 19, 1136–1141.
13. Choudhry, S.; Bagga, A.; Hari, P.; Sharma, S.; Kalaivani, M.; Dinda, A. Efficacy and Safety of Tacrolimus Versus Cyclosporine in Children with Steroid-Resistant Nephrotic Syndrome: A Randomized Controlled Trial. Am. J. Kidney Dis. 2009, 53, 760–769.
14. Jahan, A.; Prabha, R.; Chaturvedi, S.; Mathew, B.; Fleming, D.; Agarwal, I. Clinical efficacy and pharmacokinetics of tacrolimus in children with steroid-resistant nephrotic syndrome. Pediatric Nephrol. 2015, 30, 1961–1967.
15. Yang, E.M.; Lee, S.T.; Choi, H.J.; Cho, H.Y.; Lee, J.H.; Kang, H.G.; Park, Y.S.; Cheong, H.I.; Ha, I.-S. Tacrolimus for children with refractory nephrotic syndrome: A one-year prospective, multicenter, and open-label study of Tacrobell®, a generic formula. World J. Pediatric 2015, 12, 60–65.
16. Dorresteijn, E.M.; Holthe, J.E.K.-V.; Levtchenko, E.N.; Nauta, J.; Hop, W.C.J.; van der Heijden, A.J. Mycophenolate mofetil versus cyclosporine for remission maintenance in nephrotic syndrome. Pediatric Nephrol. 2008, 23, 2013–2020.
17. Gellermann, J.; Weber, L.; Pape, L.; Tönshoff, B.; Hoyer, P.; Querfeld, U. Mycophenolate Mofetil versus Cyclosporin A in Children with Frequently Relapsing Nephrotic Syndrome. J. Am. Soc. Nephrol. 2013, 24, 1689–1697.
18. Kemper, M.J.; Valentin, L.; Van Husen, M. Difficult-to-treat idiopathic nephrotic syndrome: Established drugs, open questions and future options. Pediatric Nephrol. 2017, 33, 1641–1649.
19. Purohit, S.; Piani, F.; Ordoñez, F.A.; de Lucas-Collantes, C.; Bauer, C.; Cara-Fuentes, G. Molecular Mechanisms of Proteinuria in Minimal Change Disease. Front. Med. 2021, 8, 761600.
20. Iijima, K.; Sako, M.; Kamei, K.; Nozu, K. Rituximab in steroid-sensitive nephrotic syndrome: Lessons from clinical trials. Pediatric Nephrol. 2017, 33, 1449–1455.
21. Sinha, R.; Agrawal, N.; Xue, Y.; Chanchlani, R.; Pradhan, S.; Raina, R.; Marks, S.D. Use of rituximab in paediatric nephrology. Arch. Dis. Child. 2021, 106, 1058–1065.
22. Salvadori, M.; Tsalouchos, A. How immunosuppressive drugs may directly target podocytes in glomerular diseases. Pediatric Nephrol. 2021, 1–11.
23. Fornoni, A.; Sageshima, J.; Wei, C.; Merscher-Gomez, S.; Aguillon-Prada, R.; Jauregui, A.N.; Li, J.; Mattiazzi, A.; Ciancio, G.; Chen, L.; et al. Rituximab Targets Podocytes in Recurrent Focal Segmental Glomerulosclerosis. Sci. Transl. Med. 2011, 3, 85ra46.
24. Mastrangelo, A.; Serafinelli, J.; Giani, M.; Montini, G. Clinical and Pathophysiological Insights into Immunological Mediated Glomerular Diseases in Childhood. Front. Pediatric 2020, 8, 205.
25. Akamine, K.; Punaro, M. Biologics for childhood systemic vasculitis. Pediatric Nephrol. 2018, 34, 2295–2309.
26. Brogan, P.; Yeung, R.S.M.; Cleary, G.; Rangaraj, S.; Kasapcopur, O.; Hersh, A.O.; Li, S.; Paripovic, D.; Schikler, K.; Zeft, A.; et al. Phase IIa Global Study Evaluating Rituximab for the Treatment of Pediatric Patients with Granulomatosis with Polyangiitis or Microscopic Polyangiitis. Arthritis Rheumatol. 2021, 74, 124–133.
27. Null, N. Etanercept plus Standard Therapy for Wegener’s Granulomatosis. N. Engl. J. Med. 2005, 352, 351–361.
28. Langford, C.A.; Monach, P.A.; Specks, U.; Seo, P.; Cuthbertson, D.; McAlear, C.A.; Ytterberg, S.R.; Hoffman, G.S.; Krischer, J.P.; Merkel, P.A.; et al. An open-label trial of abatacept (CTLA4-IG) in non-severe relapsing granulomatosis with polyangiitis (Wegener’s). Ann. Rheum. Dis. 2014, 73, 1376–1379.
29. Gopaluni, S.; Smith, R.; Goymer, D.; Cahill, H.; Broadhurst, E.; Wallin, E.; McClure, M.; Chaudhry, A.; Jayne, D. Alemtuzumab for refractory primary systemic vasculitis—A randomised controlled dose ranging clinical trial of efficacy and safety (ALEVIATE). Arthritis Res. Ther. 2022, 24, 81.
30. Merrill, J.T.; Shanahan, W.R.; Scheinberg, M.; Kalunian, K.C.; Wofsy, D.; Martin, R.S. Phase III trial results with blisibimod, a selective inhibitor of B-cell activating factor, in subjects with systemic lupus erythematosus (SLE): Results from a randomised, double-blind, placebo-controlled trial. Ann. Rheum. Dis. 2018, 77, 883–889.
31. Brunner, H.I.; Abud-Mendoza, C.; Mori, M.; Pilkington, C.A.; Syed, R.; Takei, S.; Viola, D.O.; Furie, R.A.; Navarra, S.; Zhang, F.; et al. Efficacy and safety of belimumab in paediatric and adult patients with systemic lupus erythematosus:

An across-study comparison. RMD Open 2021, 7, e001747.

32. Wallace, D.J.; Isenberg, D.A.; Morand, E.F.; Vazquez–Mateo, C.; Kao, A.H.; Aydemir, A.; Pudota, K.; Ona, V.; Aranow, C.; Merrill, J.T. Safety and clinical activity of atacicept in the long-term extension of the phase 2b ADDRESS II study in systemic lupus erythematosus. Rheumatology 2021, 60, 5379–5389.
33. Mundel, P.; Greka, A. Developing therapeutic ‘arrows’ with the precision of William Tell. Curr. Opin. Nephrol. Hypertens. 2015, 24, 388–392.